In previous studies performed in the community, abnormality of q, ST, and T waves, left bundle branch block (LBBB) and high amplitude R waves were categorized into major or minor abnormalities to assess the risk for CVD or coronary heart disease (CHD)[7,8], and only a few studies assessed q wave abnormality by the grade of MC respectively[1,5]. The assessment of q wave by grade is necessary to determine whether even a small q wave of an individual in the community without a history of cardiac event is a predictor for CVD. Moreover, a question remains whether the risk of q wave abnormality on CVD and its subtypes are independent of ST-T abnormality and high amplitude R waves.

To investigate the independent prognostic value of q wave for mortality due to CVD and its subtypes, we analyzed the data from a 19-year prospective study of 8,339 Japanese citizens free from CVD history at baseline.

Subjects and Methods

Study Participants

We used data from the National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980 (NIPPON DATA80). Details of the study have been described elsewhere[9-15]. In this survey, 300 areas were selected by stratified random sampling based on the national census in 1975. All residents aged 30 years or older in these areas were enrolled, and 10,546 people participated in the survey (response rate: 76.6%). Accordingly, these participants were considered to be reasonably representative of the Japanese population.

In this study, we enrolled 8,339 participants (3,694 male and 4,645 female) who were free from CVD history, atrial fibrillation (Minnesota Code (MC), 8-3), Wolff-Parkinson-White syndrome (MC, 6-4-1), and complete LBBB (MC, 7-1).

Case Identification

To determine causes of death after 19-year follow up, we used the National Vital Statistics database of Japan with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. The details of the disease classification in the present study were previously reported[16,17], and the names of the diseases according to the classification of ICD-9 and -10 are shown in **Table 1**. CVD (ICD 9 code: 393 to 459), stroke (ICD 9 code: 430 to 438), and heart disease (ICD 9 code: 393 to 398, 410 to 414, 415 to 429) were identified. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Table 1. Definition of cause of death (ICD 9 or ICD10† codes)

Causes of Death	ICD 9code (-1994)	ICD 10code (1995-)
Chronic rheumatic heart disease	393–398	I05–I09
Hypertensive disease	401–405	I10–I15
Ischemic heart disease	410–414	I20–I25
Diseases of pulmonary circulation	415–417	I26–I28
Other forms of heart disease	420–429	I30–I52
Cerebrovascular disease	430–438	I60–I69
Diseases of arteries, arterioles, and capillaries	440–448	I70–I79
Diseases of vein and lymphatics, and other diseases of circulatory system	451–459	I80–I99

†ICD 9 and ICD 10 means the 9th or 10th International Classification of Disease.

Baseline Examination

Information on the history of CVD, diabetes, medication for hypertension, and the habits of smoking and drinking were obtained from interviews by public health nurses. Blood pressure was measured after five minutes' rest by trained public health nurses at each public health center using a standard mercury sphygmomanometer. Serum total cholesterol levels were determined in a laboratory (Osaka Medical Center for Health Science and Promotion) under the quality control program of the Center for Disease Control and Prevention in the United States[18]. Casual glucose concentration was measured by the cupric-neocuproine method[19]. Original glucose values obtained by the cupric-neocuproine method were converted to those of the glucose-oxidase method, which is currently the standard, by use of an equation reported by the same laboratory[20].

A standard 12-lead ECG was recorded in the supine position. Each ECG was coded independently by two researchers according to the Minnesota Code, which was developed to document significant ECG pattern changes using objective comparison rules[21]. Codes in agreement were accepted, whereas inconsistent codes were decided by a panel of epidemiologists and cardiologists[16]. Participants were divided into three categories according to the q wave abnormality

grade as follows: 'q wave normal, mild q wave abnormality (MC, 1-3), and moderate or severe abnormality (MC, 1-1 and 1-2). Moderate or severe abnormalities were included in one group because the number of participants with moderate or severe abnormality was small.

Diagnosis of the presence of hypertension was systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current medication for hypertension[22]. Because most participants had not fasted when the baseline survey was conducted, we defined hyperglycemia as a casual glucose level ≥140 mg/dL or a history of diabetes mellitus[23]. Diagnosis of hyperlipidemia was defined as serum total cholesterol ≥200 mg/dL[24].

Statistical Analysis

To compare baseline characteristics between participants with and without q wave abnormality, we used analysis of variance or the chi-square test. Age was adjusted by analysis of covariance for continuous variables.

We used the Cox proportional hazards model to estimate hazard ratios (HR) of the presence of q wave abnormality for CVD mortality and its subtypes (stroke or heart disease). In this model, we included age at study entry, sex, body mass index (BMI), systolic blood pressure, serum total cholesterol, smoking (current or non-current), alcohol drinking (current or non-current), and the presence of hyperglycemia as confounding factors.

Further analysis was performed after exclusion for ST depression (MC, 4-1 to 4-4), T wave abnormality (MC, 5-1 to 5-4), and high amplitude R waves (MC, 3-1 to 3-3) from the source population[3, 25].

When we divided the participants according to the presence of hypertension, hyperglycemia, and hyperlipidemia, similar analysis was performed.

Results

Baseline Characteristics

The baseline characteristics of the participants with and without q wave abnormality for both sexes are shown in **Table 2**. The number of study participants with mild q wave abnormality comprised 62 (1.7%) men and 46 (1.0%) women. The number of study participants with moderate or severe q wave abnormality comprised 23 (0.6%) men (moderate: 14, severe: 9) and 13 (0.3%) women (moderate: 10, severe: 3). Age and the percentages of a history of diabetes and hyperglycemia were significantly higher in those with q wave abnormality for both sexes. Systolic blood pressure, the percentages of hypertension and medication for hypertension, and serum total cholesterol were higher in those with q wave abnormality in men. Casual glucose level was higher in those with q wave abnormality in women. Although age adjustment slightly attenuated these relations, most relations remained statistically significant.

Risk of Q Wave Abnormality for CVD Mortality and its Subtypes

There were 1578 deaths among participants, including 544 deaths due to CVD, 257 deaths due to all stroke and 257 deaths due to heart diseases.

Table 3 shows age-adjusted and multivariate-adjusted HRs for CVD death and cause-specific mortality. On the whole, age-adjusted and multivariate-adjusted HRs were almost the same as death from CVD and its subtypes. Among the participants with moderate or severe q wave abnormality, multivariate-adjusted HR for CVD deaths compared to those without q wave abnormality was 1.79 (95%CI: 0.87–3.65) in men and 1.69 (95%CI: 0.54–5.29) in women. Since there was no apparent interaction between sex for CVD mortality or its subtypes, we combined men and women. For overall participants, the HR of moderate or severe q wave abnormality was 1.75 (95%CI: 0.97–3.17) for death due to CVD, 0.48 (95%CI: 0.12–2.00) due to stroke, 2.97 (95%CI: 1.43–6.16) due to heart diseases.

The multivariate-adjusted HR of participants with mild q wave abnormality for CVD death compared to those without q wave abnormality was 1.27 (95%CI: 0.60–2.71) in men and 1.87 (95%CI: 0.92–3.80) in women. For overall participants, the HR of mild q wave abnormality was 1.50 (95%CI: 0.90–2.51) for death due to CVD, 1.05 (95%CI: 0.43–2.56) due to stroke, 1.95 (95%CI: 1.00–3.81) due to heart diseases.

For all-cause mortality, multivariate-adjusted HRs of moderate or severe q wave abnormality and mild q wave abnormality were 1.62 (95%CI: 1.05–2.50), and 1.28 (95%CI: 0.92–1.80) respectively.

After additionally excluding participants with complete A-V block (MC, 6-1), right bundle branch block (MC, 7-2), and persistent ventricular rhythm (MC, 8-2), the HRs and 95%CIs of moderate or severe q wave abnormality were 1.87 (95%CI: 1.03–3.38) for CVD mortality and 3.20 (95%CI: 1.55–6.63) for heart disease mortality. Similarly, the HRs of mild q wave abnormality for CVD and heart disease mortality were 1.47 (95%CI: 0.86–2.51) and 1.82 (95%CI: 0.90–3.70), respectively.

Table 2. Baseline characteristics of the participants according to q wave abnormality: NIPPON DATA80, 1980–1999, Japan

	q wave			*p*
	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)	
Men				
N	3,609	62	23	
Age (years)†	50±13	54±14	59±17	<0.001
Body mass index (kg/m²)†	22.5±2.8	22.9±3.1	22.1±3.1	0.500
History of diabetes mellitus (%)‡	4.0	9.7	0.0	<0.05
Systolic blood pressure (mmHg)†	138±20	141±21	150±28	<0.01
Diastolic blood pressure (mmHg)†	84±12	83±13	85±14	0.82
Hypertension (%)‡	48.9	61.3	69.6	<0.05
Medication for hypertension (%)‡	8.8	21.0	17.4	<0.01
Serum total cholesterol (mg/dL)†	187±33	194±33	203±62	<0.05
Hyperlipidemia (%)‡	31.4	40.3	39.1	0.24
Glucose (mg/dL)†	101±33	103±27	116±41	0.08
Hyperglycemia (%)‡	9.2	17.7	21.7	<0.05
Smoking (%)‡	63.4	66.1	69.6	0.76
Alcohol drinking (%)‡	75.3	74.2	56.5	0.12
Women				
N	4,586	46	13	
Age (years)†	50±13	57±14	65±13	<0.001
Body mass index (kg/m²)†	22.8±3.3	23±4.0	24.4±4.6	0.22
History of diabetes mellitus (%)‡	2.0	2.2	15.4	<0.01
Systolic blood pressure (mmHg)†	133±21	139±21	142±33	0.05
Diastolic blood pressure (mmHg)†	79±12	82±11	84±17	0.12
Hypertension (%)‡	39.6	50.0	53.8	0.21
Medication for hypertension (%)‡	37.3	45.7	53.8	0.24
Serum total cholesterol (mg/dL)†	190±34	199±34	202±50	0.09
Hyperlipidemia (%)‡	36.0	43.5	46.2	0.44
Glucose (mg/dL)†	99±28	116±78	128±58	<0.01
Hyperglycemia (%)‡	5.7	8.7	23.1	<0.05
Smoking (%)‡	8.7	15.2	0.0	0.16
Alcohol drinking (%)‡	20.3	8.7	30.8	0.10

Values after ± indicate standard deviation; †analysis of variance; ‡chi-square test.
(1-3-) or (1-1-)+(1-2-) indicates ECG codes classified by Minnesota Codes.
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current medication for hypertension.
Hyperlipidemia: total cholesterol ≥200 mg/dL.
Hyperglycemia: casual glucose ≥140 mg/dL and/or a history of diabetes mellitus.

Risk of Q Wave Abnormality After Exclusion of other ECG Abnormalities

As shown in **Table 4**, multivariate-adjusted HRs of moderate or severe q wave abnormality for mortality from CVD and heart diseases were significantly elevated even when participants with ST depression, T wave abnormality and high amplitude R waves were excluded. In similar analysis, multivariate-adjusted HRs of mild q wave abnormality were almost the same; however, the relationship was not statistically significant.

Risk of Q Wave Abnormality According to the Presence of Major CVD Risk Factors

Table 5 shows age-adjusted and multivariate-adjusted HRs for CVD death and heart disease mortality according to q wave abnormality when participants were divided by the presence of hypertension, hyperglycemia, and hyperlipidemia, respectively. For mortality from stroke, we did not perform further

Table 3. Risk of q wave abnormality for CVD mortality and its subtypes: NIPPON DATA80, 1980–1999, Japan

	CVD q wave			Stroke q wave			Heart Diseases q wave		
	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)
Men									
N	3,609	62	23	3,609	62	23	3,609	62	23
Person-years of follow-up	61,733	966	284	61,752	966	284	61,752	966	284
Case	263	7	9	136	1	2	115	5	6
Mortality (/1,000 person-years)	4.26	7.25	31.73	2.20	1.04	7.05	1.86	5.18	21.16
Age-adjusted hazard ratios	1.00	1.23 (0.58-2.61)	3.34 (1.71-6.53)*	1.00	0.33 (0.05-2.38)	1.32 (0.33-5.38)	1.00	2.06 (0.84-5.05)	5.51 (2.40-12.64)*
Multivariate-adjusted hazard ratios	1.00	1.27 (0.60-2.71)	1.79 (0.87-3.65)	1.00	0.36 (0.05-2.60)	0.74 (0.17-3.16)	1.00	2.02 (0.82-4.98)	2.93 (1.20-7.15)*
Women									
N	4,586	46	13	4,586	46	13	4,586	46	13
Person-years of follow-up	81,187	736	194	81,206	736	194	81,206	736	194
Case	254	8	3	114	4	0	125	4	2
Mortality (/1,000 person-years)	3.13	10.87	15.44	1.40	5.44	-	1.54	5.44	10.29
Age-adjusted hazard ratios	1.00	1.86 (0.92-3.77)	1.70 (0.54-5.30)	1.00	2.10 (0.77-5.71)	-	1.00	1.92 (0.71-5.21)	2.29 (0.57-9.28)
Multivariate-adjusted hazard ratios	1.00	1.87 (0.92-3.80)	1.69 (0.54-5.29)	1.00	2.06 (0.75-5.62)	-	1.00	2.02 (0.74-5.50)	2.38 (0.59-9.70)
Men and Women									
N	8,195	108	36	8,195	108	36	8,195	108	36
Person-years of follow-up	142,920	1,702	478	142,958	1,702	478	142,958	1,702	478
Case	517	15	12	250	5	2	240	9	8
Mortality (/1,000 person-years)	3.62	8.81	25.11	1.75	2.94	4.19	1.68	5.29	16.74
Age-adjusted hazard ratios	1.00	1.49 (0.89-2.50)	2.61 (1.47-4.65)*	1.00	1.00 (0.41-2.44)	0.86 (0.21-3.46)	1.00	1.99 (1.02-3.88)*	3.96 (1.95-8.03)*
Multivariate-adjusted hazard ratios	1.00	1.50 (0.90-2.51)	1.75 (0.97-3.17)	1.00	1.05 (0.43-2.56)	0.48 (0.12-2.00)	1.00	1.95 (1.00-3.81)*	2.97 (1.43-6.16)*

Values in parentheses indicate 95% confidence interval of hazard ratios. *indicates statisitically significant difference compared to the reference.
Age-adjusted hazard ratio: the grade of the q wave abnormality and age at study entry were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
Multivariate-adjusted hazard ratio: grade of q wave abnormality, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol drinking, and the presence of hyperglycemia (casual glucose ≥140 mg/dL and/or a history of diabetes mellitus) were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
(1-3-) or (1-1-)+(1-2-) indicates ECG codes classified by Minnesota Codes.

Table 4. Risk of q wave abnormality for CVD mortality and its subtypes when participants with ST depression, T wave abnormality, and high amplitude R waves were excluded: NIPPON DATA80, 1980-1999, Japan

	CVD q wave			Stroke q wave			Heart Diseases q wave		
	normal	mild (1-3-)	moderate or severe (1-1-) + (1-2-)	normal	mild (1-3-)	moderate or severe (1-1-) + (1-2-)	normal	mild (1-3-)	moderate or severe (1-1-) + (1-2-)
ST depression and T wave abnormality excluded									
N	7,389	86	19	7,389	86	19	7,389	86	19
Person-years of follow-up	130,072	1,425	258	130,072	1,425	258	130,072	1,425	258
Case	393	8	6	192	3	2	180	5	3
Mortality (/1,000 person-years)	3.02	5.62	23.24	1.48	2.11	7.75	1.38	3.51	11.62
Age-adjusted hazard ratios	1.00	1.13 (0.56-2.27)	8.12 (3.61-18.22)*	1.00	0.84 (0.27-2.63)	5.39 (1.33-21.78)*	1.00	1.58 (0.65-3.86)	8.98 (2.86-28.21)*
Multivariate-adjusted hazard ratios	1.00	1.20 (0.60-2.43)	5.33 (2.33-12.21)*	1.00	0.93 (0.30-2.91)	3.56 (0.86-14.80)	1.00	1.66 (0.68-4.05)	6.14 (1.91-19.78)*
ST depression, T wave abnormality and high amplitude R wave excluded									
N	6,350	73	14	6,350	73	14	6,350	73	14
Person-years of follow-up	112,095	1,191	197	112,095	1,191	197	112,095	1,191	197
Case	320	7	3	150	2	1	153	5	2
Mortality (/1,000 person-years)	2.85	5.88	15.23	1.34	1.68	5.08	1.36	4.20	10.15
Age-adjusted hazard ratios	1.00	1.15 (0.54-2.44)	7.11 (2.28-22.25)*	1.00	0.67 (0.17-2.71)	5.04 (0.70-36.20)	1.00	1.75 (0.72-4.30)	10.01 (2.47-40.56)*
Multivariate-adjusted hazard ratios	1.00	1.21 (0.57-2.57)	4.46 (1.39-14.32)*	1.00	0.72 (0.18-2.93)	2.89 (0.39-21.61)	1.00	1.82 (0.74-4.47)	6.83 (1.63-28.57)*

Values in parentheses indicate 95% confidence interval of hazard ratios. *indicates statisitically significant difference compared to the reference.
Age-adjusted hazard ratio: grade of q wave abnormality, sex, and age at study entry were entered in the model.
Multivariate-adjusted hazard ratio: grade of q wave abnormality, sex, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol drinking, and a hyperglycemia (casual glucose ≥140 mg/dL and/or a history of diabetes mellitus) were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
(1-3-) or (1-1-) +(1-2-) indicates ECG codes classified by Minnesota Codes (MS).
ST depression: MC 4-1 ~ 4-4. T wave abnormality: MC 5-1 ~ 5-4. high amplitude R waves: MC 3-1 ~ 3-4.

Table 5. Risk of q wave abnormality according to the presence of hypertension, hyperglycemia, and hyperlipidemia: NIPPON DATA80, 1980–1999, Japan

	CVD q wave			Heart Diseases q wave		
	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)
Hypertension (−) (N:4671)						
N	4,611	47	13	4,611	47	13
Person-years of follow-up	83,232	847	192	83,232	847	192
Case	123	4	3	69	3	2
Mortality (/1,000 person-years)	1.48	4.72	15.63	0.83	3.54	10.42
Age-adjusted hazard ratios	1.00	2.23 (0.82-6.04)	5.06 (1.59-16.14)*	1.00	2.97 (0.93-9.46)	5.58 (1.34-23.20)*
Multivariate-adjusted hazard ratios	1.00	1.76 (0.64-4.82)	4.99 (1.56-15.95)*	1.00	2.25 (0.70-7.28)	5.62 (1.34-23.50)*
Hypertension (+) (N:3668)						
N	3,584	61	23	3,584	61	23
Person-years of follow-up	59,688	855	286	59,688	855	286
Case	394	11	9	171	6	6
Mortality (/1,000 person-years)	6.60	12.86	31.48	2.86	7.02	20.99
Age-adjusted hazard ratios	1.00	1.35 (0.74-2.45)	2.17 (1.12-4.21)*	1.00	1.77 (0.78-4.01)	3.52 (1.55-7.98)*
Multivariate-adjusted hazard ratios	1.00	1.38 (0.75-2.52)	1.59 (0.80-3.17)	1.00	1.81(0.86-4.12)	2.74 (1.17-6.41)*
Hyperglycemia (−) (N:6283)						
N	6,194	69	20	6,194	69	20
Person-years of follow-up	109,575	1,186	292	109,575	1,186	292
Case	297	7	8	141	3	5
Mortality (/1,000 person-years)	2.71	5.90	27.40	1.29	2.53	17.12
Age-adjusted hazard ratios	1.00	1.72 (0.81-3.64)	3.37 (1.66-6.85)*	1.00	1.54 (0.49-4.83)	4.46 (1.81-10.99)*
Multivariate-adjusted hazard ratios	1.00	1.59 (0.75-3.37)	2.54 (1.19-5.39)*	1.00	1.45 (0.46-4.56)	3.43 (1.32-8.89)*
Hyperglycemia (+) (N:2056)						
N	2,001	39	16	2,001	39	16
Person-years of follow-up	33,345	516	186	33,345	516	186
Case	220	8	4	99	6	3
Mortality (/1,000 person-years)	6.60	15.50	21.51	2.97	11.63	16.13
Age-adjusted hazard ratios	1.00	1.22 (0.60-2.48)	1.68 (0.62-4.53)	1.00	2.32 (1.01-5.35)	3.02 (0.95-9.55)
Multivariate-adjusted hazard ratios	1.00	1.37 (0.67-2.82)	1.26 (0.46-3.46)	1.00	2.52 (1.09-5.86)*	2.41 (0.74-7.79)

analysis because there was no significant relationship between q wave abnormality and mortality from stroke after multivariate adjustment, as shown in **Table 3, 4**. Among most of these subgroups, HRs of moderate or severe q wave abnormality for mortality from CVD and heart disease were significantly elevated, and those of mild abnormality were elevated although the relationship did not reach statistical significance.

Discussion

Our study presented the risk of q wave abnormality by the grade of MC for CVD mortality and its subtypes among Japanese general population who were free from CVD history. Although the prevalence of moderate or severe q wave abnormality was low (0.4%), a significant increase of HRs was observed among participants with moderate or severe q wave abnormality for heart disease mortality. HRs of moderate or severe q wave abnormality for mortality from CVD and heart disease were also significantly elevated

	CVD q wave			Heart Diseases q wave		
	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)	normal	mild (1-3-)	moderate or severe (1-1-)+(1-2-)
Hyperlipidemia (−) (N:5494)						
N	5,410	63	21	5,410	63	21
Person-years of follow-up	94,128	1,021	282	94,128	1,021	282
Case	310	6	4	143	6	3
Mortality (/1,000 person-years)	3.29	5.88	14.19	1.52	5.88	10.64
Age-adjusted hazard ratios	1.00	0.92 (0.41-2.08)	1.97 (0.73-5.28)	1.00	2.07 (0.91-4.71)	3.28 (1.04-10.31)*
Multivariate-adjusted hazard ratios	1.00	1.06 (0.47-2.39)	1.29 (0.47-3.56)	1.00	2.19 (0.95-5.03)	2.62 (0.81-8.48)
Hyperlipidemia (+) (N:2845)						
N	2,785	45	15	2,785	45	15
Person-years of follow-up	48,792	681	196	48792	681	196
Case	207	9	8	97	3	5
Mortality (/1,000 person-years)	4.24	13.21	40.81	1.99	4.40	25.51
Age-adjusted hazard ratios	1.00	2.50 (1.28-4.88)*	3.19 (1.55-6.55)*	1.00	1.85 (0.59-5.84)	5.14 (2.05-12.89)*
Multivariate-adjusted hazard ratios	1.00	2.33 (1.19-4.56)*	2.35 (1.09-5.06)*	1.00	1.67 (0.53-5.28)	3.96 (1.51-10.39)*

Values in parentheses indicate 95% confidence interval of hazard ratios. *indicates statisitically significant increase compared to the reference.
Diagnosis of hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current medication for hypertension.
Diagnosis of hyperglycemia: casual glucose ≥140 mg/dL and/or a history of diabetes mellitus.
Diagnosis of hyperlipidemia: total cholesterol ≥200 mg/dL.
Age-adjusted hazard ratio: grade of q wave abnormality, sex, and age at study entry were entered in the model.
Multivariate-adjusted hazard ratio: grade of q wave abnormality, sex, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking habit, alcohol drinking, and the presence of hyperglycemia (casual glucose ≥140 mg/dL and/or a history of diabetes mellitus) were entered in the model.

when participants with ST, T wave abnormality and high amplitude R waves were excluded. Furthermore, when participants were divided into subgroups according to the presence of hypertension, hyperglycemia, and hyperlipidemia, HRs of moderate or severe q wave abnormality for mortality due to CVD and heart disease were also consistently elevated. Q wave abnormality was not associated with the risk of stroke mortality.

Previous studies have reported that major q wave abnormality (MC, 1-1) predicts all-cause and CVD mortality[2]; however, few studies have reported the risk of q wave abnormality by grade. Rose *et al.* reported that age-adjusted coronary heart disease mortality increased according to the grade of q wave in their five-year follow-up study[5], but they did not assess multivariate-adjusted HR of q wave abnormality.

Our study is the first report to present the risk of q wave by grade, independent from ECG abnormalities such as ST-T abnormality and high amplitude R waves and other CVD risk factors. A previous study reported that even minor ST-T abnormalities were associated with increased long-term risk of mortality or incidence due to stroke, CHD, and CVD[3, 26]. As we reported previously, high left R waves are associated with CVD mortality[25]. Accordingly, we excluded participants with ST-T wave abnormality and high amplitude R waves to assess the risk of q wave abnormality independent of other ECG abnormalities. Participants with moderate or severe q wave abnormality showed a significant increase of HR for CVD and heart disease even when ST-T wave abnormality and high amplitude R waves were excluded. People in the community with MC 1-1 and MC 1-2 are considered to be a high-risk group for death due to CVD or heart diseases regardless of ST-T change and high R waves, and should be studied to determine the specific etiology.

The risk of q wave abnormality was assessed according to the presence of three major CVD risk factors. Essentially, moderate or severe q wave abnor-

malities were associated with the risk of mortality due to CVD or heart diseases regardless of the presence of three major CVD risk factors. The vast majority of abnormal q waves are due to myocardial infarction, but a significant number is due to other causes, such as cardiomyopathy, chronic obstructive lung disease[4] and in patients with nephropathy[27]. ECG screening is a simple, inexpensive and widely available test compared to the various specific tests to screen people with those diseases in communities. Moreover, ECG is able to increase the predictive value to identify individuals at high-risk for CVD and heart disease mortality in addition to classic CVD risk factors.

The participants in this study were from a nationwide cohort study and were selected by a stratified random sampling method. Accordingly, the results of the present study would apply to the general Japanese population. Furthermore, the participants in our study were observed for 19 years, which is a long follow-up period and increases the value of our study substantially.

One of the limitations of our study is that the number of participants with q wave abnormality was small. Accordingly, we could not divide the participants into three q wave categories (MC, 1-1, 1-2, and 1-3) and assess the risk of q wave abnormality according to the subtypes of stroke and heart diseases. We also could not investigate the prognostic value of mild q wave abnormality sufficiently in this study. Secondly, MC was coded by visual reading in our study. Computerized ECG analysis is reportedly superior to visual reading for better reliability[28]; however, ECG reading in this study was performed under the best standardized quality control in 1980. Third, we could not assess the risk of q wave abnormalities according to the lead in which q waves were present to evaluate their clinical meaning because there were no data concerning the lead in the baseline survey.

In conclusion, moderate or severe q wave abnormality is associated with an elevated risk of mortality from CVD or heart diseases independent of other ECG changes among participants with no CVD history. Although the prevalence of q wave abnormality is not high among participants without a history of CVD in communities, q wave abnormality is a prominent and important predictor of CVD and heart disease mortality.

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Appendix

List of the NIPPON DATA80 Research Group

NIPPON DATA80: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged"

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Dietary Habits in Middle Age and Future Changes in Activities of Daily Living – NIPPON DATA80

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Key Words
Meat · Fish · Egg · Activities of daily living · Mortality · Cohort study

Abstract
Background: Almost no studies have investigated the relationship between food intake measured at middle age and future disability. ***Objective:*** To examine the association of meat, fish and egg intake with risk of subsequent mortality and/or future decline in activities of daily living (ADL) among the elderly. ***Methods:*** The cohort consisted of 2,316 Japanese individuals aged 47–60 at the baseline who were randomly selected throughout Japan and followed up for 19 years from 1980. ***Results:*** Those who ate meat at least once every 2 days were younger, there were more men, daily drinkers, professional workers and urban residents compared to those who ate meat less than once every 2 days. Over 19 years of follow-up, 75 participants became dependent due to impaired ADL. A higher intake of meat was associated with a statistically significant decrease in impaired ADL occurrence (odds ratio = 0.61, 95% confidence intervals 0.38–0.99, p = 0.04). Fish and egg intake were not associated with any difference in impaired ADL occurrence. None of the 3 foods were associated with any changes in mortality. ***Conclusion:*** A higher intake of meat may prevent impaired ADL occurrence, although this was not associated with a lower mortality.

Introduction

The elderly population is increasing in developed countries and improvements in health care have led to an increase in life expectancy. In 2005, Japan had the highest proportion of those aged 65 and older in the world [1]. Although both life expectancy and healthy life expectan-

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cy in Japan are among the longest in the world, the difference in the 2 expectancies is about 7 years [2], indicating people in Japan suffer from the reduction in the activity of daily living (ADL) for a long time before death. Among many environmental factors that may influence ADL in the elderly, the role played by food is important. However, almost no studies have investigated the relationship between food intake measured at middle age and future disability.

The objective of this prospective study was to clarify the relationship between food intake and impaired ADL surveyed at 19 years after a baseline survey among a general Japanese population aged 47–59 years. Previous studies on food intake as well as all-cause and cause-specific mortality led us to hypothesize that food that is known to promote atherosclerosis, such as eggs or meat, would have a negative influence on future ADL, and food that is known to prevent atherosclerosis, such as fish, would have a beneficial influence on future ADL [3–9].

Methods

Subjects and Follow-Up

The dataset of the cohort study of the National Survey on Circulatory Disorders comprising the National Integrated Project for Prospective Observation of Non-Communicable Disease and Its Trends in the Aged (NIPPON DATA) was used. A baseline survey was performed in 1980 (NIPPON DATA80) [10–13]. We analyzed the 19-year follow-up data from the NIPPON DATA80 in this study.

The study population comprised 3,227 participants (1,413 men and 1,814 women, aged 47–59) from 300 randomly selected districts in 1980. The baseline surveys were carried out at local public health centers and all participants had to be capable of reaching the examination center without assistance. The participation rate was about 77%. We excluded 286 participants who had a history of coronary heart disease (CHD) or stroke (n = 39), had missing information in the baseline survey (n = 54) or were lost to follow-up (n = 193) due to an incomplete residential address at the baseline. Thus, 2,941 were eligible for follow-up. Among them, 427 died and information about ADL was gathered from 2,514 survivors by physicians and public health nurses at public health centers in 1999. Consequently, 75% (1,889) of the survivors completed the information. No potential differences between responders and nonresponders in terms of baseline age, gender, BP values, use of antihypertensive medication, body mass index (BMI), smoking status or serum albumin concentration were observed. Participants were asked about 5 basic ADL items (feeding, dressing, bathing, toileting and transfer: walking indoors) modified from Katz et al. [14], and whether each of these could be accomplished without help, with partial help or with full help. This survey was conducted through telephone interviews (10.5%), face-to-face interviews at home (80.0%) and other methods (9.5%). In this study, we basically analyzed participants who completed the ADL information alone (n = 1,889) and together with participants who died before the ADL survey (n = 2,316). The Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000) approved the study.

Biochemical and Baseline Examinations

Baseline BP was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg or when a participant was receiving medication for high blood pressure. BMI was calculated as weight (in kilograms) divided by squared height (in meters).

A lifestyle survey was also carried out using a self-administered questionnaire which included the daily consumption of meat, eggs and fish. Egg consumption was coded as ≥2 eggs per day, about 1 egg per day, about 1 egg every 2 days, about 1–2 eggs per week and <1 egg per week. Fish and meat intake were coded separately as ≥2 times per day, about once per day, about once every 2 days, about 1–2 times per week and less than once per week. Reported information was confirmed by public health nurses through interviews with the study participants regarding food consumption, smoking, drinking habit, and present and past medical histories.

Nonfasting blood samples were drawn and centrifuged within 60 min of collection and stored at –70°C until analyses. Serum total cholesterol, albumin, uric acid and creatinine were analyzed in a sequential auto-analyzer (SMA12/60; Technicon, Tarrytown, N.Y., USA) at a single laboratory (Osaka Medical Center for Health Science and Promotion). Serum concentrations of glucose were measured by the cupric-neocuproine method [15]. Diabetes was determined by medical history or defined as a serum glucose concentration ≥200 mg/dl.

Statistical Analysis

SAS version 9.1 for Windows (SAS Institute, Cary, N.C., USA) was used. Because the number of participants was not large, participants were classified into the 2 groups according to meat consumption as less than once every 2 days and at least once every 2 days, as well as fish and egg consumption as less than once per day and at least once per day around the median of these consumption categories. The χ^2 test was used to compare dichotomous variables and Student's t test was used to compare means between the 2 groups according to food consumption. The relationship between food intake categories and impaired ADL or impaired ADL together with all-cause mortality was calculated using multiple adjusted logistic regression models, taking a lower food consumption group as a reference. Age- and sex-adjusted as well as multivariate-adjusted odds ratios (OR) were calculated. For multivariate analyses, we adjusted for age, BMI and cigarette smoking (never and former smokers, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day and current smokers ≥41 cigarettes/day), alcohol drinking (never, past, nondaily and daily), hypertension and diabetes (model 1). Model 1 was also adjusted for serum albumin and total cholesterol concentrations (model 2). Model 2 was further adjusted for job type (professional or not) and urban residence (yes or no; model 3). Interactions between sex and the effect of food intake on impaired ADL or impaired ADL together with all-cause mortality were examined.

Table 1. Baseline characteristics and outcomes of 1,042 male and 1,274 female participants in the meat, fish and egg intake groups, NIPPON DATA80, 1980–1999

	Meat		p	Fish		p	Egg		p
	<1/2 days	≥1/2 days		<1/day	≥1/day		<1/day	≥1/day	
Men									
Number	375	667		555	487		599	443	
Age, years	53.2 ± 3.6	52.9 ± 3.5	0.27	52.9 ± 3.5	53.1 ± 3.5	0.52	53.1 ± 3.5	52.9 ± 3.5	0.51
BMI	22.4 ± 2.9	22.7 ± 2.7	0.15	22.5 ± 2.9	22.7 ± 2.7	0.14	22.7 ± 2.8	22.4 ± 2.9	0.048
Smoking, %	69.9	65.4	0.13	68.5	65.3	0.28	66.9	67.0	0.97
Daily drinking, %	49.1	52.5	0.29	47.9	55.0	0.02	51.6	50.8	0.80
Hypertension, %	58.1	54.9	0.31	52.6	60.0	0.02	57.3	54.4	0.36
Diabetes, %	7.7	10.2	0.19	10.6	7.8	0.12	9.9	8.6	0.48
Albumin, mg/dl	4.4 ± 0.3	4.4 ± 0.2	0.48	4.4 ± 0.3	4.4 ± 0.2	0.47	4.4 ± 0.3	4.4 ± 0.3	0.95
TCH, mg/dl	186 ± 34	188 ± 34	0.49	188 ± 35	187 ± 33	0.53	189 ± 35	185 ± 32	0.10
Professional work, %	33.7	40.7	0.03	41.1	34.9	0.04	38.7	37.5	0.69
Urban residence, %	25.3	31.0	0.05	31.2	26.5	0.10	30.4	27.1	0.25
Incidence, %									
Death	25.1	25.5	0.88	25.2	25.5	0.93	25.2	25.5	0.91
Stroke	9.8	7.4	0.26	8.6	7.9	0.72	9.1	7.1	0.30
CHD	5.1	5.0	0.94	5.2	4.8	0.81	6.0	3.7	0.16
Leg fracture	1.5	2.1	0.54	1.7	2.0	0.80	2.3	1.2	0.29
Women									
Number	573	701		750	524		877	397	
Age, years	53.6 ± 3.8	53.1 ± 3.8	0.02	53.1 ± 3.7	53.5 ± 3.9	0.10	53.3 ± 3.8	53.3 ± 3.7	0.997
BMI	23.3 ± 3.6	23.3 ± 3.2	0.98	23.4 ± 3.4	23.2 ± 3.4	0.39	23.4 ± 3.4	23.2 ± 3.3	0.39
Smoking, %	9.8	6.0	0.01	8.8	6.1	0.08	7.8	7.6	0.90
Daily drinking, %	1.8	2.0	0.74	2.3	1.3	0.23	1.6	2.5	0.26
Hypertension, %	51.3	46.9	0.12	49.2	48.5	0.80	50.1	46.4	0.22
Diabetes, %	3.8	4.0	0.89	3.3	4.8	0.19	3.8	4.3	0.66
Albumin, mg/dl	4.4 ± 0.2	4.4 ± 0.2	0.67	4.4 ± 0.2	4.4 ± 0.2	0.80	4.4 ± 0.2	4.4 ± 0.2	0.71
TCH, mg/dl	196 ± 35	199 ± 32	0.20	197 ± 33	198 ± 33	0.73	196 ± 32	201 ± 35	0.01
Professional work, %	15.4	22.0	0.003	17.6	21.0	0.13	18.5	20.2	0.47
Urban residence, %	28.5	32.0	0.18	32.0	28.1	0.13	29.8	31.7	0.48
Incidence, %									
Death	13.8	12.0	0.34	12.3	13.6	0.50	11.9	14.9	0.14
Stroke	5.0	3.6	0.28	3.2	5.6	0.05	4.7	3.0	0.20
CHD	2.9	3.0	0.94	2.8	3.2	0.72	2.9	3.0	0.90
Leg fracture	0.8	1.8	0.16	1.7	0.9	0.26	0.9	2.4	0.05

Data are shown as percentages or means ± SD. TCH = Total cholesterol concentration.

Results

The baseline characteristics and outcomes of 1,413 male and 1,814 female study participants in each meat, fish and egg consumption category are shown in table 1. In male participants who ate meat at least once every 2 days, there were more professional workers compared to those who ate meat less than once every 2 days. In men who ate fish at least once per day, there were more daily drinkers and hypertension cases as well as fewer professional workers than in men who ate fish less than once per day. In men who ate eggs at least once per day, the mean BMI was smaller than in those who ate eggs less than once per day. In women who ate meat at least once every 2 days, there were more younger participants, more smokers and more professional workers compared to those who ate meat less than once every 2 days. In women who ate eggs at least once per day, the mean total cholesterol concentration was higher than in those who ate eggs less than once per day. No differences in crude out-

Table 2. Associations of impaired ADL or death and food intake in 2,316 participants in the meat, fish and egg intake groups, NIPPON DATA80, 1980–1999

	Meat		p	Fish		p	Egg		p
	<1/2 days	≥1/2 days		<1/day	≥1/day		<1/day	≥1/day	
Participants	948	1,368		1,305	1,011		1,476	840	
Cases with impaired ADL or death	214	288		271	231		306	196	
Odds ratio									
Age- and sex-adjusted	1	0.89 (0.72–1.09)	0.25	1	1.06 (0.86–1.30)	0.58	1	1.09 (0.88–1.34)	0.44
Model 1	1	0.91 (0.74–1.12)	0.35	1	1.09 (0.89–1.34)	0.40	1	1.10 (0.89–1.36)	0.40
Model 2	1	0.91 (0.74–1.12)	0.38	1	1.10 (0.89–1.35)	0.39	1	1.10 (0.89–1.36)	0.39
Model 3	1	0.91 (0.73–1.12)	0.36	1	1.08 (0.87–1.33)	0.50	1	1.09 (0.88–1.35)	0.43

During 19 years of follow-up, 502 participants either died or became dependent due to impaired ADL. Numbers of participants at risk and impaired ADL or death cases, age- and sex-adjusted as well as multivariate-adjusted (model 1–3) odds ratios (with 95% confidence intervals in parentheses) for death or impaired ADL are shown. Model 1 included age, sex, smoking (never and former smokers, current smokers <20, 20–40, and ≥41 cigarettes/day), alcohol drinking (never, past, nondaily, and daily), hypertension, diabetes and BMI. Model 2 included model 1 variables plus serum albumin and total cholesterol concentration. Model 3 included model 2 variables plus job type (professional or not) and urban residence.

Table 3. Associations of death and food intake in 2,316 participants in the meat, fish and egg intake groups, NIPPON DATA80, 1980–1999

	Meat		p	Fish		p	Egg		p
	<1/2 days	≥1/2 days		<1/day	≥1/day		<1/day	≥1/day	
Participants	948	1,368		1,305	1,011		1,476	840	
Cases with death	173	254		232	195		255	172	
Odds ratio									
Age- and sex-adjusted	1	0.98 (0.79–1.22)	0.87	1	1.03 (0.83–1.28)	0.79	1	1.14 (0.91–1.42)	0.26
Model 1	1	1.00 (0.80–1.25)	0.98	1	1.07 (0.86–1.33)	0.57	1	1.14 (0.91–1.43)	0.26
Model 2	1	1.00 (0.80–1.26)	0.96	1	1.07 (0.86–1.33)	0.55	1	1.14 (0.91–1.43)	0.26
Model 3	1	1.00 (0.80–1.25)	0.99	1	1.06 (0.84–1.32)	0.65	1	1.13 (0.90–1.42)	0.29

During 19 years of follow-up, 427 participants died. The numbers of participants at risk and death cases, age- and sex-adjusted as well as multivariate-adjusted (model 1–3) odds ratios (with 95% confidence intervals in parentheses) for death are shown. Model 1 included age, sex, smoking (never and former smokers, current smokers <20, 20–40, and ≥41 cigarettes/day), alcohol drinking (never, past, nondaily and daily), hypertension, diabetes and BMI. Model 2 included model 1 variables plus serum albumin and total cholesterol concentration. Model 3 included model 2 variables plus job type (professional or not) and urban residence.

comes (incidence of death, stroke, CHD or leg fracture) were noted between the 2 groups in each of the 3 food intake categories. The baseline characteristics and outcomes of the 1,889 surviving participants were basically as in table 1.

During 19 years of follow-up, 502 participants either died or became dependent due to impaired ADL. Table 2 shows the numbers of participants at risk and impaired ADL or death cases, OR and 95% confidence intervals by age- and sex-adjusted as well as multivariate-adjusted OR (model 1–3) for death or impaired ADL. Differences in any food intake were not associated with differences in composite outcome of impaired ADL and death. There was no interaction between sex and the effect of food intake on impaired ADL together with all-cause mortality.

During 19 years of follow-up, 427 participants died. Table 3 shows the numbers of participants at risk and death cases, OR and 95% confidence intervals by age- and sex-adjusted as well as multivariate-adjusted OR (model 1–3) for death. Differences in any food intake were not associated with differences in mortality. There were no interactions between sex and the effect of food intake on all-cause mortality.

Table 4. Associations of impaired ADL and food intake in 1,889 surviving participants in the meat, fish and egg intake groups, NIPPON DATA80, 1980–1999

	Meat		p	Fish		p	Egg		p
	<1/2 days	≥1/2 days		<1/day	≥1/day		<1/day	≥1/d	
Participants	775	1,114		1,073	816		1,221	668	
Cases with impaired ADL	41	34		39	36		51	24	
Odds ratio									
Age- and sex-adjusted	1	0.58 (0.36–0.93)	0.02	1	1.19 (0.75–1.89)	0.47	1	0.86 (0.52–1.42)	0.55
Model 1	1	0.61 (0.38–0.97)	0.04	1	1.25 (0.78–2.01)	0.35	1	0.89 (0.54–1.48)	0.66
Model 2	1	0.62 (0.38–0.99)	0.05	1	1.23 (0.77–1.97)	0.39	1	0.90 (0.54–1.49)	0.67
Model 3	1	0.61 (0.38–0.99)	0.04	1	1.25 (0.76–1.95)	0.42	1	0.90 (0.54–1.49)	0.68

During 19 years of follow-up, 75 participants became dependent due to impaired ADL. The numbers of participants at risk and cases with impaired ADL, age- and sex-adjusted as well as multivariate-adjusted (model 1–3) odds ratios (with 95% confidence intervals in parentheses) for impaired ADL are shown. Model 1 included age, sex, smoking (never and former smokers, current smokers <20, 20–40, ≥41 cigarettes/day), alcohol drinking (never, past, nondaily and daily), hypertension, diabetes and BMI. Model 2 included model 1 variables plus serum albumin and total cholesterol concentration. Model 3 included model 2 variables plus job type (professional or not) and urban residence. In the meat intake analysis, the covariates in model 3 that had significant contributions to the outcome were age (p = 0.0004), BMI (p = 0.009) and urban residence (p = 0.02).

During 19 years of follow-up, 75 participants became dependent due to impaired ADL. Associations of impaired ADL and food intake in the 1,889 surviving participants are shown in table 4. A higher intake of meat was associated with a statistically significant decrease in the occurrence of impaired ADL in all 4 models. The other covariates in model 3 that had significant contributions to the outcome were age (p = 0.0004), BMI (p = 0.009) and urban residence (p = 0.02). There were no interactions between sex and the effect of food intake on impaired ADL.

Discussion

We found that a higher intake of meat during middle age was associated with a statistically significant reduction in future occurrence of impaired ADL, although it was not associated with changes in composite outcome of either death or dependence due to impaired ADL. Intake of fish and eggs was not associated with the composite outcome or with impaired ADL outcome. These results were unexpected, since eggs and meat are believed to promote atherosclerosis, and fish is known to prevent atherosclerosis. Recently, it has been shown that low to normal serum albumin and total cholesterol concentrations were associated with impaired ADL using this cohort data as well as those of other studies [13, 16, 17]. However, in the present study, these concentrations were not different between the 2 groups in all 3 food intake categories.

Meat products are rich in saturated fatty acids that are thought to be atherogenic. In fact, a high intake of meat is classed as a component presumed to be detrimental to health in studies on dietary patterns, including in a Mediterranean diet [18, 19]. Surprisingly, however, there has been no prospective study to demonstrate the detrimental effects of meat intake on cardiovascular outcome. Actually, a higher meat intake had a neutral association with all-cause mortality, while a higher intake of fruits and nuts was inversely associated with all-cause mortality in a Mediterranean diet study [18]. There have been some cross-sectional studies related to associations between intake of meat and cardiovascular disease risk factors. Sadakane et al. [20] identified 3 dietary patterns from a food frequency questionnaire by factor analyses. In men, the meat pattern was associated with higher total as well as high- and low-density lipoprotein cholesterol; in women, it was associated with higher total and high-density lipoprotein cholesterol [20]. Two small studies found no effect of animal protein intake on blood pressure [21, 22]. The large-scaled INTERMAP study showed dietary animal protein intake was not associated with a higher blood pressure after adjustment for height and weight, while vegetable protein was inversely related to blood pressure [23]. To date, cross-sectional studies have failed to demonstrate any detrimental effect of meat intake or animal protein on cardiovascular disease risk factors. Interestingly, several longitudinal studies have suggested a beneficial effect of meat intake on cardiovascular outcomes. Using the Hiroshima/Nagasaki Life Span Study cohort data, Sauvaget et al. [24, 25] showed intake of animal

products had protective effects against intracerebral hemorrhage and cerebral infarction. Analyzing the Rotterdam Study data, Geleijnse et al. [26] showed CHD mortality was reduced in higher tertiles of dietary menaquinone compared to the lower tertile. Since major sources of menaquinone are meat, eggs and cheese, generally considered to be unhealthy diet, the authors thought it unlikely that the observed reduction in CHD risk was due to confounding factors. A cross-sectional study in the elderly showed protein intake, especially from animal sources, was associated with a better preservation of muscle mass [27], and a follow-up study in older, community-dwelling adults demonstrated dietary protein intake was inversely associated with a 3-year lean mass loss [28]. Recently, the intake of animal protein and fat in Japan has increased significantly; however, the current mean consumption of these nutrients in Japan is still low compared with Western countries [29–32]. It is possible that even if a very high meat intake is associated with negative outcomes, a higher intake in a lower range may have beneficial effects. Thus, there appears to be enough evidence to support our present finding that a higher intake of meat may prevent the occurrence of impaired ADL, although it was not associated with lower mortality.

Another factor that may relate to the association between meat intake and outcomes is the socioeconomic status (SES). Lower SES is associated with all-cause, as well as cardiovascular, morbidity and mortality [33–36]. In the present study, a higher intake of meat was associated with a higher prevalence of professional work and urban residence, both markers of a higher SES. Urban residence was a significant contributor to a lower risk for impaired ADL in the logistic analysis model. After adjustment for urban residence, however, a higher intake of meat remained statistically significant.

There are some limitations to this study. We did not assess the baseline ADL condition, therefore, we are not sure that all impaired ADL cases were new incidents during the follow-up period. However, because the participants came on foot to baseline examinations at local public health centers and we excluded participants who had a history of stroke, we considered the effect of any lack of information on our results to be negligible. Second, we do not have information on SES other than professional work and urban residence. Third, the time span between baseline data collection and ADL data collection is long; diets might have changed during this time in Japan. However, according to the National Health and Nutritional Survey in Japan, the average daily intakes of meat, fish and egg by Japanese aged 50–59 in 1986 were 58.7, 102.3 and 40.5 g, respectively; those by Japanese aged 60–69 in 1996 were 51.4, 106.7 and 36.4 g, respectively [37]. That is, there might not have been significant changes in diets in Japan during the study period.

In conclusion, a higher intake of meat may prevent impaired ADL occurrence, although it was not associated with a lower mortality.

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Alcohol intake and 19-year mortality in diabetic men: NIPPON DATA80

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Abstract

Although moderate alcohol intake in diabetic Caucasians is associated with a reduction in coronary heart disease mortality, no study in Japanese with diabetes has examined the association between alcohol intake and mortality outcomes. We analyzed the relationship between alcohol intake and all-cause and cause-specific mortality using the database from NIPPON DATA80. At the baseline in 1980, data on history, lifestyle, and physical examinations were collected on study participants aged 30 years and older from randomly selected areas in Japan. After excluding participants with comorbidities, we followed 4,018 male participants (3,614 nondiabetics, 195 with impaired glucose tolerance and 209 diabetic) for 19 years. During the 19 years of follow-up, there were 990 deaths; 328 were from cardiovascular disease and 157 from all-heart diseases. With the never-drinking category serving as a reference, the Cox multivariate-adjusted hazard ratios for non-daily and daily drinkers for cardiovascular mortality were 0.43 (95% confidence intervals: 0.19–0.95) and 0.45 (0.25–0.80), respectively, and 0.33 (0.12–0.91) and 0.31 (0.15–0.67) for all-heart disease mortality in the combined impaired glucose tolerance and diabetic Japanese men. Alcohol drinking in men with glucose intolerance was associated with a significant reduction in cardiovascular and all-heart disease mortality as seen in the general population in Japan.

Keywords: Alcohol; Diabetes; Glucose intolerance; Cardiovascular disease; Cohort study

Introduction

An increase in mortality from diabetes mellitus is mostly because of complications from atherosclerotic cardiovascular diseases (Calles-Escandon et al., 1999). Although epidemiological studies have shown an inverse association between moderate alcohol intake and coronary heart disease (CHD) incidence and mortality in general populations (Koppes et al., 2006), alcohol intake in diabetes is often discouraged in today's clinical practice because of concerns that alcohol adds calories without nutritional benefit; excessive alcohol intake by a person who is fasting or skipping meals can lead to hypoglycemia via inhibition of gluconeogenesis, whereas intoxication can impair a person's ability to follow a prescribed management plan or to recognize symptoms of hypoglycemia (Rimm et al., 1999). However, recent studies carried out in North America and Europe confirmed that light to moderate intake of alcohol is associated with a reduction in mortality from CHD and all-cause mortality in patients with diabetes (Ajani et al., 2000; Chalmers, 2005; Diem et al., 2003), and they are consistent with previous results in people without diabetes. However, these results cannot be extrapolated to the Japanese population because the mortality from stroke is higher than that from CHD in Japan, as well as in Korea and China (WHO, 1999), and it is known that alcohol intake differentially affects mortality from these two cardiovascular diseases in Japanese (Iso et al., 2004a; WHO, 1999). Furthermore, a study indicated that moderate to high alcohol consumption was positively associated with the incidence of diabetes in lean (body mass index [BMI] ≤ 22 kg/m^2) Japanese, and among men with a BMI > 22 kg/m^2, a small nonsignificant increase in odds ratio was observed with alcohol consumption

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(Nakamura et al., 2007), whereas other studies in Japanese and Caucasians showed moderate alcohol consumption was associated with a lower risk of diabetes (Okamura et al., 2003; de Vegt et al., 2002; Waki et al., 2005). Thus, the effect of alcohol on mortality from CHD and cardiovascular diseases in Japanese may be different.

In the present study, we analyzed the relationship between alcohol intake and all-cause and cause-specific mortality in men with and without glucose intolerance using the database of the National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged, 1980 (NIPPON DATA80). The database includes more than 4,600 male participants from randomly selected regions in Japan who were followed for 19 years (Nakamura et al., 2003, 2005).

Materials and methods

Participants

The participants in this cohort were those in the 1980 National Survey on Circulatory Disorders (Nakamura et al., 2005). A total of 10,897 community-based participants (4,795 men and 6,102 women) aged 30 years and older in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of history taking, physical examinations, blood tests, and a self-administered questionnaire on lifestyle. For the present study, we extracted 4,795 male participants because very few women in Japan drank alcohol. Participants were followed to 1999 (NIPPON DATA80, 1980–99). The participation rate of men was 73.5% before exclusion for reasons mentioned in the following.

We reviewed the residence records of all the study participants for vital status. In death cases, the causes were examined. To verify the cause of death, we used the National Vital Statistics records. The underlying cause of death was coded according to the 9th International Classification of Disease for the National Vital Statistics (ICD9) until the end of 1994 and according to the 10th International Classification of Disease from the beginning of 1995. Deaths were confirmed in each district by computer matching of data from the Vital Statistics records using the district, sex, and dates of birth and death as key codes.

Participants were excluded from follow-up because of a past history of coronary disease, stroke, or significant comorbidities, such as renal insufficiency ($N = 215$), missing baseline data ($N = 167$), or loss to follow-up ($N = 395$). The latter group was excluded because of the absence of a permanent address that was required to link to vital statistics records. The final sample comprised 4,018 male participants. There were no significant differences between participants who were lost to follow-up and those who were included in the present study in terms of several risk factors. Therefore, the potential bias regarding the 395 participants lost to follow-up is thought to be negligible. Permission to use the National Vital Statistics records was obtained from the Management and Coordination Agency, Government of Japan. Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12–18, 2000).

Biochemical and baseline examinations

The baseline surveys were conducted at public health centers. Baseline blood pressure was measured by trained research nurses using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or when a participant was receiving medication to treat high blood pressure. Height and weight were measured in stocking feet and light clothing. The BMI was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also carried out using a self-administered questionnaire. Reported information was confirmed by public health nurses through interviews with the study participants regarding food intake, smoking, drinking, and present and past medical histories. With regard to drinking, participants were asked whether they consumed alcohol, and they had to choose one of the following four categories: (1) almost never drink, (2) drink daily, (3) drink occasionally, and (4) stopped drinking, but used to drink.

Casual blood samples were drawn and centrifuged within 60 min of collection and stored at −70°C until analyses. For a few participants ($N = 105$), blood samples were drawn after overnight fasting. Total cholesterol was analyzed in a sequential auto-analyzer (SMA12/60; Technicon, Tarrytown, NY) at a single laboratory (Osaka Medical Center for Health Science and Promotion) (Bittner and McCleary, 1963). Serum concentrations of glucose were measured by the cupric-neocuproline method (Iso et al., 2004b) and the values were converted so that they better corresponded with the more widely used hexokinase method (MacKay and Mensah, 2004). Participants whose casual blood glucose was ≥200 mg/dL, or whose fasting blood glucose was ≥126 mg/dL, or who had a self-reported history of diabetes were categorized as having "diabetes mellitus." Participants with casual blood glucose concentrations between 140 and <200 mg/dL or whose fasting blood glucose concentrations fell between 100 and <126 mg/dL were categorized as having "impaired glucose tolerance (IGT)" (MacKay and Mensah, 2004; Thun et al., 1997).

Statistical analysis

SAS version 9.1 for Windows (SAS Institute, Cary, NC) was used throughout the analyses. To examine the

association between alcohol intake and all-cause and cause-specific mortality, age-adjusted and multivariate-adjusted hazard ratios were calculated using a Cox proportional hazards model for the normal and combined IGT plus diabetes groups. For multivariate analyses (Model 1), we adjusted for age, BMI, and cigarette smoking (never and former smokers, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day, and current smokers ≥41 cigarettes/day). Model 1 was further adjusted for blood glucose concentration and postprandial hours to rule out the argument that only well-controlled diabetics took alcohol (Model 2). The never-drinking category served as a reference for comparison with the other categories. The secondary analyses were performed in the IGT and diabetes groups separately.

Results

Baseline characteristics according to glucose tolerance category

There were 3,614 participants in the normal, 195 in the IGT and 209 in the diabetic groups. Table 1 shows the baseline characteristics according to glucose tolerance category. Across the categories from normal to diabetic, the prevalence of hypertension, mean age, glucose, and total cholesterol concentration increased.

Baseline characteristics according to alcohol drinking category

Table 2 shows the baseline characteristics according to alcohol drinking category in the normal group and the glucose intolerance group. In the normal groups, those in the former drinking category were older than those in the other drinking strata. In the glucose intolerance group, this was not observed.

The effect of alcohol intake on all-cause and cause-specific mortality according to alcohol intake category in the normal and abnormal glucose tolerance groups

During the 19 years of follow-up, there were 990 deaths. Among these, 328 were from cardiovascular and 662 were because of non-cardiovascular diseases. Among 662 non-cardiovascular deaths, 337 were because of cancer. Among the 328 cardiovascular deaths, 157 were because of all-heart diseases and 155 were attributed to stroke; 95 from cerebral infarction and 37 from cerebral hemorrhage. Among all 157 heart deaths, 65 were because of acute myocardial infarction and 92 to non-acute myocardial infarction, including 61 from heart failure. Table 3 shows the total person years, number of cases, mortality per 1,000 person years, hazard ratios, and 95% confidence intervals for all-cause and cause-specific mortality for each category of alcohol intake after adjustment for age and other risk factors. Here, analyses are limited to the normal glucose tolerance group with the never-drinking category serving as a reference. Non-daily drinking was associated with a significant reduction in all-cause, cardiovascular, all-heart diseases and non-acute myocardial infarction mortality in the age- and multivariate-adjusted models. No significant associations were observed between alcohol intake and stroke mortality. Daily drinking was associated with a significant increase in cancer mortality. Results of Model 2 were not shown in Table 3 because they were not different from those of Model 1.

In the glucose intolerance group, daily drinking was seen in almost half of the participants, and was associated with a significant reduction in cardiovascular and all-heart disease mortality in all the models. Daily drinking was associated with a significant reduction in acute myocardial infarction mortality in Model 2 (Table 4). Non-daily drinking in the glucose intolerance group was associated with a significant reduction in all-cause, all-heart disease and acute myocardial infarction mortality in Model 2. No significant associations were observed between alcohol intake and stroke mortality.

The secondary analyses in the diabetic men yielded similar results. No significant associations between alcohol intake and mortality were observed in the analyses in the IGT group alone, a possible consequence of limited statistical power and lower mortality as compared with those with diabetes.

Discussion

It was interesting to find that the percentage of daily drinkers among participants with glucose intolerance was

Table 1
Baseline characteristics according to glucose tolerance category—NIPPON DATA80 in 1980, men aged 30 years and older

	Normal	IGT	Diabetes
Number (total = 4,018)	3,614	195	209
Age (year)	49.8 ± 13.1	54.3 ± 14.1**	56.9 ± 11.0**
BMI (kg/m^2)	22.5 ± 2.8	22.4 ± 3.2	23.0 ± 3.2*
Current smoker (%)	63.2	64.1	65.5
Current drinker (%)	75.1	69.2	73.2
Hypertension (%)	48.0	62.6**	67.9**
Serum glucose (mg/dL)	95.6 ± 16.2	154.8 ± 21.2**	165.1 ± 88.9**
Serum TCH (mg/dL)	185.2 ± 32.3	188.9 ± 36.6	195.1 ± 35.6**

IGT = impaired glucose tolerance; BMI = body mass index; TCH = total cholesterol concentration. *$P < .05$, **$P < .01$ normal vs. IGT or diabetes.