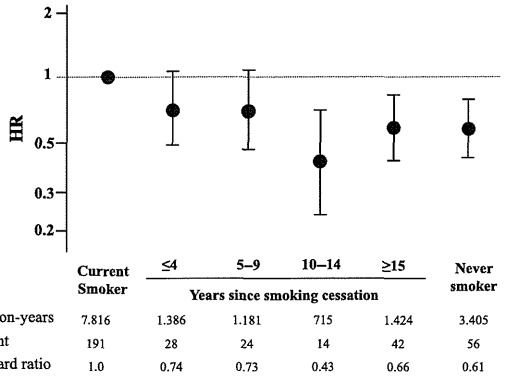

Figure 1 The multivariate-adjusted hazard ratios and 95% CIs for all-cause death by time since smoking cessation in men, the Hisayama study, 1988–2006. The vertical bars denote 95% CIs. The risks were adjusted for age, hypertension, body mass index, diabetes, total cholesterol, alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke. Information on the duration of smoking cessation was missing for two subjects.

greater pack-years of cigarette exposure were significantly associated with the risk of cancer death but not of cardiovascular death.

Figure 1 presents the change in the multivariate-adjusted HRs of all-cause death for former smokers according to the duration of smoking cessation. Compared with current smokers, the decreasing trend in the risk of all-cause death appeared within 5 years after the smoking cessation and the risk of all-cause death in subjects who had quit smoking for 10 years and over significantly decreased to a level similar to that of never smokers (figure 1): the multivariate-adjusted HR of all-cause death was 0.43 (95% CI 0.25 to 0.75; p=0.003) for subjects who had quit smoking for 10–14 years and 0.66 (95% CI 0.47 to 0.94; p=0.021) for subjects with a cessation period of 15 years or more.

Finally, we estimated the influence of smoking cessation on the risk of cause-specific death in light of the length of time since smoking cessation, which was divided into two categories of <10 years and ≥10 years (table 4). Compared with current smokers, the risk of cancer death significantly decreased in subjects who had quit smoking for ≥10 years or over, whereas significant risk reduction in cardiovascular death appeared in subjects in the group with <10 years since cessation.

DISCUSSION

The present study clearly demonstrated that smoking habits significantly increased the risk of death from any cause among Japanese men, even with a small amount of daily smoking. Notably, smoking cessation reduced the risks of all-cause and cause-specific death to levels similar to those for never smokers. The risk reduction for all-cause death appeared as soon as 5 years after smoking cessation and became significant after 10 years. With respect to cause-specific death, the favourable effect of smoking cessation for cardiovascular death appeared earlier than that for cancer death.

There is no doubt that smoking constitutes a serious risk factor for death, especially cancer death.[13] In a previous prospective study conducted in Japan, the risk for death from any cancer significantly increased for current smokers, even those smoking fewer than 20 cigarettes per day.[14] With regard to cardiovascular death, several prospective cohort studies have shown a clear association between habitual smoking and the increased risks of stroke and coronary heart disease.[10 11 15 16] These were exactly the cases for the present study. These findings suggest that tobacco smoking is harmful even for a small number of cigarettes daily. Intriguingly, our findings revealed that greater pack-years of smoking were significantly associated with the risk of cancer death but not cardiovascular death. This finding raises the possibility that the mechanisms underlying the hazardous effects of smoking on cancer death and cardiovascular death would be different, implying that the long-term smoking may have much greater impact on the occurrence of cancer. Further research is required to elucidate this issue.

The present study also showed that former smokers who had quit smoking for ≥10 years had similar levels of risk for all-cause or cause-specific death as never smokers. This finding was almost comparable to those from other Japanese prospective cohort studies.[3 9] Hirayama reported that the risk of all-cause death for male subjects who had quit smoking for ≥10 years decreased to the same levels as the risk for never smokers.[3] The Miyagi cohort study also showed that there was no evidence of difference in the risk for all-cause death between never smokers and subjects with a cessation period of 15 years or over in Japanese male subjects.[9] These findings together with ours strongly indicate the importance of smoking cessation for reduction in the risk of death.

Table 4 Multivariate-adjusted risks for cause-specific death by time since smoking cessation

	Current smoker	Years since smoking cessation		Never smoker
		0–9	≥10	
Person-years of follow-up	7816	2567	2139	3405
Cancer death				
Number	79	27	16	18
Multivariate-adjusted HR (95% CI)	1.00	1.00 (0.64 to 1.57)	0.47 (0.27 to 0.82)**	0.50 (0.30 to 0.84)**
Cardiovascular death				
Number	55	10	18	18
Multivariate-adjusted HR (95% CI)	1.00	0.44 (0.22 to 0.88)*	0.59 (0.34 to 1.04)	0.68 (0.40 to 1.16)
Death from other causes				
Number	57	15	22	20
Multivariate-adjusted HR (95% CI)	1.00	0.74 (0.41 to 1.33)	0.74 (0.44 to 1.24)	0.69 (0.41 to 1.16)

*p<0.05; **p<0.01 compared with never smoker.
Multivariate adjustment was made for age, hypertension, body mass index, diabetes, total cholesterol, alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke.
Information on duration of smoking cessation was missing for two subjects.

What this study adds

We clearly demonstrated that smoking habits significantly increased the risk of death from any cause among Japanese men, even a small amount of daily smoking. Smoking cessation is very effective in reducing the risks of all-cause and cause-specific death to levels similar to those for never smokers. The excess risk of all-cause death tended to decrease within 5 years after smoking cessation, reaching a level almost equivalent to that of never smokers.

In the present study, the preventive effect of smoking cessation for cardiovascular death appeared earlier than that for cancer death. Similar findings were observed in several prospective cohort studies[15 16] and intervention trials.[17] This time lag implies that the biological effects of smoking may be different between cardiovascular death and cancer death. With regard to the relation between smoking habits and the increased risk of cardiovascular disease, various processes such as the incitement of oxidative stress to vascular injury,[18] the enhancement of platelet aggregation[19] and the change in the fibrinolytic system[20] would be involved. Supportively, data from several clinical and epidemiological studies have indicated that excess levels of these risk factors in current smokers disappeared immediately after smoking cessation.[21 22] On the other hand, numerous carcinogenic substances in cigarettes play roles as initiators or promoters of malignancies.[23] These harmful carcinogens induce mutations that disrupt cell cycle regulation[23] or influence the immune or endocrine systems.[24 25] Since carcinogenesis goes through multistage processes,[23] long exposure to carcinogenic substances and the subsequent accumulation of these substances would increase the chance of developing and expanding malignancies. Therefore, it is likely to take a long time to diminish the influence of these substances after smoking cessation.

There are some strengths of our study. The present study was designed as a population-based prospective cohort study that eliminates the case selection bias encountered in clinical series of hospital cases. Moreover, we performed perfect follow-up of subjects, and the causes of death were confirmed by autopsy in 73.2% of subjects who died during the follow-up period. The association of smoking habits with death was also assessed after considering other confounding factors. One limitation of the present study is that we did not consider changes in smoking habits and confounding factors during the follow-up. This may have led to the misclassification of these risk factors over time. This limitation is likely to lead to the underestimation of the influence of smoking habits on the risk of death.

In conclusion, the present study confirmed that habitual smoking, even a small amount of cigarette smoking, was a significant risk factor for death from any cause among Japanese men. Moreover, risk reduction of all-cause death for smokers occurred soon after quitting smoking, and the risk level was comparable to that of never smokers before long. As Japanese men still have the highest smoking rate in the developed world, the present findings highlight the importance of smoking cessation for this population. A campaign to encourage smoking cessation would be an effective strategy to reduce the burden of death from cancer and cardiovascular disease in Japanese men.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Kyushu University.

Contributors FI conceived and designed the study, and contributed to acquisition of data, statistical analysis and drafting the manuscript. TN was responsible for acquisition and interpretation of data, and drafting of the manuscript. YD, JH and MF collected data and provided critical review of the draft. TM reviewed the manuscript. YK contributed to interpretation of data and drafting manuscript. He also obtained funding and study supervision.

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Smoking cessation improves mortality in Japanese men: the Hisayama study

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Original Article

Prevalence and Causes of Functional Disability in an Elderly General Population of Japanese: The Hisayama Study

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ABSTRACT

Background: There are limited data on the prevalence and causes of disability in the elderly general population in Japan.

Methods: In a population-based cross-sectional study of 1550 Japanese aged 65 years or older, we examined the prevalence of functional disability (defined as a Barthel Index score of ≤95) and its causes.

Results: A total of 311 of the participants had a disability (prevalence 20.1%). The prevalence of disability increased with age and doubled with every 5-year increment in age. Prevalence was higher in women than in men, especially among those aged 85 years or older. With respect to the cause of functional disability, dementia accounted for 23.5%, stroke for 24.7%, orthopedic disease for 12.9%, and other disease for 38.9% of cases in men; in women, the respective values were 35.8%, 9.3%, 31.0%, and 23.9%. Regarding age, dementia was the most frequent cause of disability in subjects aged 75 years or older, whereas stroke was most common in subjects aged 65 to 74 years. Approximately two-thirds of cases of total dependence were attributed to dementia in both sexes, whereas the main cause of slight or moderate/severe dependence was stroke in men and orthopedic disease in women. Among participants with total dependence, 94.8% resided in a hospital or health care facility.

Conclusions: Our findings indicate that functional disability is common among Japanese elderly adults and that its major cause is stroke in men and dementia in women.

Key words: functional disability; dementia; stroke; prevalence; Japanese elderly

INTRODUCTION

The elderly population has been rapidly increasing worldwide, especially in developed countries. In Japan, the proportion of adults aged 65 years or older among the whole population has been the highest in the world since 2004, and it reached 23.0% in 2010.[1] Along with this aging population, an increase in functional disability, which causes dependency and institutionalization, is a serious social, medical, and economic concern.[2,3] Studies of the prevalence, causes, and effects of functional disability among the elderly population are therefore needed for appropriate public health policy and planning. Several community-based studies have reported the prevalence of functional disability and its causes in the elderly in Western countries[4–9] and Japan.[10–14] However, participants staying in hospitals or health care facilities were not surveyed in those studies, which likely led to underestimation of the prevalence of disability. Furthermore, information from questionnaires was used to determine causes of disability in those studies. Therefore, it might be valuable to use less-biased community surveys and detailed clinical information to determine the status of functional disability and its causes in Japan. We examined the prevalence and underlying causes of functional disability in an elderly general population of Japanese.

METHODS

Study population

The Hisayama Study is a prospective cohort study of cerebrocardiovascular diseases in the town of Hisayama, a subrural community adjacent to the metropolitan area

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of Fukuoka, Japan.[15] The population of the town has distributions of age, occupational status, and nutrient intake that are almost identical to those for the whole of Japan.[15] Full community surveys of the health status and neurological conditions of residents aged 40 years or older have been repeated since 1961.[15] One characteristic of this study is that all event data on cerebrocardiovascular diseases have been verified by detailed neurological and morphological examinations, including neuroimaging.[15] Additionally, comprehensive surveys of functional disability and dementia in elderly adults have been carried out since 1985.[16] Between October 2005 and August 2006, a total of 1566 residents aged 65 or older (91.5% of the total population in this age group) participated in the examination for the present study. The examination was performed in the public hall of the town or at home. In addition, we visited hospitals and health care facilities to examine institutionalized individuals. After excluding 16 subjects for whom activity of daily living (ADL) status was not available, data from 1550 subjects (601 men and 949 women) were included in the present analysis.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. All participants gave written informed consent, which included the purpose and procedures of the research, potential risks and benefits associated with participation, voluntary participation in the study, the right of withdrawal from the research without prejudice or penalty, and the confidentiality and security of personal data.

Questionnaire

In the examination, each participant completed a self-administered questionnaire that inquired about socio-demographic data (including age, sex, marital status, employment status, and place of residence [domicile, hospital, long-term care facility, or nursing home]), Barthel Index items,[17] and past history of diseases (including stroke, coronary heart disease, fracture, head injury, hypertension, diabetes, hyperlipidemia, depression, and other conditions). The completed questionnaires were reviewed by trained nurses or physicians to identify inconsistent answers and unanswered items. To diagnose dementia, all participants took neuropsychological tests (revised version of Hasegawa's Dementia Scale [HDS-R][18] and Mini-Mental State Examination [MMSE][19]), which were performed by trained nurses and physicians. Among the participants, 395 (25.2%) with test scores below the cutoff values (21/30 for the HDS-R and MMSE) underwent an additional comprehensive investigation.

Definition of functional disability

ADL status was determined using the Barthel Index,[17] which estimates the degree of independence in ADL of subjects by using 10 items: feeding (0, 5, or 10 points), bathing (0, 5), dressing (0, 5, 10), grooming (0, 5), bladder control (0, 5, 10), bowel control (0, 5, 10), toileting (0, 5, 10), transferring from bed to a wheelchair (0, 5, 10, 15), walking on a level surface (0, 5, 10, 15), and ascending and descending stairs (0, 5, 10). Functional disability was defined as a Barthel Index score of 95 or lower, in accordance with the definition previously reported in epidemiologic studies.[17,20–22] In addition, the severity of disability was categorized into 3 levels as follows: slight dependence (a Barthel Index score of 95, which corresponds to 1 decrease in an item on the Barthel Index), moderate/severe dependence (a score of 25–90), and total dependence (a score of 0–20, which corresponds approximately to a bedridden state, with at least 8 decreased items).[17]

Cause of disability

To determine the cause of functional disability, all available past clinical information, including medical records and findings from neurologic examination and brain imaging studies, which was gathered by using the follow-up system of the Hisayama Study,[15,23] was reviewed independently by 2 of the authors (D.Y. and T.N.). Any disagreement in cause attribution was resolved by a consensus of a panel of the authors (D.Y., T.N., and Y.K). If a subject had 2 or more conditions that impaired ADL, the disease that contributed to the deterioration of at least 1 category of ADL level (eg, from moderate/severe dependence to total dependence) was defined as the major cause. For instance, if a subject had mild gait disturbance caused by stroke but gradually became bedridden due to subsequent dementia, dementia would be considered the major cause, whereas stroke would be selected if the subject became bedridden soon after a severe stroke event, even if the participant later developed dementia. Among the 311 disability cases, the 2 researchers completely agreed on the cause of functional disability in 242 (77.8%) cases. In the remaining 68 (22.1%) cases, a consensus on the cause was reached after discussion.

Causes of disability were categorized into 4 groups: dementia (vascular dementia, Alzheimer disease, and other dementia), stroke (ischemic stroke and hemorrhagic stroke), orthopedic disease (fracture, arthritis, rheumatoid arthritis, and other orthopedic disease), and other disease. Dementia and its subtypes were diagnosed according to the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R),[24] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association,[25] and the criteria of the National Institute of Neurological Disorders and Stroke–Association International pour la Recherche et l'Enseignement en Neurosciences.[26] Stroke was defined as the sudden onset of nonconvulsive and focal neurologic deficits persisting at least 24 hours. A diagnosis of stroke and its subtypes

Table 1. Characteristics of study population by functional disability (Hisayama Study, 2005)

	All subjects (n = 1550)	Subjects without disability (n = 1239)	Subjects with disability (n = 311)	P-value[a]
Age, mean ± SD	75.8 ± 7.3	74.2 ± 6.3	82.1 ± 7.7	<0.001
Women, %	61.1	58.2	72.7	<0.001
Current working status, %				<0.001
Unemployed/retired/housewife	73.1	68.9	90.4	
Working	26.9	31.1	9.6	
Marital status, %				<0.001
Never married	2.5	2.2	3.5	
Married	63.4	68.6	42.8	
Divorced/widowed/separated	34.1	29.2	53.7	
Living arrangement, %				0.04
Living alone	10.9	10.1	14.2	
Living with others	89.1	89.9	85.8	
Place of residence, %				<0.001
Home	91.6	99.3	60.5	
Hospital	5.2	0.6	23.8	
Health care facility	3.2	0.1	15.7	
ADL disability level, %				
Slight dependence	5.0	—	25.4	
Moderate/severe dependence	10.0	—	49.8	
Total dependence	5.1	—	24.8	

[a]P value, comparison between subjects with and without disability.

Table 2. Prevalence of disability by age category (Hisayama Study, 2005)

Age category	Total (n = 1550)		Men (n = 603)		Women (n = 947)		P value between sexes
	No. with disability/ participants	Prevalence, % (95% CI)	No. with disability/ participants	Prevalence, % (95% CI)	No. with disability/ participants	Prevalence, % (95% CI)	
65–69	18/366	4.9 (2.9–7.7)	9/161	5.6 (2.6–10.4)	9/205	4.4 (2.0–8.2)	0.60
70–74	38/393	9.7 (6.9–13.0)	14/171	8.2 (4.6–13.4)	24/222	10.8 (7.1–15.7)	0.38
75–79	53/331	16.0 (12.2–20.4)	18/129	14.0 (8.5–21.2)	35/202	17.3 (12.4–23.3)	0.41
80–84	75/256	29.3 (23.8–35.3)	20/91	22.0 (14.0–31.9)	55/165	33.3 (26.2–41.1)	0.06
85+	127/204	62.3 (55.2–68.9)	24/51	47.1 (32.9–61.5)	103/153	67.3 (59.3–74.7)	0.01
All ages	311/1550	20.1 (18.1–22.2)	85/603	14.1 (11.4–17.1)	226/947	23.9 (21.1–26.7)	<0.001
P for trend		<0.001		<0.001		<0.001	

was determined on the basis of medical records and brain imaging studies.[27] Hemorrhagic stroke included brain hemorrhage and subarachnoid hemorrhage. The diagnosis and classification of orthopedic disease were determined with clinical information available from the questionnaire, medical records, and annual health examinations.

Statistical analysis

The software package SAS (version 9.2; SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. The Student t-test was used to compare continuous variables, and the chi-square test was used to evaluate proportions. We calculated the prevalences of disability with 95% confidence intervals (CIs) by using a binary distribution. Trends in the prevalence of disability across 5-year age categories were tested by means of logistic regression analysis. A 2-sided P value less than 0.05 was considered statistically significant in all analyses.

RESULTS

The characteristics of study subjects according to functional disability status are shown in Table 1. The mean overall age was 76 years, and the proportion of women was 61.1%. A total of 311 subjects (85 men and 226 women) had some type of functional disability, resulting in a prevalence of 20.1%. As compared with those without disability, subjects with disability were more likely to be older, female, unemployed, living alone, and institutionalized. Among those with disability, the proportions of subjects with slight, moderate/severe, and total dependence were 25.4%, 49.8%, and 24.8%, respectively.

As shown in Table 2, the prevalence of functional disability increased with age, with a doubling in prevalence for every 5-year increment. The prevalence of disability was significantly higher in women than in men ($P < 0.001$), especially among participants aged 85 or older ($P = 0.01$). A comparable relationship was observed in subjects with total dependence,

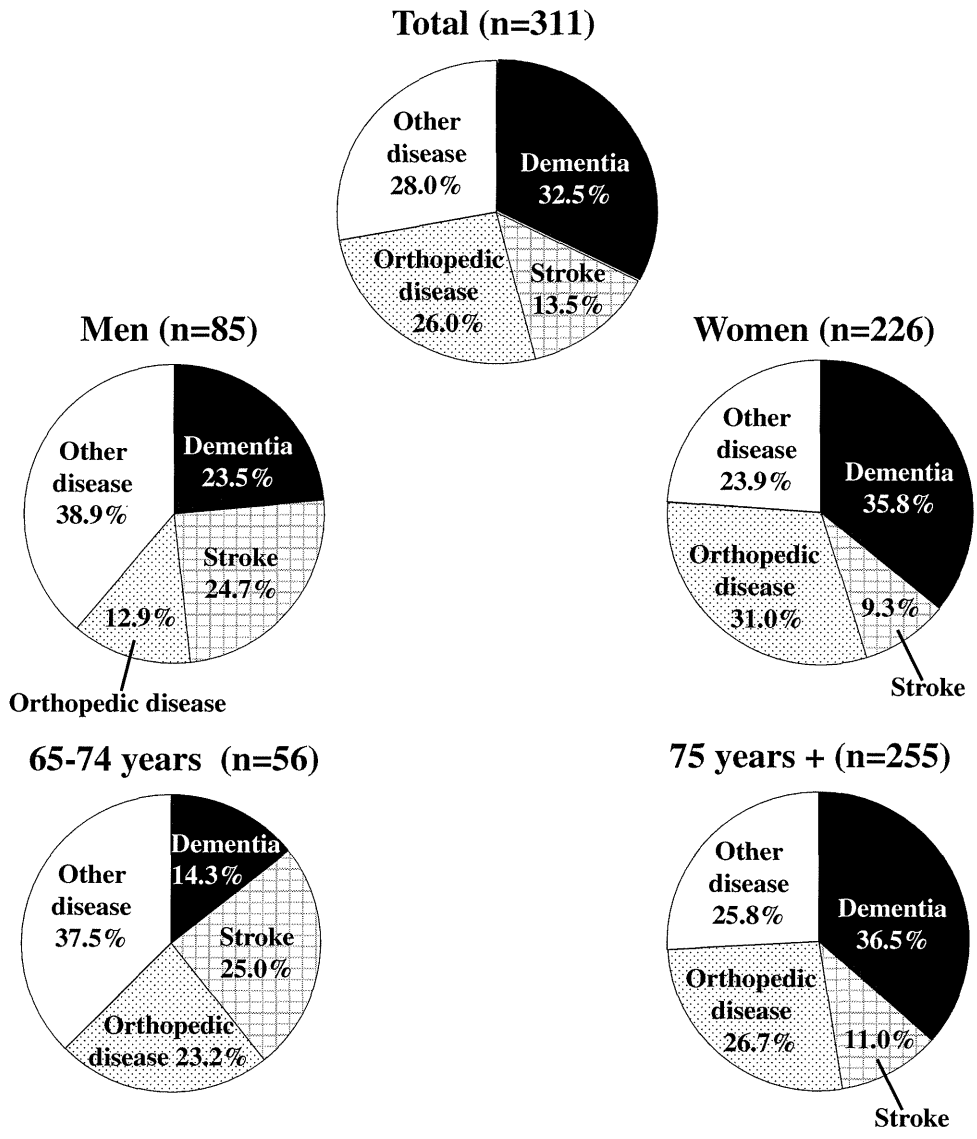

Figure 1. Causes of functional disability by sex and age (Hisayama Study, 2005).

whereas the prevalence of slight and moderate/severe dependence was not significantly different between sexes in any age category (data not shown).

Next, we investigated the causes of functional disability (Figure 1). Among the 311 disability cases, dementia accounted for 32.5%, stroke for 13.5%, orthopedic disease for 26.0%, and other disease for 28.0% of cases. Among the 101 subjects with dementia-related disability, 22 (21.8%) had a history of a stroke events that resulted in slight or moderate/severe dependence. When the results were categorized by sex, dementia accounted for 23.5%, stroke for 24.7%, orthopedic disease for 12.9%, and other disease for 38.9% of cases of functional disability in the 85 disabled men; the respective values were 35.8%, 9.3%, 31.0%, and 23.9% in the 226 disabled women. Stroke was the most common cause of disability in men, whereas dementia and orthopedic disease were more frequent in women. When the findings were analyzed by age category, dementia accounted for 14.3%, stroke for 25.0%, orthopedic disease for 23.2%, and other disease for 37.5% of disability cases in subjects aged 65 to 74 years; the respective proportions were 36.5%, 11.0%, 26.7%, and 25.8% for subjects aged 75 or older; that is, dementia was the most frequent cause of disability in subjects aged 75 or older, whereas stroke was the most common cause in subjects aged 65 to 74 years.

The subtypes of causes of functional disability by sex are shown in Table 3. Among cases of dementia, vascular dementia was most frequent in men (12.9%), whereas Alzheimer disease was most common in women (15.0%). With regard to stroke subtype, ischemic stroke was more frequent in men than in women (17.6% vs 6.2%). With regard to orthopedic disease, the proportions of fracture and arthritis were higher, especially in women (15.0% and 10.2%, respectively).

Figure 2 shows the causes of functional disability among the 311 subjects according to disability severity by sex. In subjects with total dependence, dementia was the most

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Table 3. Subtypes of causes of disability by sex (Hisayama Study, 2005)

Disease/condition	Total (n = 311)		Men (n = 85)		Women (n = 226)		P-value[a]
	Number	%	Number	%	Number	%	
Dementia	101	32.5	20	23.5	81	35.8	0.04
Vascular dementia	30	9.6	11	12.9	19	8.4	0.23
Alzheimer disease	40	12.9	6	7.1	34	15.0	0.06
Other dementia	31	10.0	3	3.5	28	12.4	0.02
Stroke	42	13.5	21	24.7	21	9.3	<0.001
Ischemic stroke	29	9.3	15	17.6	14	6.2	0.002
Hemorrhagic stroke	13	4.2	6	7.1	7	3.1	0.20
Orthopedic disease	81	26.0	11	12.9	70	31.0	0.001
Fracture	38	12.2	4	4.7	34	15.0	0.01
Arthritis	25	8.0	2	2.4	23	10.2	0.03
Rheumatoid arthritis	11	3.5	2	2.4	9	4.0	0.73
Other orthopedic disease	7	2.3	3	3.5	4	1.8	0.40
Other disease	87	28.0	33	38.8	54	23.9	0.009

[a]P value for comparison between sexes.

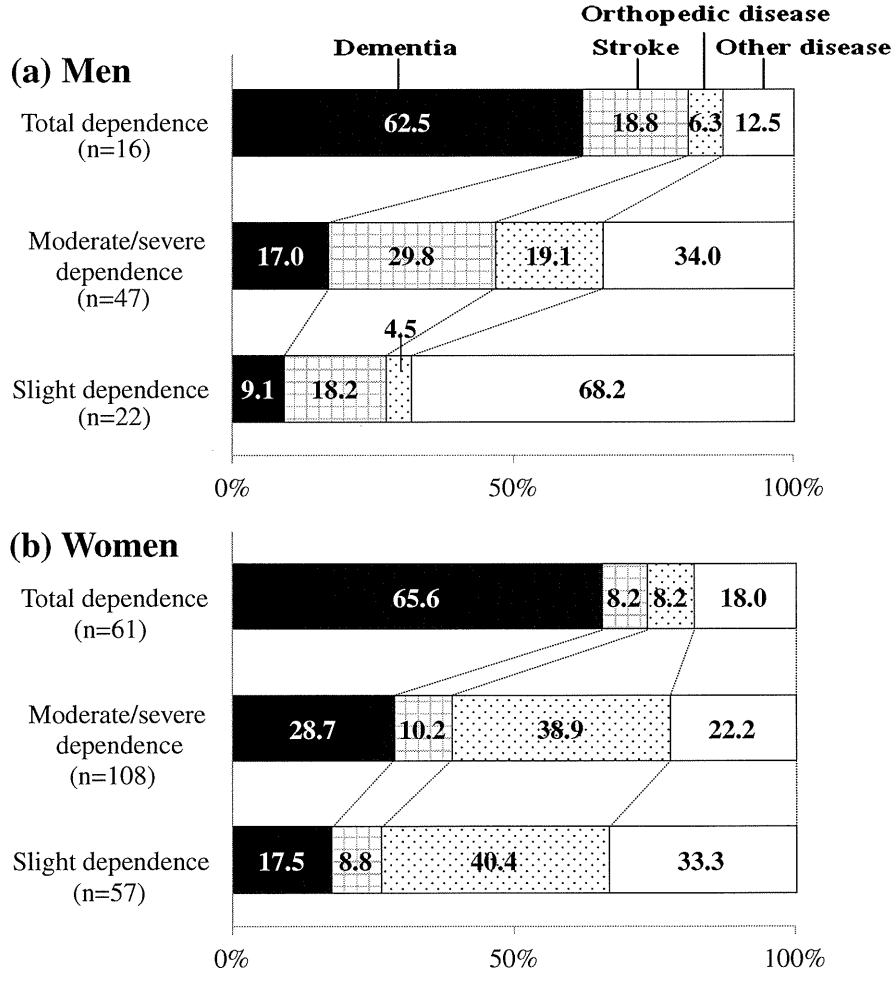

Figure 2. Causes of functional disability by severity of disability in men and women (Hisayama Study, 2005). Total dependence: Berthel Index score = 0–20. Moderate/severe dependence: Berthel Index score = 25–90. Slight dependence: Berthel Index score = 95.

frequent cause in both sexes: the proportion was 62.5% in men and 65.6% in women. In subjects with slight or moderate/severe dependence, stroke was the most common cause of disability in men, whereas orthopedic disease was the most frequent in women.

Finally, we investigated place of residence in the 311 disabled subjects according to functional severity. Among subjects with slight dependence, 91.1% lived at home, 6.3% were hospitalized, and 2.6% stayed in health care facilities; the respective values were 72.3%, 17.4%, and 10.3% for those

with moderate/severe dependence. In contrast, among subjects with total dependence, only 5.2% lived at home, whereas 54.6% and 40.2% stayed in a hospital or health care facility, respectively.

DISCUSSION

The present study demonstrated that the prevalence of functional disability was 20.1% in an elderly general population of Japanese. Additionally, we found that the prevalence of disability increased steeply with age, with a doubling of prevalence for each 5-year increment. Prevalence was higher in women than in men, especially in individuals aged 85 or older. Importantly, in our subjects the major cause of disability was stroke in men and dementia in women. In particular, dementia was the most common cause of disability in subjects with total dependence, most of whom required full-time care in hospitals or health care facilities. These findings highlight the clinical importance of effective strategies for preventing dementia. Such strategies could reduce the social and economic burden of functional disability among elderly Japanese.

Prevalence of disability

There is considerable divergence in the prevalence of disability reported in community-based studies, with values ranging from 6% to 34.5%.[4–13] For aged Japanese populations, these studies have reported a disability prevalence ranging from 8% to 17%,[10–13] which is lower than that obtained in the present study. A possible reason for this discrepancy is the difference in the proportion of old old adults in the studies, as this group is at high risk for functional disability. Among people aged 65 years or older, the proportion of those aged 85 years or older was 4.5% to 8.7% in previous studies, which were conducted from 1977 to 1996,[1,10–13] as compared with 11.4% in the present study, performed in 2005. These findings indicate that the proportion of old old has increased over time in Japan, which has led to a recent increase in the prevalence of functional disability. In addition, some selection bias was likely in previous studies, because subjects staying in hospitals or health care facilities might not have been fully examined. In contrast, the participation rate was high (91%) in our study, and we included institutionalized subjects in the study to minimize selection bias. This bias in previous studies would lead to underestimation of the prevalence of disability. Furthermore, the discrepant findings may have been due to a difference in the definition of disability across studies. The Barthel Index, which was used in our study, has been reported to be more sensitive in detecting disability as compared with other indices with fewer ADL domains (eg, the Katz Index), which were used in other studies.[6,28] Indeed, in a sensitivity analysis using the Katz Index—in which functional disability was defined as need for assistance in 1 or more activities of 6 ADL domains, including feeding, bathing, dressing, toileting, transferring, and continence—the prevalence of disability declined to 18.3% in our study.

Sex differences in disability

In our study, the prevalence of disability was higher in women than in men, especially among persons aged 85 or older. Comparable findings were observed in previous community-based studies in Sweden and Japan.[8,29,30] However, there is no consensus on the interpretation of this sex difference. A possible explanation is that there are sex differences in death rates for underlying diseases; that is, women might survive with some form of disability after developing cardiovascular disease, whereas men might be more likely to die immediately after the incident disease, since the underlying comorbidity may be more severe in men than in women.[31,32] Another possible explanation is that musculoskeletal disease may have a greater influence on functional limitations in women than in men. For example, a population-based study in the United States indicated that musculoskeletal impairments were attributed to disability more frequently in women than in men.[33] In our subjects, disabled women also had a greater incidence than men of orthopedic diseases such as fracture and arthritis.

Cause of disability

In the present study, dementia was the most frequent cause of functional disability in both sexes, especially among those aged 75 or older. In agreement with this finding, the Adult Health Study in Hiroshima, Japan and a community-based study in Stockholm, Sweden showed that dementia had a greater influence on the development of disability and ADL decline than did stroke, orthopedic disease, or other chronic diseases.[34,35] Furthermore, our study found that the proportion of stroke was high in subjects aged 65 to 74 years. Previous community-based prospective studies in Japan and the United States have also shown that stroke was associated with risk of functional disability.[36–38] A systematic review reported that more than one-third of patients with recurrent stroke later developed dementia.[39] We also revealed that 21.8% of subjects with dementia-related disability had a history of stroke events with slight or moderate/severe dependence. These findings indicate that it is important to prevent stroke events to reduce the risk of future dementia and total dependence. Interestingly, orthopedic disease such as fracture and arthritis contributed mainly to slight dependence and moderate/severe dependence in women. Further investigations will be needed to determine the effect of orthopedic disease on subsequent ADL level.

Place of residence and severity of disability

To date, few studies of general populations have classified ADL level according to place of residence. In our study, approximately 95% of subjects with total dependence were institutionalized in hospitals or health care facilities. Most of

these subjects had dementia and were bedridden. The increase in patients hospitalized or staying in health care facilities is a major social and economic burden in Japan. Therefore, it is imperative to establish effective strategies for preventing the development of dementia and subsequent deterioration of ADL.

Study strengths and limitations

The strength of our study is that selection bias was minimized by including more than 90% of all Hisayama residents aged 65 years or older and by examining subjects staying in hospitals and health care facilities. In addition, cardiovascular events and dementia were evaluated using not only questionnaires but also detailed clinical information, as these parameters are main endpoints of the ongoing Hisayama Study.[15,23] A limitation is that this was a cross-sectional study. Consequently, causal relationships cannot be inferred between underlying diseases and functional disability.

Conclusion

Our study revealed that functional disability is common among Japanese elderly adults and that dementia is the most frequent cause of disability, especially in persons with total dependence. Stroke is a major cause of disability in men and in individuals aged 65 to 74 years (the young old). In countries such as Japan, where the elderly population is increasing rapidly, it is important to establish effective prevention strategies for dementia and stroke to reduce the risk of disability and extend healthy life expectancy in later life.

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Conflicts of interest: None declared.

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Insulin Resistance and the Development of Cardiovascular Disease in a Japanese Community: the Hisayama Study

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Aims: Although several surrogate measures of insulin resistance have been proposed, their associations with cardiovascular disease (CVD) have not been evaluated sufficiently.
Methods: A total of 2,356 community-dwelling Japanese individuals aged 40 to 79 years who underwent a 75 g oral glucose tolerance test were followed up for 14 years. The status of insulin resistance was estimated by using the Matsuda index or homeostasis model assessment of insulin resistance (HOMA-IR).
Results: During follow-up, 260 subjects developed CVD. The age- and sex-adjusted hazard ratios of CVD significantly decreased with an increasing Matsuda index and rose with increasing HOMA-IR levels (both p for trend <0.05). After adjustment for age, sex, serum total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise, the risk of CVD was significantly lower in the third to fifth quintiles of the Matsuda index and higher in the fifth quintile of HOMA-IR values compared with the first quintile of the corresponding index (Matsuda index Q3: hazard ratio (HR)=0.59 [95% confidence interval 0.40-0.87]; Q4: HR=0.66 [0.45-0.97]; and Q5: HR=0.67 [0.47-0.97]; HOMA-IR Q5: HR=1.55 [1.05-2.29]); however, these associations were attenuated after further adjustment for the metabolic syndrome status. In regard to CVD subtypes, the risks for stroke and coronary heart disease significantly decreased with an increasing Matsuda index, while elevated HOMA-IR levels were a significant risk factor for stroke, but not for coronary heart disease.
Conclusion: Our findings suggest that insulin resistance significantly increases the risk of incident CVD through metabolic syndrome in Japanese.

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Key words; Epidemiology, Cardiovascular disease, Insulin resistance, Cohort study, General populations

Introduction

Insulin resistance and compensatory hyperinsulinemia are closely related to obesity and are considered to be the underlying features of elevated blood pressure[1,2] and metabolic disorder, including impaired glucose tolerance[3,4] and dyslipidemia[5,6], which are collectively identified as metabolic syndrome (MetS)[7]. Prospective population-based studies have shown that subjects with MetS had a significantly higher risk of incident cardiovascular disease (CVD)[8-10], but the association between CVD and insulin resistance itself is less clear. Several surrogate indices have been proposed to evaluate insulin resistance[11-13], because the glucose clamp method, the gold standard for the measurement of insulin resistance, is impractical for use in clinical and epidemiological studies. Homeostasis model assessment of insulin resistance (HOMA-IR), derived from fasting glucose and insulin values, has a strong correlation with insulin sensitivity directly measured by the euglycemic hyperinsulinemic clamp

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method[11, 14] and has been commonly used as a surrogate index of insulin resistance; however, it is uncertain whether insulin resistance estimated by HOMA-IR values is significantly associated with incident CVD[15-22]. Matsuda *et al.* proposed an index of insulin sensitivity calculated by measuring glucose and insulin levels before and after oral glucose loading[12, 13]. Although the Matsuda index also correlates well with directly measured insulin resistance[12, 23], to our knowledge, no prior prospective study has evaluated the association between the Matsuda index and incident CVD.

The purpose of this study was to investigate the associations of the Matsuda index and HOMA-IR levels with the development of CVD in a cohort study of a Japanese population, taking into account various comprehensive risk factors, including the MetS status.

Methods

Study Population

The Hisayama Study is a long-term prospective population-based cohort survey of CVD and its risk factors. It was begun in 1961 in Hisayama, a town of approximately 8,000 people located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan[24]. In 1988, a screening survey for the present study was performed in the town. A detailed description of this study has been published previously[25]. In brief, 2,587 residents aged 40 to 79 years (80.2% of the total population of this age range) consented to participate in the examination. After exclusion of 82 subjects who had already had breakfast, 10 who were receiving insulin therapy for diabetes, and 15 who refused a 75-g oral glucose tolerance test (OGTT) due to complaints of nausea or general fatigue during the ingestion of glucose, 2,480 subjects completed the OGTT. Among these, 2 subjects who had died before the start of follow-up, 60 with a past history of stroke or coronary heart disease, 3 for whom either fasting or 2-hour postload insulin levels were not obtained, and 59 who were taking oral hypoglycemic agents were excluded, and the remaining 2,356 subjects (1,006 men and 1,350 women) were included in this study.

Follow-Up Survey

The baseline subjects were followed up prospectively for 14 years from December 1988 through November 2002 by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new events of CVD, including suspected cases. When stroke or coronary heart disease occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. When a subject died, an autopsy was performed in the Department of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 393 subjects died, of whom 292 subjects (74.3%) underwent autopsy examination.

Definition of Cardiovascular Events

In the present study, incident CVD was defined as the development of stroke or coronary heart disease. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. The diagnosis of stroke was based on the clinical history, neurological examination, all available clinical data, including brain computed tomography and magnetic resonance imaging, and autopsy findings. Coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, and coronary artery disease treated by coronary artery angioplasty or bypass grafting. Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: 1) typical symptoms, including prolonged severe anterior chest pain; 2) cardiac enzyme levels more than twice the upper limit of the normal range; 3) evolving diagnostic electrocardiographic changes; and 4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes. During the 14-year follow-up, 260 subjects experienced a first-ever CVD event (139 men and 121 women). Of these, 183 had stroke events (83 men and 100 women) and 98 developed coronary heart disease (68 men and 30 women).

Risk Factors

At the baseline examination, after an overnight fast of at least 12 hours, the OGTT was performed with blood samples taken at 0 and 120 min. Plasma glucose levels were determined by the glucose-oxidase method. Serum insulin levels were determined by a commercial double-antibody solid-phase radioimmu-

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noassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). Insulin sensitivity was evaluated by the Matsuda index, calculated as 10,000 per square root of [fasting glucose (mg/dL) × fasting insulin (μU/mL) × postload glucose (mg/dL) × postload insulin (μU/mL)] according to the previously reported method[13]. Insulin resistance was estimated by HOMA-IR values, calculated as [fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)] / 405[11]. Diabetes was defined as fasting plasma glucose concentrations of ≥7.0 mmol/L (126 mg/dL), 2-hour postload glucose concentrations of ≥11.1 mmol/L (200mg/dL), and/or the use of antidiabetic medication. Serum total and high-density lipoprotein (HDL) cholesterols and triglyceride concentrations were determined enzymatically. Freshly voided urine samples were collected at the screening, and proteinuria was defined as a value of 1+ or more using a reagent strip.

Waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes of rest. The mean of the 3 measurements was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mmHg and/or current treatment with antihypertensive agents.

Electrocardiogram (ECG) abnormalities were defined as left ventricular hypertrophy (Minnesota Code, 3-1), ST depression (4-1, 2, 3), and/or atrial fibrillation (8-3).

Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a self-administered questionnaire. We also asked whether subjects were taking antihypertensive agents, oral hypoglycemic agents and/or insulin. Alcohol consumption and smoking status were classified as either current use or not. Subjects engaging in sports at least 3 times per week during their leisure time were defined as a regular exercise group.

Subjects were diagnosed as having MetS if 3 or more of the following components were present at baseline: 1) waist circumference ≥90 cm in men and ≥80 cm in women; 2) fasting triglyceride concentrations ≥150 mg/dL (1.7 mmol/L); 3) HDL cholesterol concentrations <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women; 4) blood pressure ≥130/85 mmHg or use of antihypertensive drugs; and 5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or use of antidiabetic medications[26].

Statistical Analysis

The SAS software package version 9.2 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. The Matsuda index, HOMA-IR values, fasting plasma insulin, 2-hour postload insulin, and serum triglyceride levels were transformed into logarithms to improve the skewed distribution. The frequencies of possible risk factors at baseline were adjusted for age and sex by a direct method and compared by logistic regression analysis. The age- and sex-adjusted mean values of risk factors at baseline were estimated and compared by analysis of covariance. To analyze the Matsuda index and HOMA-IR values as categorical variables, these levels were divided into sex-specific quintiles: Matsuda index: men, Q1, 0.88 to 4.03; Q2, 4.04 to 6.21; Q3, 6.22 to 8.77; Q4, 8.78 to 13.73; and Q5, 13.74 to 59.72; women, Q1, 0.47 to 4.06; Q2, 4.07 to 5.74; Q3, 5.75 to 7.82; Q4, 7.83 to 10.99; and Q5, 11.00 to 49.21; HOMA-IR: men, Q1, 0.53 to 0.78; Q2, 0.79 to 1.17; Q3, 1.18 to 1.58; Q4, 1.59 to 2.22; and Q5, 2.23 to 16.79; women, Q1, 0.55 to 0.90; Q2, 0.91 to 1.25; Q3, 1.26 to 1.61; Q4, 1.62 to 2.20; and Q5, 2.21 to 15.24. The incidence rates of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method using 10-year age groupings of the overall study population. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the use of the Cox proportional hazards model. The linear trends of HRs across the Matsuda index and HOMA-IR levels were also tested using the Cox proportional hazards model. $P<0.05$ was considered significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from the participants.

Results

The baseline characteristics of subjects stratified by the presence or absence of incident CVD are shown in **Table 1**. The mean values of age, HOMA-IR, fasting and 2-hour postload glucose, fasting plasma insulin, and systolic and diastolic blood pressures, and the frequencies of men, MetS, diabetes, hypertension, ECG abnormalities, proteinuria, and smoking were higher in subjects who developed CVD than in those who did not. In addition, subjects with incident CVD had lower Matsuda index values and a lower frequency of regular exercise. No differences were observed between subjects with and without

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Table 1. Age- and sex-adjusted baseline clinical characteristics of subjects with or without incident cardiovascular disease, 1988

	Incident CVD n=260	No incident CVD n=2,096	p
Age, years	64 (0.6)	56 (0.2)	<0.001
Men, %	56.3	41.3	<0.001
Fasting plasma glucose, mmol/L	6.0 (0.07)	5.7 (0.03)	<0.001
Two-hour postload glucose, mmol/L	8.1 (0.19)	7.1 (0.07)	<0.001
Fasting plasma insulin, pmol/L	43.6 (41.1-46.3)	40.3 (39.4-41.2)	0.01
Two-hour postload insulin, pmol/L	223.4 (204.1-244.5)	208.9 (202.1-216.0)	0.18
Matsuda index	6.2 (5.7-6.7)	7.0 (6.8-7.3)	0.003
HOMA-IR	1.6 (1.5-1.7)	1.4 (1.38-1.45)	0.002
Diabetes mellitus, %	20.0	9.1	0.001
Waist circumference, cm	82.5 (0.6)	81.3 (0.2)	0.05
Systolic blood pressure, mmHg	141.0 (1.2)	131.9 (0.4)	<0.001
Diastolic blood pressure, mmHg	80.6 (0.7)	77.3 (0.3)	<0.001
Hypertension, %	55.0	36.0	<0.001
Total cholesterol, mmol/L	5.35 (0.07)	5.31 (0.02)	0.57
HDL-cholesterol, mmol/L	1.27 (0.02)	1.30 (0.01)	0.17
Triglycerides, mmol/L	1.25 (1.17-1.33)	1.18 (1.15-1.21)	0.14
Metabolic syndrome, %	49.8	32.6	<0.001
ECG abnormalities, %	23.3	15.5	0.03
Proteinuria, %	8.0	5.2	0.02
Current smoking, %	31.4	24.4	0.02
Current drinking, %	36.9	31.6	0.35
Regular exercise, %	5.3	10.5	0.02

CVD: cardiovascular disease; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; ECG: electrocardiogram. Values are given as the means (standard error) or as a percentage. Matsuda index, HOMA-IR, fasting plasma insulin, 2-hour postload insulin, and triglycerides are shown as the geometric means and 95% confidence intervals due to the skewed distribution. Hypertension: blood pressures of ≥140/90 mmHg and/or current use of antihypertensive medicine. Diabetes: fasting ≥7.0 mmol/L, 75 g postload or postprandial glucose levels ≥11.1 mmol/L, and/or use of hypoglycemic agents. ECG abnormalities: left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, or 3), and/or atrial fibrillation (8-3).

CVD in the mean values of 2-hour postload insulin, waist circumference, total cholesterol and HDL cholesterols, and triglycerides and the frequency of alcohol intake.

Compared with those within the first quintile of the Matsuda index, the age- and sex-adjusted HR for the development of CVD significantly decreased in subjects in the third to fifth quintiles (model 1 of **Table 2**). As shown in model 2 for the Matsuda index, this association remained unchanged even after adjustment for age, sex, serum total cholesterol, ECG abnormalities, proteinuria, smoking, alcohol intake, and regular exercise (Q3: multivariable-adjusted HR 0.59, 95% CI 0.40 to 0.87, p=0.008; Q4: HR 0.66, 95% CI 0.45 to 0.97, p=0.03; Q5: HR 0.67, 95% CI 0.47 to 0.97, p=0.04). On the other hand, the age- and sex-adjusted HR for CVD was significantly higher in subjects in the fifth quintile of HOMA-IR than in those in the first quintile. This association also remained robust even after adjustment for the aforementioned confounding factors (Q5: HR 1.55, 95% CI 1.05 to 2.29; p=0.03). However, these associations between the Matsuda index or HOMA-IR and CVD outcomes were attenuated and became non-significant after further adjustment for the MetS status (model 3). By contrast, MetS was a significant risk factor for CVD events in the model 3 for both indices (for the Matsuda index: HR, 1.53, 95% CI 1.15 to 2.04; p= 0.003; for HOMA-IR: HR, 1.57, 95% CI 1.19-2.08; p=0.002). Similar findings were also observed for a 1 SD increment in the Matsuda index and HOMA-IR values as continuous variables.

In **Table 3**, when CVD was divided into stroke and coronary heart disease, the age- and sex-adjusted incidences and HRs for stroke and coronary heart disease significantly decreased with increasing Matsuda index (p for trend <0.05). By contrast, elevated HOMA-IR levels were a risk factor for stroke, but not

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Table 2. Age- and sex-adjusted incidences and adjusted hazard ratios and their 95% confidence intervals of cardiovascular disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Matsuda index								
No. of events	73	56	39	43	49			
Population at risk	471	471	473	470	471			
Incidence per 1,000 person-years	13.0	10.6	7.6	8.2	8.9			
Model 1 HR (95% CI)	1.00 (reference)	0.78 (0.55 to 1.10)	0.53 (0.36 to 0.78)	0.60 (0.41 to 0.88)	0.65 (0.45 to 0.93)	0.006	0.75 (0.63 to 0.89)	0.001
Model 2 HR (95% CI)†	1.00 (reference)	0.86 (0.61 to 1.22)	0.59 (0.40 to 0.87)	0.66 (0.45 to 0.97)	0.67 (0.47 to 0.97)	0.01	0.76 (0.64 to 0.91)	0.003
Model 3 HR (95% CI)‡	1.00 (reference)	0.96 (0.67 to 1.37)	0.68 (0.45 to 1.02)	0.82 (0.55 to 1.23)	0.87 (0.58 to 1.31)	0.33	0.86 (0.71 to 1.05)	0.14
HOMA-IR								
No. of events	45	52	48	52	63			
Population at risk	467	479	468	474	468			
Incidence per 1,000 person-years	8.1	9.4	9.6	9.7	11.6			
Model 1 HR (95% CI)	1.00 (reference)	1.14 (0.76 to 1.69)	1.13 (0.76 to 1.70)	1.18 (0.79 to 1.76)	1.63 (1.11 to 2.39)	0.02	1.45 (1.17 to 1.78)	0.02
Model 2 HR (95% CI)†	1.00 (reference)	1.19 (0.80 to 1.78)	1.20 (0.80 to 1.81)	1.28 (0.85 to 1.94)	1.55 (1.05 to 2.29)	0.03	1.41 (1.14 to 1.74)	0.001
Model 3 HR (95% CI)‡	1.00 (reference)	1.15 (0.77 to 1.72)	1.09 (0.72 to 1.65)	1.11 (0.73 to 1.68)	1.19 (0.77 to 1.81)	0.55	1.23 (0.98 to 1.56)	0.08

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.
Model 1: adjustment was made for age and sex.
Model 2: adjustment was made for age, sex, total cholesterol, electrocardiogram abnormalities, proteinuria, smoking habits, alcohol intake, and regular exercise.
Model 3: adjustment was made for the variables used in Model 2 and metabolic syndrome.

for coronary heart disease.

Discussion

Using data from a 14-year follow-up study of a general Japanese population, we found that surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels were clearly involved in the development of CVD after adjustment for confounding factors. In regard to CVD subtypes, the Matsuda index was a risk factor for the development of both stroke and coronary heart disease, while HOMA-IR levels were associated only with stroke incidence; however, these associations were attenuated after further adjustment for MetS status.

The strong associations between insulin resistance and cardiovascular risk factors, including metabolic abnormalities, are well known; however, studies on the influence of directly measured insulin sensitivity on the risk of CVD are limited: only a prospective cohort study in Sweden has revealed a significant inverse association between insulin sensitivity measured by an euglycemic insulin clamp and CVD risk[27, 28]. The methods used to directly measure insulin sensitivity are invasive, complex, and generally too expensive for clinical practice. Thus, some surrogate indices have been developed using insulin and/or glucose levels in the fasted state alone or in combination with insulin and glucose levels on the OGTT. Among these, HOMA-IR levels based on fasting measurements have been most commonly used as a surrogate marker of insulin resistance in epidemiological studies, but findings on the association between HOMA-IR and incident CVD have been inconsistent[15-22]. On the other hand, the Matsuda index derived from OGTT samples has been reported to show the strongest correla-

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Table 3. Age- and sex-adjusted incidences and hazard ratios and their 95% confidence intervals of stroke and coronary heart disease according to quintiles of the Matsuda index and HOMA-IR levels, 1988-2002

	Quintile level of insulin resistance					*p* for trend (across categories)	Continuous log scale*	*p* for trend (continuous)
	Q1	Q2	Q3	Q4	Q5			
Stroke								
Matsuda index								
No. of events	55	33	29	31	35			
Incidence per 1,000 person-years	9.8	6.2	5.7	5.7	6.1			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	0.62 (0.40 to 0.95)	0.53 (0.34 to 0.84)	0.59 (0.38 to 0.91)	0.63 (0.41 to 0.96)	0.03	0.76 (0.61 to 0.94)	0.01
HOMA-IR								
No. of events	33	34	33	36	47			
Incidence per 1,000 person-years	5.9	5.9	6.4	6.6	8.6			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.00 (0.62 to 1.62)	1.05 (0.65 to 1.70)	1.11 (0.69 to 1.79)	1.62 (1.03 to 2.52)	0.03	1.47 (1.14 to 1.88)	0.003
Coronary heart disease								
Matsuda index								
No. of events	25	26	14	17	16			
Incidence per 1,000 person-years	4.0	4.7	2.5	3.3	3.0			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.58 to 1.75)	0.52 (0.27 to 1.00)	0.69 (0.37 to 1.28)	0.59 (0.31 to 1.10)	0.04	0.71 (0.53 to 0.94)	0.02
HOMA-IR								
No. of events	18	21	19	17	23			
Incidence per 1,000 person-years	3.1	3.9	3.7	3.1	3.8			
Age- and sex-adjusted HR (95% CI)	1.00 (reference)	1.16 (0.62 to 2.17)	1.16 (0.62 to 2.17)	0.98 (0.50 to 1.89)	1.59 (0.86 to 2.96)	0.28	1.38 (0.98 to 1.95)	0.07

HR: hazard ratio; CI: confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance.
*HR for 1 standard deviation increase of the log Matsuda index or log HOMA-IR.

tions with directly measured insulin sensitivity among surrogate indices[12, 13, 23]; however, it is not known if the Matsuda index is associated with the development of incident CVD. To our knowledge, this is the first population-based prospective study reporting the association of the Matsuda index with incident CVD. Our results showed that the elevated Matsuda index levels were significantly and inversely associated with the risk of stroke and coronary heart disease, while HOMA-IR levels were a risk factor for the development of stroke, but not for coronary heart disease. These findings imply that the measurement of Matsuda index levels might be more valuable for identifying individuals at high risk of CVD than the measurement of HOMA-IR levels.

Although the precise reasons are not clear, one possible explanation for the finding that the Matsuda index was more strongly associated with the risk of coronary heart disease than with HOMA-IR levels is as follows. HOMA-IR values are derived from fasting plasma glucose and insulin concentrations[11]. Since hepatic glucose production is the primary determinant of fasting plasma glucose concentrations[29], and fasting plasma insulin concentrations are the primary regulator of hepatic glucose production[30], the parameters of fasting plasma glucose and serum insulin, such as HOMA-IR, may reflect mainly hepatic insulin resistance. This hypothesis has been confirmed in a study of subjects who received tritiated glucose to measure hepatic glucose production[31]. On the other hand, the Matsuda index calculated from the OGTT is likely to represent insulin resistance of the whole body, which consists mainly of a combination of hepatic and muscle insulin resistance[12]. Thus, a stronger association of

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the Matsuda index with coronary heart disease might be observed, since the Matsuda index more accurately reflects insulin resistance than HOMA-IR levels[32].

In our study, both surrogate indices of insulin resistance, the Matsuda index and HOMA-IR levels, were significantly involved in the development of CVD, but these associations were attenuated after further adjustment for MetS status. MetS has also been used as a surrogate measure of the insulin resistance phenotype and as a practical tool for identifying individuals at high risk of CVD. To date, prospective studies in several different communities have examined the associations between MetS and the risk of CVD, but there has been controversy over whether MetS captures all CVD risks associated with insulin resistance. In some epidemiological studies of Western populations, CVD risk significantly increased along with the elevations in surrogate indices of insulin resistance, even after adjusting for MetS and other cardiovascular risk factors[17-22]. On the other hand, in a Chinese population, insulin resistance indices including HOMA-IR levels were also associated with CVD risk, but these associations disappeared after adjustment for MetS[15]. These findings were in accordance with ours. Although the reason for this difference among the studies is unclear, the diversity of insulin resistance levels among races might explain it. Insulin resistance results in a spectrum of metabolic disturbances that includes inflammation[33], endothelial dysfunction[34], and hypercoagulability[35] in addition to the MetS status. For example, Asians have been shown to have much lower levels of systemic inflammation than other ethnic groups[36]. Thus, pathways other than MetS in the insulin resistance state might play more important roles in the development of CVD in Western populations.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, complete follow-up of subjects, sufficient number of cardiovascular events, and accuracy of the diagnosis of CVD, including stroke and coronary heart disease. However, two limitations of our study should be discussed. The primary limitation is that our findings were based on a single measurement of plasma glucose and insulin concentration, as was the case in other epidemiological studies. During follow-up, risk factor levels could have changed due to modifications of lifestyle or medication, and thus misclassification of insulin resistance was possible. However, this source of variability could not account for the associations observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Thus, the true association could be stronger than that observed in our study. Another limitation is that the values of the Matsuda index were not derived from 5 times of sampling, as reported in the initial publication of the index, but rather were calculated using samples from only 0 and 120 min; however, DeFronzo *et al.* reported that the Matsuda index calculated using 2-point samples, 0 and 120 min, had a strong correlation with the values determined by the original method[13]. If the calculation using 2-point samples were inferior to that of full-point samples, this would also weaken the association found in this study. Thus, we believe that such a bias does not invalidate the present findings.

In conclusion, the present analysis clearly showed that elevated insulin resistance indices estimated by the Matsuda index and HOMA-IR levels were significant risk factors for the incidence of CVD in a Japanese community. The measurement of these indices may help to identify individuals at high risk of CVD. Further studies are needed to investigate the associations between these indices and CVD.

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Disclosures

The authors report no conflicts of interest.

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