Mortality Risk Attributable to Atrial Fibrillation in Middle-Aged and Elderly People in the Japanese General Population

Nineteen-Year Follow-up in NIPPON DATA80

Masaki Ohsawa, MD; Akira Okayama, MD*; Tomonori Okamura, MD**;
Kazuyoshi Itai, PhD; Motoyuki Nakamura, MD†; Kozo Tanno, MD;
Karen Kato, MD; Yumi Yaegashi, MA; Toshiyuki Onoda, MD;
Kiyomi Sakata, MD; Hirotsugu Ueshima, MD**
for the NIPPON DATA80 Research Group

Background The extent to which atrial fibrillation (AF) contributes to mortality in the Japanese general population has not been clarified.

Methods and Results A randomly sampled general population from all over Japan (4,154 men, 5,329 women; age ≥ 30 years) was enrolled. Single electrocardiogram recordings were taken in the baseline survey. Stroke death, cardiovascular deaths and all-cause deaths during the subsequent 19 years were analyzed by the presence of AF at baseline. Cox's regression analysis was carried out to estimate the hazard ratios (HRs) of each cause of death attributable to AF after adjusting for other risk factors. Prevalence of AF was 0.64% in the study. The observed person-years were 162,980 among persons without AF and 699 among persons with AF. There were 1,919 deaths. Multivariate adjusted HRs for stroke death, cardiovascular death and all-cause death were 2.69, 2.76 and 1.88, respectively ($p < 0.05$). These HRs were 14.7, 9.63 and 4.00 among persons aged 64 years or younger ($p < 0.05$).

Conclusion AF affects stroke mortality, cardiovascular mortality and all-cause mortality in the Japanese general population. Careful attention should be paid to persons with AF in order to prevent future cardiovascular events. (Circ J 2007; 71: 814–819)

Key Words: Atrial fibrillation; Japanese; Mortality; Stroke

Atrial fibrillation (AF) is a strong risk factor for death, especially from stroke,¹ and ischemic stroke associated with AF frequently results in a serious outcome.² Thus, AF contributes not only to an increase in mortality risk but also to the burden of disability, which combined with the medical costs associated with AF has become a critical issue.³

The prevalence of AF among patients with ischemic stroke has been reported to be approximately 15%⁴ and has been increasing over the past 2 decades⁵ because of the aging population,⁶ and the age-specific prevalence of AF has been increasing in Western countries, especially among men.^{7,8}

Stroke incidence and mortality rates are higher than for coronary artery disease in Japanese people compared with Westerners.^{9–12} AF is an independent risk factor for stroke, resulting in an approximately 3- to 5-fold excess risk in the Japanese general population,¹³ and Japan has the most rapidly aging population in the world. The estimated number of Japanese adults with AF was 391,000 in 1980 and 729,000 in 2000, and in 2030 it is predicted to be 1,081,000.¹⁴ Consequently, there are expected increases in mortality, morbidity and the burden of disability associated with AF.

Therefore, determining the relative risk for mortality attributable to AF in Japan is an urgent task, but the extent to which AF contributes to mortality in the Japanese general population has not been clarified. In this study, we investigated the relative risks for stroke death, cardiovascular death and all-cause death attributable to AF in a representative Japanese population.

Methods

Subjects

The National Survey on Circulatory Disorders 1980 investigated household members aged 30 years or older ($n=13,771$) in 300 districts from all over Japan using the stratified random sampling method based on the national

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Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka, *Department of Preventive Cardiology, National Cardiovascular Center, Suita, **Department of Health Science, Shiga University of Medical Science, Otsu and †Department of Internal Medicine II, School of Medicine, Iwate Medical University, Morioka, Japan

Members of the NIPPON DATA80 Research Group are listed in Appendix 1.

Mailing address: Masaki Ohsawa, MD, Department of Hygiene and Preventive Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan. E-mail: masakio@iwate-med.ac.jp

Table 1 Baseline Characteristics of Participants With/Without AF in NIPPON DATA80

	Men		Women	
	Non-AF	AF	Non-AF	AF
<i>n</i>	4,127	27	5,296	33
Age (years)	50.6 (13.2)	63.4 (15.5)**	50.3 (13.1)	68.8 (10.3)**
BMI (kg/m ²)	22.5 (2.9)	23.0 (2.9)	22.9 (3.4)	23.4 (4.0)
SBP (mmHg)	138.4 (20.8)	141.3 (21.9)	133.9 (21.4)	145.2 (21.5)*
DBP (mmHg)	83.5 (12.3)	83.5 (10.7)	79.5 (11.8)	85.7 (16.5)
TC (mg/dl)	186.1 (32.8)	181.0 (36.8)	190.9 (34.1)	198.6 (32.6)
PG (mg/dl)	130.8 (38.1)	145.3 (49.2)	29.2 (33.7)	142.9 (38.5)
HT	2,066 (50.1%)	17 (63.0%)	2,193 (41.4%)	23 (69.7%)†
DM	285 (6.9%)	5 (18.5%)	216 (4.1%)	4 (12.1%)†
VHD	20 (0.5%)	3 (11.1%)‡	31 (0.6%)	6 (18.2%)‡
LVH	621 (15.0%)	4 (14.8%)	253 (4.8%)	5 (15.2%)
Smoker	2,612 (63.3%)	10 (37.0%)†	469 (8.9%)	0 (0.0%)
Drinker	1,978 (47.9%)	12 (44.4%)	150 (2.8%)	1 (3.0%)

Data are means (standard deviations) or numbers of persons (percentages).

P values were obtained by Student's *t*-test, chi-square test.

p*<0.05, *p*<0.01 by Student's *t*-test; †*p*<0.05, ‡*p*<0.01 by chi-square test.

AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; PG, plasma glucose; HT, hypertension; DM, diabetes mellitus; VHD, valvular heart disease; LVH, left ventricular hypertrophy; Smoker, current smoker; Drinker, regular drinker.

census in 1975. A total of 10,897 persons (response rate: 79.4%) participated in the survey.¹⁵

A study group was formed in 1994 to conduct a follow-up study of 10,546 participants in the Survey under the auspices of the Ministry of Health and Welfare (The National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged: NIPPON DATA80).^{16,17}

Initial Investigation

The initial investigations in the National Survey on Circulatory Disorders 1980 were conducted by public health centers and consisted of a questionnaire, measurements of blood pressure and anthropometric data, blood and urine tests, and a resting electrocardiogram (ECG). Public health nurses confirmed information on smoking and drinking habits, and present and past histories of myocardial infarction, stroke, valvular heart disease, hypertension (HT) and diabetes mellitus (DM) using questionnaires. Participants were asked to record whether they were current smokers, ex-smokers or non-smokers. Smokers were asked to note the number of cigarettes smoked per day. All participants were asked to record whether they were non-drinkers, ex-drinkers or current drinkers. Regular drinking was defined as a current drinker consuming alcohol every day or occasionally.

Participants were asked to avoid eating or exercise for 30 min before the measurements. Body weight was measured while the participants wore light clothing and no shoes, and the body mass index (BMI) was calculated. Single blood pressures and pulse rates were measured by a trained public health nurse in each public health center using a standard sphygmomanometer on the right arm of the seated subject after a 5-min rest.

Non-fasting blood samples were drawn and then centrifuged within 60 min of collection and stored at -70°C until analyses. Serum total cholesterol (TC) levels were analyzed in a sequential autoanalyzer (SMA12; Technicon, Tarrytown, USA) by the Liebermann-Burchard direct method at a laboratory (Osaka Medical Center for Health Science and Promotion). Casual blood glucose levels were determined in the same laboratory using the neocaprotine-

copper method. Therefore, determined glucose levels in this survey tended to be 20–30 mg/dl higher than those measured by the deoxidized method. The laboratory belonged to the Cholesterol Reference Method Laboratory Network (CRMLN), and the measurement precision and accuracy for serum cholesterol were certified in the lipid Standardization Program administered by the Centers for Disease Control and Prevention in the United States. Details have been published elsewhere.^{16,17}

HT was defined as systolic blood pressure (SBP) ≥140, diastolic blood pressure (DBP) ≥90 mmHg, use of anti-hypertensive agents or a combination of these. DM was defined as serum glucose level ≥200 mg/dl, a past history of diabetes, or both.

The ECG findings were independently evaluated by 2 trained doctors in each of 12 institutes (Department of Health Science, Jichi Medical School; Department of Public Health Science, Dokkyo Medical University; Fourth Department of Internal Medicine, Tokyo University; Tokyo Metropolitan Institute of Gerontology; National Institute of Public Health; Chiba University School of Nursing; Saku Central Hospital; Nagoya University Faculty of Medicine; Aichi Medical University; Department of Epidemiology, National Cardiovascular Center; Department of Preventive Cardiology, National Cardiovascular Center) according to the Minnesota Code. In cases of inconsistent judgments, the final judgments were made by the Approval Committee on Coding. AF was defined as 8-3 and left ventricular hypertrophy (LVH) was defined as 3-1 according to the Minnesota Code.¹⁵

Follow-up Surveys and Determination of Causes of Death

Follow-up surveys were performed in 1994 and 1999 to ascertain the status of each of the participants: 9,638 (91.4%) of the 10,546 original respondents were available. For longitudinal analyses, we excluded an additional 155 persons because they had a history of stroke (110 persons) or myocardial infarction (45 persons). Finally, the data from 9,483 subjects (4,154 men, 5,329 women) were used for the analyses.

National Vital Statistics were used to clarify the underlying causes of death. In accordance with Japan's Family

Table 2 Person-Years, Numbers of Deaths and Age-Adjusted Mortality Rate (per 100,000 Person-Years) and RR for Stroke Death, Cardiovascular Death and All-Cause Death by 19-Year Follow-up of NIPPON DATA80

	Non-AF	AF	RR (95%CI)
<i>Men and women</i>			
Total number	9,423	60	
Person-years	162,980	699	
Stroke death	308 (115)	10 (342)	2.51 (1.37–4.62)
Cardiovascular death	674 (249)	24 (1,342)	2.76 (1.87–4.08)
All-cause death	1,878 (713)	41 (2,173)	1.87 (1.38–2.62)
<i>Men</i>			
Total number	4,127	27	
Person-years	69,915	356	
Stroke death	163 (156)	2 (227)	0.99 (0.25–3.98)
Cardiovascular death	343 (328)	5 (366)	1.24 (0.51–2.99)
All-cause death	1,014 (983)	15 (1,429)	1.37 (0.82–2.27)
<i>Women</i>			
Total number	5,296	33	
Person-years	93,065	343	
Stroke death	145 (100)	8 (689)	5.43 (2.89–10.2)
Cardiovascular death	331 (217)	19 (5,711)	5.41 (3.59–8.15)
All-cause death	864 (587)	26 (6,398)	4.59 (2.19–9.77)

Data are number of deaths (age-adjusted mortality rates) and RR (95%CI).

Direct age adjustment was performed based on the Japan standard population of 1985.

Age-adjusted RR and 95%CI were estimated by the Mantel-Haenszel procedure.

RR, relative risks; CI, confidence intervals. Other abbreviation see in Table 1.

Registration Law, all death certificates issued by medical doctors are forwarded centrally to the Ministry of Health and Welfare via the public health centers in the area of residency. From 1980 to 1994 the underlying causes of death were coded according to the International Classification of Diseases (ICD) 9th Revision and from 1995 to 1999 were coded according to the ICD 10th Revision.

We confirmed deaths by computer matching of data from the Vital Statistics, using area, sex, dates of birth and death as key codes.¹⁶ Death from stroke was defined as ICD 9 code numbers 430–438 or ICD 10 code numbers I60–I69. Death from cardiovascular disease was defined as ICD 9 code numbers 390–459 or ICD 10 code numbers I00–I99.

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12-18, 2000).

Statistical Analysis

Student's t-test was used to test differences of several parameters between 2 groups. The chi-square test was used to compare the frequencies among the categories. Age-adjusted mortality rates were calculated by the direct method using the Japanese standard population of 1985. Age-adjusted relative risks and 95% confidence intervals were calculated using the Mantel-Haenszel procedure. Multivariate adjusted relative risks attributable to AF for all-cause mortality and cause-specific mortality were calculated using Cox's proportional hazard model with adjustments for age, SBP, BMI, serum TC levels, plasma glucose levels, presence of valvular heart disease or LVH on ECG, current smoking and regular drinking. All probability values were 2-tailed, and values less than 0.05 were considered to be statistically significant. The Statistical Package for Social Sciences (SPSS Japan Inc version 11.0 Tokyo, Japan) was used for the analyses.

Results

The prevalence of AF was 0.64% in this study (0.65% among men and 0.62% among women). Table 1 shows the baseline characteristics of participants with AF (AF group) and those without AF (non-AF group). Mean ages in the male and female AF groups (63.4 years and 68.8 years, respectively) were significantly higher than those in the non-AF groups (50.6 years and 50.3 years, respectively). In women, mean SBP and the percentages of participants with LVH or HT in the AF group were significantly higher than those in the non-AF group (SBP: 145.2 vs 133.9; LVH: 15.2% vs 4.8%; HT: 69.7% vs 41.4%). The proportion of subjects with valvular heart disease in the AF groups was significantly higher than in the non-AF group in both men and women (11.1% vs 0.5% in men; 18.2% vs 0.6% in women). Prevalence of current smokers in the male AF group was significantly lower than in the male non-AF group (37.0% vs 63.3%).

Table 2 shows the results of age-adjusted mortality rates based on the Japan standard population of 1985 (per 100,000 person-years) and relative risks for stroke death, cardiovascular death and all-cause death. The observed person-years were 163,679. A total of 1,919 deaths occurred during this period (1,878 in the non-AF group and 41 in the AF group). Age-adjusted mortality rates in both sexes were 713 in the non-AF group and 2,173 in the AF group. Age-adjusted relative risks in both sexes attributable to AF for stroke death, cardiovascular death and all-cause death were 2.51, 2.76 and 1.87, respectively.

Among men, age-adjusted mortality rates were 983 in the non-AF group, 1,429 in the AF group. Age-adjusted relative risks attributable to AF for stroke death, cardiovascular death and all-cause death were 0.99, 1.24 and 1.37, respectively (NS).

On the other hand, age-adjusted relative risks attributable to AF for stroke death, cardiovascular death and all-cause death among women were 5.43, 5.41 and 4.59, respectively (all p values <0.05).

Table 3 shows the results of Cox's regression analysis

Table 3 Multivariate Adjusted RR (95% CI) Attributable to AF by Cox's Regression Analysis, NIPPON DATA80, 19-Year Follow-up

	All participants RR (95%CI)	<65 years RR (95%CI)	≥65 years RR (95%CI)
Men and women	9,483 (60 [†])	7,922 (24 [†])	1,561 (36 [†])
Stroke death	2.69 (1.42–5.10)	14.7 (4.59–47.2)	1.93 (0.90–4.14)
CVD death	2.76 (1.81–4.20)	9.63 (4.30–21.6)	2.06 (1.26–3.39)
All-cause death	1.88 (1.37–2.58)	4.00 (2.21–7.25)	1.47 (1.01–2.13)
Men	4,154 (27 [†])	3,477 (12 [†])	677 (15 [†])
Stroke death	1.27 (0.31–5.18)	9.31 (1.24–70.1)	0.67 (0.09–4.85)
CVD death	1.38 (0.56–3.43)	3.44 (0.47–25.0)	1.09 (0.39–3.05)
All-cause death	1.39 (0.82–2.35)	2.83 (1.05–7.63)	1.10 (0.59–2.05)
Women	5,329 (33 [†])	4,445 (12 [†])	863 (21 [†])
Stroke death	3.75 (1.80–7.82)	19.0 (4.41–82.1)	2.83 (1.21–6.60)
CVD death	3.96 (2.46–6.37)	10.8 (3.80–30.9)	2.87 (1.62–5.08)
All-cause death	2.28 (1.53–3.38)	5.00 (2.16–11.6)	1.73 (1.07–2.78)

Data are multivariate adjusted RR (95%CI).

Multivariate adjusted RR (exponential) and 95%CI were estimated by Cox's regression analysis after adjusting for age, body mass index, systolic blood pressure, blood glucose level, total cholesterol level, history of valvular heart disease, existence of left ventricular hypertrophy, regular drinking and current smoking status.

[†]Number of participants with atrial fibrillation.

CVD, cardiovascular disease. Other abbreviation see in Tables 1,2.

Fig 1. Cox's regression survival curves for subjects with and without atrial fibrillation (AF) in the 19-year follow-up of NIPPON DATA80. Survival curves were determined by Cox's regression analysis stratified by existence of AF after adjusting for age, body mass index, systolic blood pressure, blood glucose level, total cholesterol level, history of valvular heart disease, existence of left ventricular hypertrophy, regular drinking, and current smoking status. Cox's regression curves for (A) subjects of all ages, (B) subjects aged 64 years or younger, (C) subjects aged 65 years or older.

with adjustments for other risk factors. At all ages, multivariate adjusted relative risks for both sexes attributable to AF for stroke death, cardiovascular death and all-cause death were 2.69, 2.76 and 1.88, respectively (all p values <0.05). These were 1.27, 1.38 and 1.39 among men (NS) and 3.75, 3.96 and 2.28 among women (all p values <0.05). Among persons aged 64 years or younger, relative risks for stroke death, cardiovascular death and all-cause death attributable to AF were higher than among participants of

all ages. Relative risks for stroke death were notably high in both men and women. Among persons aged 65 years or older, relative risks for death from each cause were lower than among participants of all ages.

Fig 1 shows the Cox's regression survival curves for subjects with or without AF. The survival curve in the AF group was below that in the non-AF group (Fig 1A). The difference between survival rates in the AF group and the non-AF group was more evident among persons aged 64

years or younger (Fig 1B), with the difference being somewhat vague among persons aged 65 years or older (Fig 1C).

Discussion

This study shows that AF contributes to stroke mortality, cardiovascular mortality and all-cause mortality in both sexes of the Japanese general population, especially the young generation (<65 years old). Although the prognosis of AF has been reported for Westerners, the extent to which AF contributes to mortality in the Japanese general population has not been fully elucidated. Some researchers tried to reveal the difference in Japanese subjects between the prognosis of patients with sustained AF and that of patients without AF after cardioversion; however, those studies did not determine whether AF contributes to mortality in Japanese people.^{18,19} Moreover, the difference in mortality attributable to AF in elderly and middle-aged people has not been addressed in a representative Japanese general population until now.

The Framingham Heart Study showed that AF contributed to an increase in stroke incidence, even in elderly people²⁰ and so careful attention is needed to interpret the result that suggested a low relative risk for mortality attributable to AF among elderly persons in the present study. Because the prevalence of AF has been reported to be less than 1% among Japanese persons aged less than 70 years,¹⁴ participants aged less than 65 years at the time of registration would be less likely to develop AF and elderly persons more likely to develop AF during the follow-up period. This would attenuate the relative risk for death from each cause attributable to AF among the elderly.

The present study also showed obvious sex difference in the risk for death from each cause attributable to AF. A significant interaction between AF and sex certainly exists. In the Framingham Heart Study, AF was no longer significantly associated with increased mortality among men after elimination of 30-day mortality, in contrast to the results for women.²¹ Other studies also showed that AF was a greater risk for mortality in women than in men.^{22–24} In a recent study the greater risk for ischemic stroke attributable to AF in women than in men was also confirmed, as well as the risk for mortality.²⁵ The reason why a sex difference exists in the relationship between AF and mortality and in the relationship between AF and ischemic stroke is unknown.

We estimated age-adjusted mortality rates using direct age adjustment based on the Japanese standard population of 1985. All-cause mortality in female participants with AF exceeded 6,000 per 100,000 person-years, which seems to be an overestimation of the actual status, although the relative risk determined by using the Mantel-Haenszel procedure was similar to the multivariate adjusted relative risk estimated by Cox's regression analysis. The small number of subjects with AF, especially in the female younger generation, may have distorted the results and caused overestimation of the mortality rate. Analysis of a small number of subjects with AF may also lack robustness, because a different result would be obtained if several cases had other outcomes.

Study Limitations

Since the original survey in 1980 was not designed for a prospective study, retrospective analyses of the data have several limitations. Risk factors were only observed once at baseline and changes in lifestyle or risk factor levels were

not considered. The risk attributable to risk factors may have been underestimated and confounding effects of risk factors may not have been fully adjusted. Assessment of relative risks attributable to AF for mortality analyzed by the presence of AF based on a single recording of ECG at baseline does not take into account subsequent development of AF and, therefore, tolerates underestimation of the relative risks. A follow-up study of the incident cases is preferable for estimating the actual risks for mortality attributable to diseases such as AF, which have an age-dependent prevalence. Paroxysmal AF can not be always detected by a single recording of ECG, so the lack of cases of paroxysmal AF results in underestimation of the relative risks for mortality attributable to AF. Lack of information on the history of anticoagulant therapy also seems to be a study limitation.

Persons with AF may have impaired cardiac function and therefore already have developed asymptomatic organic heart disease. Although we estimated the mortality risk after adjusting for other risk factors, including presence of valvular heart disease or LVH, this analytical procedure may not have been fully adjusted for the effect of heart failure on prognosis.

We estimated the relative risks for mortality attributable to AF using data from the Vital Statistics, but we did not estimate relative risks for cardiovascular morbidity attributable to AF. AF is an important predisposing factor for both heart failure²⁶ and hospital admission.²⁷ Whether AF affects cardiovascular morbidity among Japanese people remains to be determined.

Despite its several limitations, this study has some strong points. One is the representative Japanese population randomly selected from throughout Japan in the 1980s. Therefore, the total mortality rate and cause-specific mortality rate in this study should be considered as representing the actual status of Japanese adults living in the 1980s and may reflect results from the era before anticoagulant therapy became widespread. Another strong point of this study is the high follow-up rate despite a long follow-up period. There were 163,679 person-years and the mean follow-up period exceeded 17.

Conclusions

AF affects stroke mortality, cardiovascular mortality and all-cause mortality in the Japanese general population. Careful attention should therefore be paid to persons with AF in order to prevent future cardiovascular events.

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Appendix 1

The NIPPON DATA80 Research Group

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

Consultants: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo), Teruo Omae (National Cardiovascular Center, Suita), Kazuo Ueda (School of Health Science, Kyusyu University, Fukuoka), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya).

Research Members: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita), Kazunori Kodama, Fumiyoishi Kasagi (Radiation Effects Research Foundation, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu), Shigeyuki Saito (Internal Medicine II, Cardiology and Nephrology, Sapporo Medical University, Sapporo), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo), Yoshikazu Nakamura (Department of Public Health, Jichi Medical School, Minamikawachi), Hiroshi Horibe (Keisen Clinic, Akashi), Masumi Minowa (Department of Epidemiology, National Institute of Public Health, Wako).

Research Associate Members: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano and members of 300 public health centers in Japan, Minoru Iida (Kansai University of Welfare Science, Osaka), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako), Sohel R Choudhury (Department of Community Medicine, School of Medical Sciences University Sains Malaysia), Yutaka Kiyohara (Department of Medicine and Clinical Science, Kyusyu University, Fukuoka), Tsutomu Hashimoto (Wakayama Red Cross Blood Center, Wakayama), Atsushi Terao (Hikone Public Health Center, Hikone), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Saitama).