a weaker relationship between smoking and the incidence of CHD in southern Europe than in Northern Europe and Yugoslavia.[6] People living in Asia and in southern Europe at the time of the early follow up by the Seven Countries Study had low average total cholesterol (TC) levels.[4–6] Furthermore, some recent studies investigating the aetiology of subclinical atherosclerosis found that low-density lipoprotein cholesterol is more important for early atheroma formation, whereas smoking plays a more important role at the later stages of atherosclerosis.[7,8]

Japanese studies reported before 2000 indicated that cigarette smoking is not a consistent risk factor for stroke.[9–11] However, recent analyses have revealed a close relationship between cigarette smoking and stroke in Japan.[12–15] Some investigators have postulated that this change is due to a recent increase in dietary fat intake and a relative increase of the blood TC level in the general population.[3,13] Thus, the association between smoking and cardiovascular diseases (CVD) might differ according to TC level. The aim of the present study was to determine whether TC level affects the association between smoking and CVD using a representative Japanese sample.

Methods

The subjects of this cohort study participated in the Japanese 1980 National Cardiovascular Survey, which was conducted together with a National Nutrition Survey. Nutrition is surveyed annually in Japan using standardized procedures and a questionnaire.[13,16] All household members aged 30 years or older in 300 randomly selected census tracts throughout Japan are included. The 1980 survey included medical examinations, blood pressure (BP) measurements, blood tests and a self-administered questionnaire about lifestyle. Trained staff at local health centres in the respective districts performed the medical examinations at local health and community centres. A history of illness, including heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and body weight were measured, while the subjects wore light clothing and no shoes. The participants were questioned about whether they were current smokers, ex-smokers or had never smoked. Smokers were asked to describe the number of cigarettes smoked per day. Similarly, alcohol consumption was determined as never, past, current occasionally or current daily. A standard sphygmomanometer was used to measure systolic and diastolic BP. The precision and accuracy of serum TC in non-fasting blood samples were verified by the Lipid Standardization Program administered by the Center for Disease Control and Prevention, Atlanta, GA, USA.[17] Diabetes was defined as non-fasting serum glucose of 11.1 mmol/l (200 mg/dl) or a self-reported history of diabetes.

A total of 10 546 individuals, aged 30 years or older, for whom baseline information regarding age, gender and blood pressure was complete in the 1980 data set constituted the study cohort (NIPPON DATA80).[13,16] We excluded those with a history of stroke ($n=117$), CHD ($n=163$), other heart disease ($n=475$), no information about confounding factors ($n=4$), those without complete information about smoking or TC ($n=28$) and 847 participants who were lost to follow-up. Consequently, we analysed data from 8912 participants.

As described elsewhere,[12,15] the underlying causes of death in the Japanese National Vital Statistics were coded according to the 9th (ICD-9) and 10th (ICD-10) International Classifications of Disease for deaths through 1994 and thereafter, respectively. Details about the classification and permission to use the National Vital Statistics were obtained from the Management and Coordination Agency of the Government of Japan. The Institutional Review Board of the Shiga University of Medical Science approved the study protocol (No. 12–18, 2000).

Statistical analysis

To examine the association between cigarette smoking and CVD mortality according to TC level, participants were divided into quartiles Q4, Q3, Q2 and Q1 according to TC levels of $\geqslant 5.40$ mmol/l ($\geqslant 209$ mg/dl), 4.81–5.39 mmol/l (186–208 mg/dl), 4.26–4.80 mmol/l (165–185 mg/dl) and Q1 (TC, <4.25 mmol/l (<164 mg/dl). We compared the basic characteristics among the groups according to a combination of smoking and TC levels using the mean for continuous variables and ratios (%) for dichotomous variables.

Age-adjusted CVD mortality rate, relative hazards (RH) and the 95% confidence intervals (95%CI) for cigarette smoking was estimated according to TC level using the Cox proportional hazard model. Individuals who had never smoked were categorized as the reference group. We estimated the RH using age-adjusted and multivariate-adjusted models, and included the following possible confounding factors in the latter model: age, body mass index (BMI), systolic BP, use of anti-hypertensive medication, diabetes and alcohol consumption (never, past, occasional and daily). The significance of multiplicative interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model. The interaction was assessed for CVD mortality, CHD mortality, ischaemic stroke mortality and ischaemic CVD (composite endpoint of CHD and ischaemic stroke) mortality. We also separately analysed the relationship between smoking and CVD or ischaemic CVD mortality according to cholesterol level by age group ($\leqslant 69$ and >69 years, as the median age of the deceased was 69 years). SAS software (version 9.1) was used for all statistical analyses.

Results

The mean $\pm$ SD baseline age of the participants was 50.1 ± 13.1 years and 55.5% were women. The mean TC level was 4.81 ± 0.85 mmol/l (186.2 ± 32.8 mg/dl) for men and 4.91 ± 0.88 mmol/l (190.2 ± 33.9 mg/dl) for women. Proportions of current smokers, ex-smokers and never smokers were 63.7, 18.1 and 18.2% for men and 8.8, 2.1 and 89.2% for women, respectively.

Table 1 shows the baseline characteristics of the study participants according to smoking status and TC level. Proportions of current smokers across ascending TC groups were 68.8, 65.6, 62.0 and 57.6% for men and 7.7, 8.6, 9.3 and 9.3% for women in Q1, Q2, Q3, and Q4, respectively. The mean BMI and systolic BP were higher in groups of both men and women with higher TC. Similarly, the proportion of participants

Table 1 Baseline characteristics of participants according to smoking status and total cholesterol level. NIPPON DATA80, 1980, Japan

Total cholesterol level	Q1(<4.25 mmol/l)[a]			Q2+Q3 (4.26–5.39 mmol/l)[a]			Q4(≥5.40 mmol/l)[a]		
Smoking status	Never	Ex-smoker	Current	Never	Ex-smoker	Current	Never	Ex-smoker	Current
Men									
Number of participants	173	149	709	366	361	1283	184	207	531
Age (years)	51.1	54.3	50.1	51.0	52.0	49.1	48.7	53.1	47.8
Total cholesterol (mmol/l)	3.84	3.80	3.83	4.81	4.80	4.77	5.93	6.01	5.97
Body mass index (kg/m^2)	22.4	21.7	21.4	22.9	22.7	22.3	24.0	23.3	23.5
Systolic blood pressure (mmHg)	136.3	138.9	136.2	137.5	139.1	138.2	141.1	141.7	137.7
Antihypertensive medication (%)	9	11	7	12	9	8	11	14	9
Diabetes (%)	1	5	6	7	4	7	8	10	10
Drinking status									
Never (%)	28	25	17	29	16	18	25	21	18
Past (%)	3	8	5	5	7	4	4	11	5
Occasional (%)	39	21	25	34	26	24	33	24	25
Daily (%)	29	46	53	33	49	54	38	44	52
Women									
Number of participants	1074	22	91	2152	50	217	1187	31	125
Age (years)	44.6	48.8	47.3	50.0	53.3	50.7	55.1	58.7	54.5
Total cholesterol (mmol/l)	3.87	3.89	3.81	4.81	4.91	4.83	6.03	6.16	5.98
Body mass index (kg/m^2)	22.2	21.2	21.5	22.8	22.9	22.0	23.7	24.2	23.7
Systolic blood pressure (mmHg)	128.1	134.7	127.4	132.3	136.8	131.1	139.6	146.6	141.1
Antihypertensive medication (%)	6	9	7	9	10	7	17	29	14
Diabetes (%)	2	5	2	4	12	3	6	3	7
Drinking status									
Never (%)	81	50	45	82	52	53	82	52	58
Past (%)	1	9	2	1	6	6	1	16	4
Occasional (%)	16	32	37	15	34	29	15	19	29
Daily (%)	2	9	15	2	8	12	2	13	9

[a]<4.25 mmol/l,<164 mg/dl; 4.26–5.39 mmol/l, 165–208 mg/dl; ≥5.40mmol/l, ≥ 209 mg/dl.

taking anti-hypertensive medication was higher in the groups with higher TC. The mean age of the women was higher in the higher TC group, but this did not apparently differ among the men. Compared with current smokers and those who had never smoked, ex-smokers tended to be older and more of them were taking anti-hypertensive medication and had diabetes. The proportions of those who had never consumed alcohol were higher among those who had never smoked.

After 19 years of follow-up, 313 men and 291 women died of CVD. Table 2 shows the risk of CVD mortality associated with cigarette smoking according to TC levels. The adjusted RH of current cigarette smoking for CVD mortality among men was the highest in Q4 (RH = 2.36; 95%CI: 1.14–4.87) and the lowest in Q1 (RH = 0.85; 95%CI: 0.49–1.49). The *P*-value for interactions between smoking status (ever vs never) and TC level (continuous) for CVD mortality were 0.01. This interaction was also unchanged, when we excluded ex-smokers (*P* for interaction <0.01). Table 2 indicates that the findings for women were inconsistent.

Because the higher CVD mortality rate in those who had never smoked with lower TC was due to frailty, we further excluded early death that occurred within 5 years. However, the observed significant interactions were unchanged (*P* for interaction, 0.02).

Disease-specific analyses revealed that the *P*-values for interactions between smoking status and total cholesterol were 0.03 for CHD deaths and 0.01 for ischaemic CVD (CHD + ischaemic stroke) in men (Table 3). Although an interaction between smoking status and TC for total CVD mortality was not apparent in women, the relationship between cholesterol and ischaemic CVD was closer in smokers than in non-smokers among women (*P* for interaction, 0.02 for ischaemic CVD).

Because the age distribution differed by TC categories in women, we analysed interactions between smoking and cholesterol for CVD or ischaemic CVD separately by age group (≤69 and >69 years). For most of the age-specific analyses except the relationship between smoking and CVD mortality according to TC level in women aged >69 years, the relationship of TC with diseases was also closer in current smokers than in those who had never smoked (data not shown).

Discussion

The present study found that the relationship between cigarette smoking and CVD mortality is affected by TC level in men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women.

Table 2 Relative hazards (RH) and 95% confidence intervals (95%CI) of cardiovascular disease (CVD) mortality in relation to cigarette smoking status according to total cholesterol level. NIPPON DATA80, 1980–1999, Japan

	Men			Women		
Total Cholesterol	Never smoked	Ex-smoker	Current smoker	Never smoked	Ex-smoker	Current smoker
Q1(<4.25 mmol/l)						
Person-year	2839.5	2281.1	11807.8	19283.8	364.7	1512.2
n of CVD mortality	20	12	51	36	2	9
Age-adjusted CVD mortality rate	4.1	2.5	2.9	3.5	5.9	7.3
Age-adjusted RH	1	0.56 (0.27–1.15)	0.70 (0.42–1.17)	1	1.60 (0.39–6.67)	2.65 (1.27–5.53)
Multivariate-adjusted RH	1	0.64 (0.31–1.34)	0.85 (0.49–1.49)	1	1.42 (0.33–6.02)	3.11 (1.37–7.04)
Q2(4.26–4.80 mmol/l[a])						
Person-year	2973.2	3084.5	11623.3	18863.6	316.2	1777.1
n of CVD mortality	11	11	54	53	1	4
Age-adjusted CVD mortality rate	1.2	2.6	4.2	3.2	5.0	2.5
Age-adjusted RH	1	1.42 (0.61–3.31)	1.94 (1.00–3.74)	1	0.94 (0.13–6.78)	0.75 (0.27–2.09)
Multivariate-adjusted RH	1	1.32 (0.56–3.11)	1.72 (0.88–3.37)	1	0.44 (0.06–3.47)	0.52 (0.17–1.60)
Q3(4.81–5.39 mmol/l[a])						
Person-year	3263.6	3106.0	10416.8	19286.7	499.4	1991.9
n of CVD mortality	14	17	51	62	4	8
Age-adjusted CVD mortality rate	3.0	3.4	3.9	3.0	6.6	2.8
Age-adjusted RH	1	1.03 (0.51–2.10)	1.58 (0.87–2.88)	1	1.40 (0.51–3.89)	0.90 (0.43–1.89)
Multivariate-adjusted RH	1	1.53 (0.72–3.23)	1.81 (0.98–3.33)	1	1.52 (0.51–4.56)	1.03 (0.48–2.22)
Q4(⩾5.40mmol/l[a])						
Person-year	3279.6	3488.2	9248.6	20833.7	527.2	2098.7
n of CVD mortality	10	19	43	91	4	17
Age-adjusted CVD mortality rate	2.0	3.2	4.7	3.2	3.7	5.9
Age-adjusted RH	1	1.35 (0.63–2.90)	2.07 (1.04–4.16)	1	1.28 (0.47–3.49)	2.11 (1.26–3.55)
Multivariate-adjusted RH	1	1.52 (0.69–3.35)	2.36 (1.14–4.87)	1	1.16 (0.38–3.50)	2.67 (1.55–4.58)

In multivariate-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes, and drinking category (never, past, occasional and daily).
[a]<4.25 mmol/l, < 164 mg/dl; 4.26–4.80 mmol/l, 165–185 mg/dl, 4.81–5.39 mmol/l: 186–208 mg/dl, ⩾5.40mmol/l: ⩾ 209 mg/dl.
TC, total cholesterol; *n*, numbers; CVD, cardiovascular disease; Crude CVD mortality rate, Crude CVD mortality rate per 1000 person-years.

Table 3 Interaction between smoking and total cholesterol for cause specific mortality. NIPPON DATA80 1980–99

	Never smoker				Current smoker				
	N	*n*	Age-adjusted mortality rate	RH	*N*	*n*	Age-adjusted mortality rate	RH	***P* for interaction[b]**
Men									
Coronary heart diseases									
Q1(<4.25 mmol/l[a])	173	4	1.3	1	709	4	0.2	0.48 (0.10–2.22)	
Q2(4.26–4.80 mmol/l[a])	177	2	0.4	1	678	5	0.5	0.38 (0.06–2.27)	
Q3(4.81–5.39 mmol/l[a])	189	3	1.0	1	605	14	1.2	2.07 (0.57–7.57)	
Q4(≥5.40 mmol/l[a])	184	4	1.2	1	531	15	1.5	1.64 (0.52–5.19)	
Total	723	13		0.70 (0.32–1.54)[c]	2523	38		2.00 (1.46–2.74)[c]	0.03
Ischaemic stroke									
Q1(<4.25 mmol/l[a])	173	4	0.6	1	709	17	0.8	1.77 (0.51–6.17)	
Q2(4.26–4.80 mmol/l[a])	177	3	0.4	1	678	22	1.7	3.50 (0.96–12.75)	
Q3(4.81–5.39 mmol/l[a])	189	4	0.6	1	605	11	0.9	1.37 (0.40–4.69)	
Q4(≥5.40 mmol/l[a])	184	1	0.1	1	531	12	1.4	7.99 (0.84–76.14)	
Total	723	12		0.55 (0.21–1.43)[c]	2523	62		1.09 (0.79–1.50)[c]	0.09
Ischaemic cardiovascular diseases									
Q1(<4.25 mmol/l[a])	173	8	1.9	1	709	21	1.0	1.07 (0.42–2.74)	
Q2(4.26–4.80 mmol/l[a])	177	5	0.8	1	678	27	2.1	2.01 (0.72–5.63)	
Q3(4.81–5.39 mmol/l[a])	189	7	1.6	1	605	25	2.1	1.70 (0.71–4.08)	
Q4(≥5.40 mmol/l[a])	184	5	1.3	1	531	27	2.8	2.60 (0.94–7.18)	
Total	723	25		0.65 (0.36–1.19)[c]	2523	100		1.42 (1.13–1.80)[c]	0.01
Women									
Coronary heart diseases									
Q1(<4.25 mmol/l[a])	1074	9	0.9	1	91	2	1.6	2.18 (0.34–14.11)	
Q2(4.26–4.80 mmol/l[a])	1063	8	0.5	1	102	0	0.0	–	
Q3 (4.81–5.39 mmol/l[a])	1089	11	0.5	1	115	3	1.0	2.49 (0.62–10.00)	
Q4(≥5.40 mmol/l[a])	1187	16	0.6	1	125	4	1.4	3.77 (1.21–11.74)	
Total	4413	44		0.88 (0.61–1.28)[c]	433	9		1.12 (0.46–2.73)[c]	0.28
Ischaemic stroke									
Q1(<4.25 mmol/l[a])	1074	8	0.8	1	91	1	0.9	1.50 (0.16–14.33)	
Q2(4.26–4.80 mmol/l[a])	1063	14	0.8	1	102	0	0	–	
Q3(4.81–5.39 mmol/l[a])	1089	13	0.6	1	115	1	0.4	0.55 (0.06–4.97)	
Q4(≥5.40 mmol/l[a])	1187	22	0.8	1	125	6	2.2	4.65 (1.73–12.52)	
Total	4413	57		0.96 (0.70–1.34)[c]	433	8		1.98 (0.45–8.73)[c]	0.71

(continued)

Table 3 Continued

	Never smoker				Current smoker				
	N	*n*	Age-adjusted mortality rate	RH	*N*	*n*	Age-adjusted mortality rate	RH	*P* for interaction[b]
Women									
Ischaemic cardiovascular diseases									
Q1(<4.25 mmol/l[a])	1074	17	1.7	1	91	3	2.5	1.86 (0.45–7.62)[d]	
Q2(4.26–4.80 mmol/l[a])	1063	22	1.3	1	102	0	0.0	–	
Q3(4.81–5.39 mmol/l[a])	1089	24	1.2	1	115	4	1.4	1.37 (0.43–4.34)	
Q4(≥5.40 mmol/l[a])	1187	38	1.3	1	125	10	3.6	4.24 (2.02–8.88)	
Total	4413	101		0.92 (0.72–1.18)[c]	433	17		1.28 (0.65–2.50)[c]	0.02

Age-adjusted mortality rate, age-adjusted mortality rate per 1000 person-years.
In multivariate-adjusted model, we adjusted for age, body mass index, systolic BP, use of anti-hypertensive medication, diabetes and drinking category (never, past, occasional, and daily).
[a]<4.25 mmol/l, <164 mg/dl; 4.26–4.80 mmol/l, 165–185 mg/dl; 4.81–5.39 mmol/l, 186–208 mg/dl; ≥5.40 mmol/l, ≥209 mg/dl.
[b]*P* for interactions: interactions between TC (continuous) and smoking status were examined using cross-product terms in the regression model.
[c]Relative hazards of cholesterol increase per 1 mmol/l(continuous) for cause specific deaths.
[d]Because of questionable model fitting, we have excluded diabetes and anti-hypertensive medication from the model.
TC, total cholesterol; *N*, numbers of participants; *n*, numbers of mortality.

The strengths of our study are that we used a representative Japanese population from a national survey, as well as a validated and standardized TC measurement.

Several possibilities could explain the interaction. From a biological viewpoint, the findings that the association of smoking with ischaemic CVD is closer among individuals with higher, than with lower TC, were consistent with those of recent studies indicating that smoking is associated more closely with advanced, than with early, subclinical atherosclerosis.[7,8] In both the Atherosclerosis Risk in Communities (ARIC) study and in the Multiethnic Study of Atherosclerosis, Sharrett *et al.* showed that smoking was more closely associated with severe atherosclerosis (lower extremity artery disease or severe carotid artery intimal medial thickness, IMT) than with moderate IMT, and that low density lipoprotein cholesterol (LDL-C) was a more important determinant than smoking of the earliest ultrasound-detectable stage of atherosclerosis. A study of young adults similarly found that the determinants of carotid IMT were only lifetime LDL-C and (inversely) high density lipoprotein cholesterol (HDL-C), but not smoking pack-years or diabetes.[18] Thus, the impact of smoking could be higher in those with high TC and lower in those with low TC. The second possibility is that higher CVD mortality among those who never smoked with lower TC explains the interaction. Although men with lower TC who had never smoked had a preferable CVD risk factor profile, they had a higher age-adjusted CVD mortality rate. We considered two explanations for this. One is that the risk of haemorrhagic stroke mortality is higher in men who had never smoked with low TC. Haemorrhagic stroke is not atheromatous, and is affected by hypertension but not by serum TC. Furthermore, some epidemiological studies suggested that lower TC is associated with higher haemorrhagic stroke risk[19]. Thus, haemorrhagic stroke might increase the CVD risk. However, the higher CVD mortality rates in men with lower TC who had never smoked persisted even when CHD or ischaemic CVD were the end-points. Another explanation for the higher CVD mortality rate in the subgroup of non-smokers with low TC might be personal characteristics. Most Japanese men, especially the elderly, have smoked cigarettes at some point during their lives. For example, almost 80% (77.5%) of men aged ≥20 years smoked in 1970,[20] and the remainder of those who had never smoked might have some degree of frailty. Although the exclusion of early death that occurred within 5 years did not alter the interaction, some residual confounding might have remained. For example, some might have had respiratory conditions before starting to smoke, such as tuberculosis or childhood asthma. Participants with poor nutrition, irrespective of symptoms, might have a higher CVD risk. Since information on history of respiratory diseases was unavailable, we could not determine the validity of this speculation. Unknown confounding factors might also exist that could explain the higher mortality in never smoked with lower TC. Further studies are required to understand the relationship between TC and CVD among Japanese who have never smoked. Regardless, both biological mechanisms and personal characteristics in men with lower TC who had never smoked might explain the interaction.

Our findings are consistent with recent changes in the relationship between smoking and CVD in Japan.[2,13] In the two

Japanese cohorts (Tanushimaru and Ushibuka) in the Seven Countries Study, which collected baseline data between 1957 and 1964 and followed participants for 25 years, excess CHD or stroke-associated mortality[8] did not significantly differ among smokers and non-smokers. Although most prospective studies have found a significant relationship between smoking and CHD,[10,13,14] older studies did not find a significantly increased multiple-adjusted risk of stroke among smokers.[9–11] However, recent studies, in which TC levels are higher, have established a significant and closer relationship between cigarette smoking and stroke, especially ischaemic stroke.[12–15] Thus, our findings appear to be relevant and are also supported by several other epidemiological studies. The Hisayama study found that the relative risk of smoking for CHD was obviously greater among those with high, than low, TC.[10] However, they did not formally test the effect-modification. A recent finding from the ARIC study also revealed a modest but significant interaction between smoking and LDL-C for CHD incidence.[21] However, two large Korean studies (with shorter follow-ups) and a US study found that lower serum TC levels did not modify the risk relationship between smoking and CVD.[5,22,23]

One of the limitations of this study is the use of mortality data. Lower-quality nutrition might determine early death after CVD events. Thus, the risk of TC might have been under-estimated. Another limitation is the low mortality rate, especially among men who had never smoked and among women who current smoked. Our findings should be substantiated by longer studies of larger cohorts using CVD incidence data.

Mean levels of TC in Japan are rapidly increasing in Japan.[2] The National Nutrition Survey in Japan conducted in 2000 reported that the mean level of TC in Japan is 5.16 mmol/l (199.7 mg/dl) for men and 5.36 mmol/l (207.5 mg/dl) for women.[24] The prevalence of cholesterol values of $\geqslant$6.22 mmol/l ($\geqslant$240 mg/dl) in the 2000 survey (12.0% for men and 17.4% for women) was double that found in an identical national survey in 1980, which was the source of our cohort data (6.1% for men and 8.5% for women).[24] In the same report in 2000, although the prevalence of current cigarette smoking was <50% overall (45.6% for men and 10.5% for women), it was higher among younger populations (56.8% and 55.0% in men aged 30–39 and 40–49 years, respectively; 18.5 and 13.7% in women aged 30–39 and 40–49 years).[22] Thus, the impact and contribution of smoking or TC to CVD mortality, especially ischaemic CVD in Japan could increase.

In conclusion, we found that powerful effect modifications between smoking and TC for CVD mortality among Japanese men. This pattern was also observed for CHD mortality and ischaemic CVD in men and for ischaemic CVD mortality in women. Thus, the weak association of cigarette smoking with CVD mortality in Japan may be partly explained by a lower TC level. Since TC is increasing among Japanese, especially among younger men who often smoke,[25] greater efforts to reduce smoking are warranted in Japan and in other Asian countries.

Acknowledgements

This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare, under the auspices of the Japanese Association for Cerebro-cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, and H17,18-chouju-012). The authors thank all members of Japanese Association of Public Health Center, Directors and all staffs of the public health centres that cooperated with our study. The authors also would like to thank Professor Aaron R Folsom for his valuable comments on this article.

Conflict of interest: None declared.

References

1 U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

2 Ueshima H. Trends in Asia. *Coronary Heart Disease Epidemiology From Aetiology to Public Health*. 2nd edn. Edited by Marmot N and Elliot P. USA: Oxford University Press, 2005. pp. 102–12.

3 Sekikawa A, Kuller LH, Ueshima H *et al.* Coronary heart disease mortality trends in men in the post World War II birth cohorts aged 35-44 in Japan, South Korea and Taiwan compared with the United States. *Int J Epidemiol* 1999;**28:**1044–49.

4 Robertson TL, Kato H, Gordon T *et al.* Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: coronary heart disease risk factors in Japan and Hawaii. *Am J Cardiol* 1977;**39:**244–49.

5 Jee SH, Suh I, Kim IS, Appel LJ. Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: The Korea Medical Insurance Corporation Study. *JAMA* 1999;**282:**2149–55.

6 Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, Massachusetts: Harvard University Press, 1980. pp. 136–60.

7 Sharrett AR, Coady SA, Folsom AR, Couper DJ, Heiss G. ARIC Study. Smoking and diabetes differ in their associations with subclinical atherosclerosis and coronary heart disease-the ARIC Study. *Atherosclerosis* 2004;**172:**143–49.

8 Sharrett AR, Ding J, Criqui MH *et al.* Smoking, diabetes, and blood cholesterol differ in their associations with subclinical atherosclerosis: the Multiethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2006;**186:**441–47.

9 Jacobs DR Jr, Adachi H, Mulder I *et al.* Cigarette smoking and mortality risk: twenty-five-year follow-up of the Seven Countries Study. *Arch Intern Med* 1999;**159:**733–40.

10 Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens* 1990;**8 (Suppl):**S9–15.

11 Ueshima H, Iida M, Shimamoto T *et al.* Multivariate analysis of risk factors for stroke. Eight-year follow-up of farming villages in Akita, Japan. *Prev Med* 1980;**9:**722–40.

12 Yamagishi K, Iso H, Kitamura A *et al.* Smoking raises the risk of total and ischemic strokes in hypertensive men. *Hypertens Res* 2003;**26:**209–17.

13 Ueshima H, Choudhury SR, Okayama A *et al.* Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004;**35:**1836–41.

[14] Iso H, Date C, Yamamoto A *et al.*, JACC Study Group. Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Am J Epidemiol* 2005;**161**:170–79.

[15] Mannami T, Iso H, Baba S *et al.* Japan Public Health Center-based prospective study on cancer and cardiovascular disease group. Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. *Stroke* 2004;**35**:1248–53.

[16] Okamura T, Tanaka H, Miyamatsu N *et al.*, for the NIPPON DATA80 research group. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis* 2007;**190**:216–23.

[17] Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003;**10**:145–53.

[18] Zieske AW, McMahan CA, McGill HC Jr *et al.* Smoking is associated with advanced coronary atherosclerosis in youth. *Atherosclerosis* 2005;**180**:87–92.

[19] Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;**320**:904–10.

[20] Health and Welfare Statistics Association, Tokyo. *J Health Welfare Stat* 2006;**53**:81 (In Japanese).

[21] Hozawa A, Folsom AR, Sharrett AR, Payne TJ, Chambless LE. Does the impact of smoking on coronary heart disease differ by low density lipoprotein cholesterol level? The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation J* 2006;**70**:1105–10.

[22] Jee SH, Park J, Jo I *et al.* Smoking and atherosclerotic cardiovascular disease in women with lower levels of serum cholesterol. *Atherosclerosis* 2007;**190**:306–12.

[23] Blanco-Cedres L, Daviglus ML, Garside DB *et al.* Relation of cigarette smoking to 25-year mortality in middle-aged men with low baseline serum cholesterol: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 2002;**155**:354–60.

[24] The Fifth National Survey of Cardiovascular Diseases. Chuo-Hoki Publisher, Tokyo, Japan, 2003. (In Japanese).

[25] Sekikawa A, Horiuchi BY, Edmundowicz D *et al.* A 'natural experiment' in cardiovascular epidemiology in the early 21st century. *Heart* 2003;**89**:255–57.

Appendix

List of the NIPPON DATA 80 Research Group.

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

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

Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).

Participating Researchers: Akira Okayama (The First Institute of Health Service, Japan Anti-Tuberculosis Association, Chyioda-ku, Tokyo), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Fukushima), Shinichi Tanihara (Department of Hygiene and Preventive Medicine, Fukuoka University School of Medicine, Fukuoka, Fukuoka), Shigeyuki Saito (Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Public Health, Jichi Medical University School of Medicine, Shimotsuke, Tochigi), Fumihiko Kakuno (Higashiomi Public Health Center, Higashiomi, Shiga).

Participating Research Associates: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Shigemichi Tanaka (Department of Cardiology, Cardiovascular Center, Teine Keijinkai, Sapporo, Hokkaido), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

Lower Levels of Serum Albumin and Total Cholesterol Associated with Decline in Activities of Daily Living and Excess Mortality in a 12-Year Cohort Study of Elderly Japanese

Tomonori Okamura, MD,[*†] *Takehito Hayakawa, PhD,*[‡] *Atsushi Hozawa, MD,*[*] *Takashi Kadowaki, MD,*[*] *Yoshitaka Murakami, PhD,*[*] *Yoshikuni Kita, PhD,*[*] *Robert D. Abbott, PhD,*[*§] *Akira Okayama, MD,*[‖] *and Hirotsugu Ueshima, MD,*[*] *for the NIPPON DATA80 Research Group*

OBJECTIVES: To examine the association between levels of serum albumin and total cholesterol (TC) and risk of subsequent mortality and future decline in activities of daily living (ADLs) in elderly people.

DESIGN: Population-based cohort study.

SETTING: National Integrated Project for Prospective Observation of Non-Communicable Disease and Its Trends in the Aged, 1980.

PARTICIPANTS: One thousand eight hundred forty-four Japanese individuals aged 60 to 74 randomly selected throughout Japan and followed for 12.4 years.

MEASUREMENTS: Decline in ADLs and mortality.

RESULTS: After adjusting for other covariates, the multivariable odds ratios (ORs) of impaired ADLs were highest in the lowest albumin quartile (≤40 g/L) for women. The multivariable OR of having a composite outcome of death or impaired ADL for the lowest albumin quartile compared with the highest was 1.56 (95% confidence interval (CI) = 1.94–2.57) for men and 3.06 (95% CI = 1.89–4.95) for women. Serum albumin was significantly and inversely associated with a composite outcome of death or impaired ADLs in the group below the median of TC in both sexes (multivariable OR for 1-g/L increase in serum albumin = 0.88 for men (95% CI = 0.79–0.97) and 0.79 for women (95% CI = 0.72–0.87)), which was not significantly associated in the group with TC at or above the median.

CONCLUSION: In the Japanese general population, low-normal serum albumin and TC levels are associated with loss of activity during old age, especially for women. J Am Geriatr Soc 56:529–535, 2008.

Key words: serum albumin; cholesterol; activities of daily living; mortality; cohort studies

Several studies have found that low concentrations of serum albumin, a measure of nutritional or antiinflammatory status, are related to greater all-cause mortality.[1–5] Low serum albumin also correlates with impaired activities of daily living (ADLs) in community-dwelling individuals,[6–8] poor lower extremity function,[9] and low skeletal muscle mass,[10] especially in elderly people. Several prospective studies have similarly identified a relationship between low blood cholesterol level, which might also reflect depleted nutritional status, and noncoronary mortality[11–13] and physical disability.[14] Serum albumin and cholesterol are both included in routine serum biochemistry measurements. Accordingly, applying these two parameters might improve predictions of mortality or disability with low cost.

However, few studies have investigated the predictive value of low serum albumin stratified according to serum total cholesterol (TC) for identifying persons at risk of subsequent mortality and functional decline,[8,15,16] especially in populations with constitutionally lower serum TC levels, such as Japanese.[17]

It was postulated that lower serum albumin and TC levels would be useful for predicting the risk of subsequent mortality and impaired physical functional status in elderly Japanese. This hypothesis was examined using data from a prospective study of a representative sample of the Japanese population.

From the *Department of Health Science, Shiga University of Medical Science, Otsu, Shiga, Japan; †Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka, Japan; ‡Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; §Division of Biostatistics and Epidemiology, University of Virginia School of Medicine, Charlottesville, Virginia; ‖The First Institute for Health Promotion and Health Care, Japanese Anti-Tuberculosis Association, Tokyo, Japan.

Members of the NIPPON DATA80 Research Group are listed in Okamura et al.[18]

Address correspondence to Tomonori Okamura, MD, Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu City, Shiga 520-2192, Japan. E-mail: tokamura@belle.shiga-med.ac.jp

DOI: 10.1111/j.1532-5415.2007.01549.x

0002-8614/08/$15.00

METHODS

Subjects and Follow-Up

Two cohort studies of the National Survey on Circulatory Disorders constitute the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA). Baseline surveys were performed in 1980 (NIPPON DATA80) and 1990 (NIPPON DATA90), and details of these cohorts have been reported.[17–20] The 14-year follow-up data from NIPPON DATA80 were analyzed, because the baseline survey of NIPPON DATA90 did not include serum albumin measurements, and the first follow-up survey of ADLs for survivors aged 65 and older in 1994 was performed in NIPPON DATA80.

The study population comprised 2,150 inhabitants (945 men and 1,205 women aged 60–74) from 300 randomly selected districts in 1980. The baseline surveys were conducted at local public health centers, and all participants had to be capable of reaching the examination center without assistance. The participation rate was approximately 77%. Three hundred six participants who had a history of coronary heart disease or stroke (n = 125) or missing information in the baseline survey (n = 32) or were lost to follow-up (n = 149) were excluded. Data from 1,844 participants (797 men and 1,047 women) were analyzed.

Physicians and public health nurses at public health centers collected information about ADLs in the survivors (n = 1,275) in 1994. Participants were asked about five basic ADL items (feeding, dressing, bathing, toileting, and transfer (walking indoors)) modified from Katz et al.[21] and whether each of these could be accomplished without help, with partial help, or with full help. This survey was conducted through telephone interviews (30.5%), face-to-face interviews at home (43.5%), mail (9.0%), and other methods (17.0%). Impaired ADLs was defined as partial or full support needed to perform any of the five basic ADL items.

Biochemical and Physical Examinations

Nonfasting blood samples were separated using centrifugation within 60 minutes of collection in 1980 and stored at −70°C. Serum albumin and TC were measured using a sequential autoanalyzer (SMA12/60; Technicon, Tarrytown, NY) using bromocresol-green staining for albumin and the Lieberman-Burchard direct method for TC at the Center for Adult Diseases (Osaka, Japan) (now called the Osaka Medical Center for Health Science and Promotion). Measurement precision and accuracy for serum TC were certified in the Lipid Standardization Program administered by the Centers for Disease Control and Prevention.[22] Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 minutes of rest. Hypertension was defined as systolic blood pressure (SBP) of 140 mmHg or more, diastolic blood pressure (DBP) of 90 mmHg or more, use of antihypertensive agents, or any combination of these. Serum glucose was measured using cupric-neocuproine,[23] and diabetes mellitus was defined as a nonfasting serum glucose level of 200 mg/dL or more. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided by height (m^2). Public health nurses obtained data including smoking habit and alcohol consumption, as well as current health status and medical history.

Statistical Analysis

Sex-specific data were analyzed using the SPSS, version 14.0J (SPSS Japan Inc., Tokyo, Japan). Analysis of variance for means or chi-square tests for proportions were applied. The relationship between albumin and total mortality or impaired ADLs was described by dividing the participants into quartiles of serum albumin. The multivariable-adjusted hazard ratio (HR) for all-cause mortality was calculated using the Cox proportional hazard model adjusted for age, TC, hypertension, diabetes mellitus, body mass index, cigarette smoking (never, previous, and two levels of current smokers: ≤20 and >20 cigarettes/d, with "never" being defined as the reference group), and alcohol consumption (never, previous, occasional, and daily consumption, with "never" being defined as the reference group). The highest albumin quartile was defined as the reference group. Further analyses were repeated excluding deaths within the first 5 years of follow-up, because individuals with severe but subclinical disease might have had low albumin or TC levels. The fit of the proportional hazards model was evaluated by examining discrete regression models and permitting the proportionality assumption to vary with time. Assessments of nonlinearity involving associations with serum albumin levels were also made. Although statistical power may have been limited, there were no apparent reasons to suggest that the proportionality assumption was inappropriate or that the fit of the Cox model was inadequate. The odds ratio (OR) for having impaired ADLs or a composite outcome of death or impaired ADLs was also calculated using multiple logistic regression analysis.

The model with continuous serum albumin values instead of quartiles of serum albumin was also examined. The significance of multiplicative interaction between serum albumin and cholesterol for total mortality or impaired ADLs was examined using cross-product terms in the model. The subgroup stratified according to the median of serum TC level (the median of serum TC: 180 mg/dL for men and 200 mg/dL for women) was similarly analyzed.

All probability values were two-tailed, and all confidence intervals (CIs) were estimated at the 95% level. The institutional review board of Shiga University of Medical Science approved the study.

RESULTS

The means ± standard deviations of baseline serum albumin values were 42.3 ± 2.6 g/L for men and 42.9 ± 2.3 g/L for women. Individuals with clinically abnormal serum albumin levels (≤35 g/L) were rare (6 men and 1 woman). The prevalence of clinically low serum albumin levels defined according to another cutoff point (38 g/L) was also low. Only 7.2% of men and 2.6% of women had serum albumin levels of 38 g/L or less. Total person-years were 22,785, and the mean follow-up period was 12.4 years. During follow-up, 305 men and 134 women died. At the end of follow-up in 1994, 47 men and 98 women with impaired ADLs remained alive.

Table 1 shows the mean values and prevalence of risk characteristics at baseline for those who had died and those who were alive with or without impaired ADLs. For both

Table 1. Sex-Specific Prevalence of Risk Characteristics at Baseline (1980) in a 12-Year Prospective Study of 1,844 Japanese Men and Women Aged 60 to 74

Risk Characteristic	Alive without Impaired ADLs	Alive with Impaired ADLs	Dead	*P*-Value
Men	n = 445	n = 47	n = 305	
Age, mean ± SD	64.9 ± 3.6	66.6 ± 4.0	67.7 ± 4.1	<.001
Albumin, g/L, mean ± SD	42.7 ± 2.5	42.3 ± 2.4	41.8 ± 2.6	<.001
Total cholesterol, mg/dL, mean ± SD	185 ± 32	184 ± 37	179 ± 30	.03
SBP, mmHg, mean ± SD	147 ± 20	149 ± 22	154 ± 23	<.001
DBP, mmHg, mean ± SD	85 ± 12	85 ± 12	87 ± 13	.22
Hypertension, %*	67.2	68.1	76.1	.03
Diabetes mellitus, %†	1.1	2.1	2.6	.30
Body mass index, kg/m^2, mean ± SD	22.2 ± 2.9	22.1 ± 3.2	21.4 ± 3.0	.004
Smoking, %				
Never smoker	20.4	4.3	16.1	.12
Ex-smoker	24.7	34.0	23.9	
Current smoker, <1 pack/d	43.4	46.8	46.6	
Current smoker, ≥1 pack/d	11.5	14.9	13.4	
Drinking, %				
Never drinker	21.1	31.9	29.5	.023
Ex-drinkers	7.6	10.6	10.5	
Occasional drinker	23.8	10.6	17.7	
Daily drinker	47.4	46.8	42.3	
Women	n = 685	n = 98	n = 264	
Age, mean ± SD	64.9 ± 3.8	68.0 ± 4.1	67.9 ± 4.1	<.001
Albumin, g/L, mean ± SD	43.2 ± 2.2	42.4 ± 2.4	42.4 ± 2.4	<.001
Total cholesterol, mg/dL, mean ± SD	204 ± 34	201 ± 32	197 ± 37	.03
SBP, mmHg, mean ± SD	144 ± 21	148 ± 21	150 ± 25	.001
DBP, mmHg, mean ± SD	82 ± 12	83 ± 11	84 ± 13	.11
Hypertension, %*	63.1	71.4	71.6	.02
Diabetes mellitus, %†	1.8	2.0	3.8	.17
Body mass index, kg/m^2, mean ± SD	23.0 ± 3.5	23.5 ± 3.5	22.5 ± 3.8	.04
Smoking, %				
Never smoker	87.4	89.8	85.8	.048
Ex-smoker	3.1	1.0	3.5	
Current smoker, <1 pack/d	8.8	9.2	9.8	
Current smoker, ≥1 pack/d	0.7	0	0.9	
Drinking, %				
Never drinker	81.8	88.8	80.7	.048
Ex-drinker	1.8	1.0	3.0	
Occasional drinker	13.1	8.2	9.5	
Daily drinker	3.4	2.0	6.8	

*Systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, use of antihypertensive agents, or some combination of these.
†Nonfasting serum glucose level ≥200 mg/dL.
ADLs = activities of daily living; SD = standard deviation.

sexes, mean age was lowest in participants who were alive without impaired ADLs. In contrast, serum albumin and TC were highest in participants who were alive without impaired ADLs. In both sexes, the highest SBP, DBP, and serum glucose levels were found in those who had died. Smoking or alcohol consumption differed significantly between the three groups. The highest prevalence of those who had never smoked or consumed alcohol was found in those who were alive without impaired ADLs in men.

Table 2 shows sex-specific adjusted HRs of all-cause mortality and ORs of having impaired ADLs according to quartiles of serum albumin. The multivariable HR of all-cause mortality for the lowest albumin quartile compared with the highest was 1.48 (95% CI = 1.01–2.17) for men and 1.70 (95% CI = 1.16–2.51) for women. As a continuous variable, serum albumin was significantly and inversely associated with all-cause mortality (HR = 0.93, 95% CI = 0.88–0.97 for men, HR = 0.92, 95% CI = 0.87–0.97 for women, for 1-g/L increase in serum albumin). This relationship remained significant after excluding deaths within 5 years of follow-up (data not shown). In women, the multivariable OR of survivors having impaired ADLs at

Table 2. Likelihood of All-Cause Mortality and of Having Impaired Activities of Daily Living (ADLs) According to Quartile of Serum Albumin in a 12-Year Prospective Study of 1,844 Japanese Men and Women Aged 60 to 74

Serum Albumin	Stratum Mean (g/L)	Participants at Baseline Survey (n)	Person-Years	Deaths (n)	Dead, Multivariable Hazard Ratio (95% CI)*	Cases Alive at End of Follow-Up (n)	Cases Alive with Low ADL at End of Follow-Up (n)	Impaired ADLs, Multivariable Odds Ratio (95% CI)*
Men (n = 797)								
Serum albumin level								
≤40	38.8	174	1,938	87	1.48 (1.01–2.17)	87	8	1.10 (0.36–3.36)
41–42	41.5	246	2,867	103	1.36 (0.95–1.95)	143	15	1.56 (0.61–4.01)
43–44	43.5	212	2,603	69	1.06 (0.73–1.55)	143	15	1.62 (0.64–4.07)
≥45	45.9	165	2,080	46	1.00	119	9	
1-g/L increase in serum albumin								
Analysis for all participants					0.93 (0.88–0.97)			0.93 (0.81–1.06)
P for interaction with serum total cholesterol					.60			0.11
Total cholesterol								
<Median (n = 393)†					0.91 (0.85–0.98)			0.92 (0.76–1.12)
≥Median (n = 404)†					0.94 (0.88–1.01)			0.97 (0.79–1.19)
Women (n = 1,047)								
Serum albumin level								
≤40	39.2	143	1,700	58	1.70 (1.16–2.51)	85	22	4.12 (1.82–9.36)
41–42	41.5	289	3,592	78	1.18 (0.82–1.68)	211	31	1.84 (0.91–3.72)
43–44	43.4	358	4,698	72	0.91 (0.64–1.29)	286	29	1.36 (0.69–2.70)
≥45	45.9	257	3,308	56	1.00	201	16	
1-g/L increase in serum albumin								
Whole population					0.92 (0.87–0.97)			0.86 (0.77–0.96)
P for interaction with serum total cholesterol					.006			.12
Total cholesterol								
<Median (n = 537)†					0.87 (0.81–0.94)			0.77 (0.65–0.91)
≥Median (n = 510)†					0.98 (0.90–1.07)			0.95 (0.81–1.11)

* Adjusted for age, total cholesterol, diabetes mellitus, hypertension, body mass index, cigarette smoking, and alcohol drinking.
† Median of total cholesterol was 180 mg/dL for men and 200 mg/dL for women.
CI = confidence interval.

the end of follow-up was significantly higher in the lowest albumin quartile than in the highest quartile. A significant interaction between serum albumin and cholesterol for all-cause mortality was observed in women. After stratification at the median of serum cholesterol, the HR associated with a 1-g/L increase in serum albumin for women was 0.87 (95% CI = 0.81–0.94) in the group below the median of TC and 0.98 (95% CI = 0.90–1.07) in the group with TC at or above the median.

Table 3 shows multivariable ORs of having a composite outcome of impaired ADLs or death according to quartiles of serum albumin. The multivariable OR for the lowest albumin quartile compared with the highest was 1.56 (95% CI = 0.94–2.57) for men and 3.06 (95% CI = 1.89–4.95) for women. This relationship was more evident in the group below the median of TC (multivariable OR for the lowest albumin quartile = 1.91 for men, 95% CI = 0.88–4.15, and 4.50 for women, 95% CI = 2.25–9.02). As a continuous variable, serum albumin was significantly and inversely associated with a composite outcome of death or impaired ADLs in the group below the median of TC and not in the group with TC at or above the median in men and women.

When compared with women with serum albumin levels above the 25th percentile (40 g/L) and TC levels at or above the median (200 mg/dL), women who had serum albumin and TC concentrations that were simultaneously lower had the highest multivariable adjusted OR of having a composite outcome of impaired ADLs or death (3.76, 95% CI = 2.31–6.12). The corresponding OR became 1.35 (95% CI = 0.67–2.71) in the group with low albumin (≤25th percentile) and high TC (≥median). Using the same cutpoints (>40 g/L for serum albumin and ≥median for TC) as a reference for men, the multivariable OR was also highest for men whose albumin and TC levels were simultaneously lower (1.34, 95% CI = 0.74–2.43). The corresponding OR was similar for those with low albumin and high TC concentrations (1.34, 95% CI = 0.83–2.16).

These results were not substantially affected when participants with clinically abnormal serum albumin levels (≤35 g/L or ≤38 g/L) were excluded from the analysis.

DISCUSSION

To the authors' knowledge, this is the first prospective study of the relationship between serum albumin and all-cause mortality and impaired ADLs in a non-Western population. The unique finding of the present prospective study is that the relationship between low albumin, even when within

Table 3. Likelihood of Having a Composite Outcome of Impaired Activities of Daily Living (ADLs) or Death According to Quartile of Serum Albumin in a 12-Year Prospective Study of 1,844 Japanese Men and Women Aged 60 to 74

Serum Albumin	Stratum Mean (g/L)	Participants at Baseline Survey, n	Deaths or Cases Alive with Impaired ADLs at the End of Follow-Up	Deceased or Impaired ADLs, Multivariable Odds Ratio* (95% Confidence Interval)
Men (n = 797)				
Serum albumin level				
≤40	38.8	174	95	1.56 (0.94–2.57)
41–42	41.5	246	118	1.45 (0.92–2.29)
43–44	43.5	212	84	1.13 (0.72–1.80)
≥45	45.9	165	55	1.00
1-g/L increase in serum albumin				0.92 (0.86–0.98)
P for interaction with serum total cholesterol				.19
<Median total cholesterol (n = 393)†				
≤40	38.7	113	62	1.91 (0.88–4.15)
41–42	41.4	137	67	1.96 (0.94–4.09)
43–44	43.4	90	36	1.46 (0.67–3.21)
≥45	45.6	53	17	1.00
1-g/L increase in serum albumin				0.88 (0.79–0.97)
≥Median total cholesterol (n = 404)†				
≤40	38.9	61	33	1.40 (0.68–2.92)
41–42	41.6	109	51	1.27 (0.69–2.33)
43–44	43.5	122	48	1.08 (0.60–1.97)
≥45	45.9	112	38	1.00
1-g/L increase in serum albumin				0.95 (0.87–1.04)
Women (n = 1,047)				
≤40	39.2	143	80	3.06 (1.89–4.95)
41–42	41.5	289	109	1.39 (0.93–2.07)
43–44	43.4	358	101	1.07 (0.73–1.57)
≥45	45.9	257	72	1.00
1-g/L increase in serum albumin				0.87 (0.82–0.93)
P for interaction with serum total cholesterol				.001
<Median total cholesterol (n = 537)†				
≤40	39.1	100	61	4.50 (2.25–9.02)
41–42	41.5	179	74	1.72 (0.92–3.20)
43–44	43.4	171	43	1.02 (0.54–1.94)
≥45	45.8	87	21	1.00
1-g/L increase in serum albumin				0.79 (0.72–0.87)
≥Median total cholesterol (n = 510)†				
≤40	39.5	43	19	1.57 (0.73–3.41)
41–42	41.6	110	35	1.10 (0.62–1.94)
43–44	43.4	187	58	1.22 (0.74–2.01)
≥45	45.9	170	51	1.00
1-g/L increase in serum albumin				0.98 (0.89–1.08)

* Adjusted for age, total cholesterol, diabetes mellitus, hypertension, body mass index, cigarette smoking, and alcohol drinking.
† Median of total cholesterol was 180 mg/dL for men and 200 mg/dL for women.
CI = confidence interval.

the clinically normal range, and total mortality and impaired ADLs was more evident in elderly Japanese with cholesterol levels below the median.

Few studies have examined the effect of low serum albumin on mortality or ADLs stratified according to serum cholesterol level.[8,15–17] A follow-up study of 937 U.S. men and women aged 70 to 79 found that those with low albumin (≤38 g/L) and low cholesterol (≤167 mg/dL) had the highest relative risks for 3- and 5-year mortality and a composite outcome of death and decline in functional status after 3 years.[8] Another study reported that functional performance was three times as likely to decline in Dutch men aged 55 to 85 years with lower serum albumin (≤43 g/L) and lower serum total cholesterol (≤200 mg/dL) as in those with higher levels after 3 years of follow-up.[16] Similar results were observed in the present study.

In contrast, a 5-year follow-up study of 820 Dutch males aged 64 to 84 found an inverse relationship between serum albumin and the incidence of coronary heart disease in individuals with serum cholesterol levels of 250 mg/dL or higher.[15] Furthermore, it was previously reported that a combination of low albumin (≤43 g/L) and above-average cholesterol levels (≥185 mg/dL) is associated with excess cardiovascular mortality in Japanese men and women aged 30 to 59.[17] The combination of low serum albumin and high serum cholesterol may be associated with excess risk of cardiovascular disease when mean serum cholesterol is high or when the study cohort is young, which might be due to the antioxidative effect of serum albumin on serum low-density lipoprotein cholesterol.[24] To the contrary, in older populations with low serum cholesterol, the combination of low serum albumin and low serum cholesterol might be associated with excess risk of all-cause mortality and impaired ADLs.

The exclusion of participants with clinically low levels of serum albumin (≤35 g/L or ≤38 g/L) did not affect the study results. Accordingly, it is likely that an outlier phenomenon did not cause the relationship between low albumin and a composite outcome of death or impaired ADLs. To the contrary, these results, especially for women, suggest that there exists a threshold at which the risk of the above-mentioned composite outcome is greater when serum albumin levels fall below a range from 38 to 40 g/L. However, some previous studies describe a linear association between serum albumin and mortality within a normal range of serum albumin.[1,3] The results of the current study suggest the need for more research to determine at what albumin level risk for death or impaired ADLs begins to rise for elderly people.

For the risk of low ADLs, different results were observed for men and women. In men, the OR of having impaired ADLs in survivors failed to reach a maximum in the lowest albumin quartile. Consequently, for men, the OR of a composite outcome of impaired ADLs or death in the lowest albumin quartile was diminished, although it remained highest in the lowest quartile. One reason may be the difference in life expectancy for elderly men and women. Crude mortality in men (32/1,000 person-years) was much higher than in women (20/1,000 person-years). Accordingly, for men, impaired ADLs constituted a smaller fraction of the composite outcome of death or impaired ADLs. The long period of time between the baseline examination and the follow-up survey for ADL might also have masked the relationship between serum albumin and impaired ADLs, especially for men, because most elderly participants died before ADL assessment. However, a 3-year follow-up study showed that a combination of low albumin and low cholesterol levels predicted functional decline, especially for men.[16] Further studies are warranted to determine whether the sex difference observed in the current report is real.

Although the causal mechanism remains unclear, serum albumin is a biological indicator of poor nutrition, muscle loss,[10] subclinical disease with inflammation, and vascular injury or neoplasm,[25] especially in elderly people. Serum albumin is also a negative marker of the acute-phase inflammatory response.[26] Cytokines such as serum interleukin-6, which are high in acute or chronic inflammatory status, decrease serum albumin levels.[27]

The present findings are based on a long-term follow-up study of community dwelling participants in the Japanese general population. Low-normal serum albumin levels, especially when coexisting with low serum TC, predicted all-cause mortality during 12 years of follow-up. Furthermore, low-normal serum albumin levels combined with low serum TC, even when both were within clinically normal ranges, were associated with impaired ADLs for women more than 10 years later, which might reflect mild nutritional deficiency or chronic inflammatory process. Accordingly, adequate nutrition counseling or screening for subclinical chronic inflammation should be considered for those whose serum albumin and TC concentrations are simultaneously low. Such interventions may be especially important for women as a means of preserving ADLs.

A limitation of the present study is that information about ADL was available only at a single time point at the end of follow-up. Another limitation is the lack of information on nutritional change or recent weight loss at the baseline survey. However, individuals whose baseline data revealed stroke, which is the largest cause of impaired ADL status in Japan, were excluded.[28] Furthermore, the present follow-up period (14 years) was so long that it would have been difficult for individuals with impaired ADLs at baseline to survive to the end of follow-up. It is also unlikely that individuals with impaired ADLs or severe subclinical disease with weight loss such as cancer were members of the study cohort, because each participant was community dwelling and attended local public health centers without assistance. Thus, it is likely that few individuals with impaired baseline ADLs or severe subclinical disease were included in the present analysis.

In conclusion, low-normal serum albumin levels with low serum TC, even when within the clinical normal range, was associated with loss of ability to perform physical activities in elderly Japanese, especially women. Because albumin and TC are inexpensive and easy to monitor serum biochemistry parameters, they might represent a useful predictor for identifying individuals at high risk for ADL decline and death in the early stages of old age.

ACKNOWLEDGMENTS

The authors thank all public health centers that cooperated with our study.

Conflict of Interest: This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebrocardiovascular Disease Control; a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare; and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, H17-chouju-012, and H19-chouju-014), and Dr. Robert D. Abbott was supported by Japan Society for the Promotion of Science invitation fellowship programs for research in Japan.

Author Contributions: All authors contributed to the concept, design, analysis, interpretation of data, and preparation of the manuscript.

Sponsor's Role: The sponsors did not participate in the design or conduct of the study; the collection; management,

analysis, or interpretation of the study; or preparation, review, or approval of the manuscript.

REFERENCES

1. Phillips A, Shaper AG, Whincup PH. Association between serum albumin and mortality from cardiovascular disease, cancer and other causes. Lancet 1989;2:1434–1436.
2. Gillum RF, Makuc DM. Serum albumin, coronary heart disease, and death. Am Heart J 1992;123:507–513.
3. Corti MC, Guralnik JM, Salive ME et al. Serum albumin level and physical disability as predictors of mortality in older persons. JAMA 1994;272:1036–1042.
4. Fried LP, Kronmal RA, Newman AB et al. Risk factors for 5-year mortality in older adults. The cardiovascular health study. JAMA 1998;279:585–592.
5. Schalk BW, Visser M, Bremmer MA et al. Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal aging study Amsterdam. Am J Epidemiol 2006;164:969–977.
6. Jensen GL, Kita K, Fish J et al. Nutrition risk screening characteristics of rural older persons: Relation to functional limitations and health care charges. Am J Clin Nutr 1997;66:819–828.
7. Hubert HB, Bloch DA, Fries JF. Risk factors for physical disability in an aging cohort: The NHANES I epidemiologic follow up study. J Rheumatol 1994; 20:480–488.
8. Reuben DB, Ix JH, Greendale GA et al. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur studies of successful aging. J Am Geriatr Soc 1999;47:402–406.
9. Ferucci L, Pennninx BW, Leveille SG et al. Characteristics of nondisabled older persons who perform poorly in objective tests of lower extremity function. J Am Geriatr Soc 2000;48:1102–1110.
10. Baumgartner RN, Koehler KM, Romero L et al. Serum albumin is associated with skeletal muscle in elderly men and women. Am J Clin Nutr 1996;64: 552–558.
11. Jacobs D, Blackburn H, Higgins M et al. Report of the conference on low blood cholesterol: Mortality associations. Circulation 1992;86:1046–1060.
12. Schuit AJ, Van Dijk CE, Dekker JM et al. Inverse association between serum total cholesterol and cancer mortality in Dutch civil servants. Am J Epidemiol 1993;137:966–976.
13. Schatz IJ, Masaki K, Yano K et al. Cholesterol and all-cause mortality in elderly people from the Honolulu heart program. Lancet 2001;358:351–355.
14. Ranieri P, Rozzini R, Franzoni S et al. Serum cholesterol levels as a measure of frailty in elderly patients. Exp Aging Res 1998;24:169–179.
15. Weijenberg MP, Feskens EJM, Souverijn JHM et al. Serum albumin, coronary heart disease risk, and mortality in an elderly cohort. Epidemiology 1997; 8:87–92.
16. Schalk BW, Visser M, Deeg DJ et al. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: The longitudinal aging study Amsterdam. Age Ageing 2004;33:266–272.
17. Okamura T, Hayakawa T, Kadowaki T et al. A combination of serum low albumin and above-average cholesterol level was associated with excess mortality. J Clin Epidemiol 2004;57:1188–1195.
18. Okamura T, Kadowaki T, Hayakawa T et al. Data80 research group. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–180.
19. Ueshima H, Choudhury SR, Okayama A et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. Stroke 2004;35: 1836–1841.
20. Okamura T, Tanaka H, Miyamatsu N et al. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis 2007;190:216–223.
21. Katz S, Downs TD, Cash HR et al. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.
22. Nakamura M, Sato S, Shimamoto T. Current status of CDC lipid standardization and international needs for standardization in epidemiological studies and clinical trials in Japan. J Atheroscler Thromb 2004;11:35–37.
23. Bittner D, McCleary M. The cupric-phenanthroline chelate in the determination of monosaccharides in whole blood. Am J Clin Pathol 1963;40: 423–424.
24. Krijgsman B, Papadakis JA, Ganotakis ES et al. The effect of peripheral vascular disease on the serum levels of natural anti-oxidants: Bilirubin and albumin. Int Angiol 2002;21:44–52.
25. Law MR, Morris JK, Wald NJ et al. Serum albumin and mortality in the BUPA study. Int J Epidemiol 1994;23:38–41.
26. Danesh J, Collins R, Appleby P et al. Association of C-reactive protein, albumin, or leukocyte count with coronary heart disease: Meta-analyses of prospective studies. JAMA 1998;279:1477–1482.
27. Bauer J, Herrmann F. Interleukin-6 in clinical medicine. Ann Hematol 1991; 62:203–210.
28. Hayakawa T, Okayama A, Ueshima H et al. Prevalence of impaired activities of daily living and impact of stroke and lower limb fracture on it in Japanese elderly people. CVD Prev 2000;3:187–194.

Diabetologia (2008) 51:575–582
DOI 10.1007/s00125-007-0915-6

ARTICLE

Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. NIPPON DATA80

S. Kadowaki · T. Okamura · A. Hozawa · T. Kadowaki · A. Kadota · Y. Murakami · K. Nakamura · S. Saitoh · Y. Nakamura · T. Hayakawa · Y. Kita · A. Okayama · H. Ueshima · for the NIPPON DATA Research Group

Received: 10 July 2007 / Accepted: 22 November 2007 / Published online: 16 January 2008

Abstract
Aims/hypothesis High fasting blood glucose is one of the well-known risk factors for CHD. However, in certain settings, patients cannot always be expected to fast. For example, community screenings for cardiovascular disease (CVD) risk factors in Japan are performed under non-fasting conditions to achieve high participation rates. Thus, we examined a representative cohort of the Japanese population (n=9,444, follow-up period 17.3 years) to clarify whether high casual blood glucose (CBG) can predict CVD mortality.
Methods We defined CBG groups as follows: high CBG≥ 11.1 mmol/l or participants with a history of diabetes mellitus; borderline high, 7.77≤CBG<11.1 mmol/l; higher normal, 5.22≤CBG<7.77 mmol/l); and lower normal, CBG<5.22 mmol/l. The multivariate-adjusted hazard ratios (HRs) for CHD, CVD and all-cause mortality were calculated.
Results The crude CHD mortality rate was 0.84 per 1,000 person-years. Age- and sex-adjusted HRs for CHD mortality were high among participants with CBG levels ≥7.77 mmol/l, regardless of time since last meal. Multivariate-adjusted HRs (95% CI) of CHD mortality in high and borderline high CBG groups were 2.62 (1.46–4.67) and 2.43 (1.29–4.58), respectively. Similar results were observed for both CVD

Electronic supplementary material The online version of this article (doi:10.1007/s00125-007-0915-6) contains a full list of the NIPPON DATA research group members, which is available to authorised users.

S. Kadowaki (✉) · A. Hozawa · T. Kadowaki · A. Kadota · Y. Murakami · K. Nakamura · Y. Kita · H. Ueshima
Department of Health Science,
Shiga University of Medical Science,
Seta Tsukinowa-cho,
Otsu 520-2192, Japan
e-mail: sayakado@belle.shiga-med.ac.jp

T. Okamura
Department of Preventive Cardiology,
National Cardiovascular Center,
Suita, Japan

A. Kadota
Department of Internal Medicine,
Shiga University of Medical Science,
Otsu, Japan

S. Saitoh
Second Department of Internal Medicine,
Sapporo Medical University,
Sapporo, Japan

Y. Nakamura
Cardiovascular Epidemiology,
Kyoto Women's University,
Kyoto, Japan

T. Hayakawa
Department of Hygiene and Preventive Medicine,
School of Medicine, Fukushima Medical University,
Fukushima, Japan

A. Okayama
The First Institute for Health Promotion and Health Care,
Japan Anti-Tuberculosis Association,
Tokyo, Japan

and all-cause mortality. Even within the normal blood glucose range, each 1 mmol/l increase in CBG was associated with a statistically significant increase in the HR for CVD mortality (1.12, 95% CI 1.02–1.22). Population-attributable fractions of the combined groups of high and borderline high CBG for CHD, CVD and all-cause mortality were 12.0, 4.9 and 3.5%, respectively.

Conclusions/interpretation Increases in CBG, even within the normal range, predict CVD mortality.

Keywords Cardiovascular disease · Casual blood glucose · Cohort study · Coronary heart disease · Diabetes mellitus · Japanese · Mortality · Population-attributable fraction

Abbreviations

CBG	casual blood glucose
CVD	cardiovascular disease
HR	hazard ratio
ICD	International Classification of Diseases
NIPPON DATA80	National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980
PAF	population-attributable fraction

Introduction

Impaired glucose tolerance and diabetes mellitus are well-known risk factors for coronary heart disease (CHD) and cardiovascular disease (CVD) [1–4]. A fasting blood glucose level or a fasting blood glucose level plus 2 h post-glucose load (75 g OGTT) are usually used to diagnose diabetes mellitus [5]. However, in some settings, it is unrealistic to require all participants to fast. It is impractical to require either of these tests from clinic patients, especially those who visit at night or in the afternoon. Furthermore, in Japan, general screenings for CVD risk factors are performed under non-fasting conditions to improve the participation rates. Thus, the question of whether a casual blood glucose (CBG) level, whose value can be obtained at any time of the day regardless of time since last meal, can predict CHD or CVD mortality is of great interest. Only one prospective study has reported this relationship between CBG and CHD [6], though some prospective studies have reported the relationship between CHD and fasting blood glucose or OGTT [7–9]. We investigated the relationship of CBG with CHD, CVD and all-cause mortality in a 17.3-year follow-up study with a representative sample from the Japanese population. We also investigated whether a CBG level predicts CHD or CVD mortality within a normal glucose range and examined what proportion of CHD or CVD deaths was attributable to high CBG or borderline high CBG levels.

Methods

Population The cohort studies of the National Survey on Circulatory Disorders 1980 were called the National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980 (NIPPON DATA80). Details of these cohorts have been previously reported [10–14]. Briefly, 13,771 participants were randomly selected in 300 districts from the overall population aged 30 years or older in Japan by the Japanese Ministry of Health and Welfare. Among them, 10,546 individuals completed a baseline survey, namely, the National Survey of Circulatory Disorders, in 1980. All participants were assured a right to refuse the participation in this survey. The participation rate in this survey was 76.6% (10,546 of 13,771). They were followed-up until 15 November 1999 by using the national Vital Statistics. Of the 10,546 participants, 1,102 were excluded for the following reasons: past history of CHD (n=45) or stroke (n=108); information missing at the baseline survey (n=41); or lost to further contact due to incomplete residential access information at the first survey (n=908). The remaining 9,444 participants (4,134 men, 5,310 women) were included in the analysis.

Baseline examination Blood was drawn from seated patients into a plain, siliconised glass tube and the serum was separated. The serum was centrifuged soon after blood coagulation at 1,500×g. Fasting was not required prior to blood draw. The blood was gathered and analysed at one specific laboratory (formerly Center for Adult Diseases, Osaka; now named Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Since April 1975, this laboratory has been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (Atlanta, GA, USA) [15]. Blood glucose levels were measured at this site using the cupric-neocuproine method [16] between 1975 and 1986 [17]. Because blood glucose levels are now widely measured with the hexokinase method, the serum glucose levels were adjusted by using a formula ([0.047×(glucose concentration in mg/dl)]−0.541) previously reported by the same laboratory, which gives levels in mmol/l [17]. Iso et al. [17] reported that this formula was obtained from 60 random samples of blood with the regression line (r^2=0.93). Total cholesterol levels were also measured. BMI was calculated as weight (kg) divided by the square of height (m). Obesity was defined as BMI≥25 kg/m^2 [18]. Public health nurses obtained information about past history of diabetes mellitus, time since last

meal, smoking, drinking and medication histories. The nurses measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants after a 5 min rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these. Residential districts were classified as urban, suburban, sub-rural and rural based on the population size of the municipality in which the participants lived [19].

Follow-up survey For deceased participants, the underlying cause of death obtained from National Vital Statistics was coded according to the International Classification of Diseases (ICD), using the 9th revision (ICD9) for the period between 1980 and 1994, and the 10th revision (ICD10) for the period between 1995 and 1999. Deaths from CHD (ICD9: 410–414, ICD10: I20–I25), all heart diseases (ICD9: 410–429, ICD10: I20–I25, I30–I52) and CVD (ICD9: 390–459, ICD10: I00–I99) were defined according to ICD9 and ICD10 codes. The details of the classification in the present study have been described elsewhere [20]. Permission to use National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (number 12–18, 2000).

Statistical analysis Participants were divided into the following three groups according to their CBG levels: (1) less than 7.77 mmol/l (normal); (2) 7.77 to <11.1 mmol/l (borderline high CBG); and (3) ≥11.1 mmol/l or patients with a history of diabetes mellitus (high CBG). In some analyses, the 'normal' CBG group was divided into two groups at their median, i.e. higher normal (CBG 5.22 to <7.77 mmol/l) and lower normal (CBG<5.22 mmol/l). The 'borderline high CBG' and 'high CBG' groups were categorised on the basis of OGTT criteria [21]. According to the OGTT criteria, blood glucose levels from 7.77 to <11.1 mmol/l and ≥11.1 mmol/l at 2 h after glucose intake are defined as impaired glucose tolerance and diabetes mellitus, respectively. In some analyses, we combined higher normal and lower normal into one category.

The risk characteristics of each group at the baseline survey and cause-specific mortality were described as means, standard deviation (SD) for continuous variables and proportions for categorical variables. Analysis of variance was used for comparisons of multiple group means and the χ^2 test was used to compare proportions.

We calculated age- and sex-adjusted hazard ratios (HRs) for CHD deaths for the participants whose CBG levels were ≥7.77 mmol/l by comparing the death rate with that for the group whose CBG levels were <7.77 mmol/l. We divided the participants into four groups by time since last meal to examine the effect of that time on CHD deaths. The four groups were defined as 1, 2, 3–4, and ≥5 h since the last meal. The multivariate-adjusted HRs of all four blood glucose categories for CHD, CVD, all-heart or all-cause morality were calculated using a Cox proportional hazard model adjusted for age, total cholesterol, BMI, hypertension, smoking categories (never smokers, past smokers, smoking ≤20 cigarettes per day or smoking ≥21 cigarettes per day), drinking categories (never drinkers, past drinkers, occasional drinkers or everyday drinkers) and residential districts. We applied dummy variables to the smoking and drinking categories. We defined the lower normal group (i.e. CBG≤5.22 mmol/l) as the reference group. We included sex in the model when analysing the combined dataset of men and women. The trend tests were performed by allocating scores 1, 2, 3 and 4 for all participants in lower normal, higher normal, borderline high CBG and high CBG, respectively. To assess whether the positive relationship between CBG and CHD or CVD mortality was observed in participants within the normal blood glucose range, we analysed the relationship between CBG (continuous levels) and CHD or CVD mortality in participants whose blood glucose levels were <7.77 mmol/l. Additionally, we divided the participants whose blood glucose levels were <7.77 mmol/l into quintiles and calculated multivariate adjusted HRs of CVD mortality to check for a threshold within normal and higher normal CBG. We used a Cox proportional hazard model adjusted for age, total cholesterol, BMI, hypertension, smoking categories, drinking categories and residential districts.

Population-attributable fractions (PAFs) for CHD, all heart disease, CVD and all-cause mortality were calculated as pd×(HR−1)/HR [22], where pd is the proportion of death cases in the groups exposed to the risk, i.e. the borderline high CBG groups and the high CBG groups, and the multiple-adjusted HRs were used for the calculations. When calculating the PAF of the borderline high CBG group alone, the results for the high CBG group were not included. We calculated all PAFs using the combined dataset of men and women.

All confidence intervals were estimated at the 95% level. A p value of <0.05 was considered significant. The Statistical Package for the Social Science (version 11.0J; SPSS Japan, Tokyo, Japan) was used for the analysis.

Results

The age (mean±SD) at the baseline survey for all participants was 50.4±13.2 for men and 50.8±13.3 for women. The mean level of adjusted serum glucose with the hexokinase method was 5.67±1.82 mmol/l for men and 5.59±1.60 mmol/l for women. Table 1 shows baseline

Table 1 Prevalence characteristics stratified by CBG levels at the baseline survey in 1980, NIPPON DATA80

	CBG levels at baseline (mmol/l)				
	Lower normal (<5.22)	Higher normal (5.22≤CBG<7.77)	Borderline high (7.77≤CBG<11.1)	High[a] (≥11.1)	*p* value
Men					
n	1,915	1,814	187	218	<0.01
Age (years)	48.3±12.2	51.3±13.7	54.8±14.0	57.0±11.1	<0.01
S glucose (mmol/l)	4.64±0.50	6.02±0.64	8.83±0.90	9.14±5.03	<0.01
S total chol (mmol/l)	4.80±0.81	4.80±0.86	4.80±0.94	5.06±0.92	<0.01
Current smoker (%)	64.1	61.8	65.3	66.0	0.66
Current drinker (%)	77.0	73.2	66.3	73.0	<0.01
Hypertension (%)	43.1	54.3	61.5	67.0	<0.01
Obesity (%)	18.3	19.8	17.6	24.8	0.11
Residential districts					
Urban (%)	31.7	31.0	28.9	35.3	0.19
Suburban (%)	24.8	22.9	21.9	23.9	
Sub-rural (%)	15.7	15.0	15.5	15.6	
Rural (%)	25.0	28.9	29.9	21.1	
Women					
n	2526	2467	175	142	<0.01
Age (years)	47.4±12.5	53.5±13.3	56.7±11.6	60.3±11.5	<0.01
S glucose (mmol/l)	4.67±0.44	6.00±0.60	8.95±0.88	10.7±5.22	<0.01
S total chol (mmol/l)	4.83±0.84	5.02±0.91	5.12±0.86	5.32±0.86	<0.01
Current smoker (%)	9.0	8.6	9.7	9.1	0.54
Current drinker (%)	21.4	19.0	16.0	15.5	0.19
Hypertension (%)	32.1	48.3	61.1	69.0	<0.01
Obesity (%)	19.6	25.2	25.7	36.6	<0.01
Residential districts					
Urban (%)	31.7	32.3	31.4	32.4	<0.01
Suburban (%)	26.4	21.4	26.3	26.8	
Sub-rural (%)	16.0	15.0	15.4	15.5	
Rural (%)	23.4	28.6	25.7	23.2	

Unless indicated otherwise, values are means (±SD)
ANOVA was used for comparisons of multiple group means and the χ^2 test was used to compare frequencies
Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these. Obesity was defined as BMI≥25 kg/m^2
[a] Participants with a history of diabetes mellitus were placed in the high CBG group
S glucose, serum glucose; S total chol, serum total cholesterol

characteristics of the participants according to the serum glucose category. The higher glucose groups for both sexes had a higher age and higher prevalence of hypertension than lower glucose groups. Serum total cholesterol mean values for women were higher in the higher glucose groups. The prevalence of current smoking for men was higher in the higher glucose groups, but this difference was not statistically significant. The prevalence of obesity was highest in the high CBG groups in both sexes. The prevalence of current drinking and the residential districts for both sexes was not associated with glucose categories.

Diabetes prevalence in our data per 10 year age groups was 1.0% for those in their 30s and 2.4, 5.0, 7.2, 7.3 and 4.8% for those in their 40s, 50s, 60s, 70s and 80s, respectively. When borderline high CBG was included, the prevalence was 3.1, 5.4, 9.7, 13.0, 12.8 and 11.6% for the age groups above. Total person-years were 163,044 (69,946 for men, 93,098 for women) and the mean follow-up period was 17.3 years. During follow-up, we observed 1,911 all-cause deaths (1,025 for men, 886 for women), 137 CHD deaths (68 men, 69 women), 336 all heart diseases (164 men, 172 women) and 692 CVD deaths (345 men, 347 women).

Figure 1 shows age- and sex-adjusted HRs for CHD mortality of participants whose blood glucose levels for given time categories since last meal were ≥7.77 mmol/l compared with those whose CBG levels were <7.77 mmol/l. All HRs were positive regardless of the time since the last meal, though the HR was not statistically significant in the 1 h since last meal category.

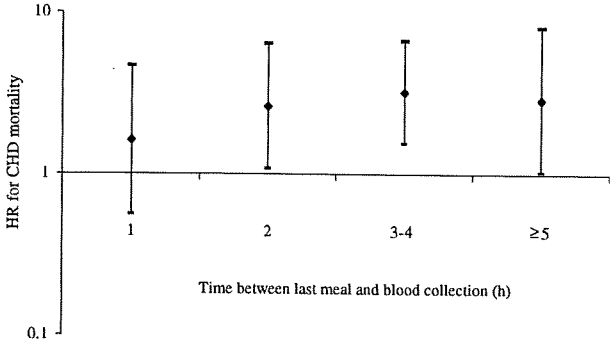

Fig. 1 Age- and sex-adjusted HRs with 95% CIs for CHD deaths in participants whose CBG levels were ≥7.77 mmol/l or who self-reported diabetes mellitus compared with those whose CBG levels were <7.77 mmol/l. Results are grouped according to time in hours between last meal and blood collection time, and a log scale was used. Participants per time category: n=1,164, 1,148, 2,822 and 4,310 for 1, 2, 3–4 and ≥5 h, respectively. HRs per time category: HR=1.62, 2.62, 3.22 and 2.89 for 1, 2, 3–4 and ≥5 h, respectively

Table 2 shows the number of deaths and multivariate adjusted HRs for CHD, all heart diseases, CVD and all-cause mortality. The crude CHD mortality rate was 0.84 per 1,000 person-years in men and women combined (0.97 for men, 0.74 for women). HRs for any cause-specific CVD mortality suggested a graded relationship with glucose categories. HR values for CHD mortality were consistently higher in the high CBG and the borderline high CBG groups than in the reference groups. The HRs for CHD mortality were also higher in the higher normal blood glucose groups than in the reference groups. HRs for CVD and all heart diseases mortality showed similar tendencies. Because no interaction between sex and CBG was observed for CVD (p=0.91), we combined men and women in the following analyses. When we combined lower normal and higher normal into one category as the reference group (i.e. CBG≤7.77 mmol/l), the HRs for CHD mortality were 2.12 (95% CI 1.19–3.79) for borderline high CBG and 2.29 (95% CI 1.36–3.86) for high CBG. Similar findings were observed in both sexes (data not shown). Even when we restricted the analysis to participants with values within the normal blood glucose range (CBG≤7.77 mmol/l), each 1 mmol/l increase in CBG was associated with a significant increase in the HR for CVD mortality (HR 1.12, 95% CI 1.02–1.22). The HR for CHD mortality per 1 mmol/l increase in CBG was similar to that for CVD, but this increase was not significant (HR 1.09, 95% CI 0.89–1.34). When we divided participants within the normal blood glucose range (CBG≤7.77 mmol/l) into quintiles, HRs for CVD mortality

Table 2 The number of deaths and multivariate-adjusted HRs for CHD, all heart diseases, CVD and all-cause mortality according to CBG levels

	Baseline serum CBG, men and women combined			
	Lower normal	Higher normal	Borderline high	High
Glucose (mmol/l)	<5.22	5.22≤CBG<7.77	7.77≤CBG<11.1	≥11.10
n	4,441	4,281	362	360
Person-years	78,635	73,005	5,939	5,465
Cause of death				
CHD				
Deaths (n)	38	69	13	17
Mortality rate[a]	0.5	0.9	2.2	3.1
HR (95% CI)[b]	1	1.24 (0.83–1.86)	2.43 (1.29–4.58)	2.62 (1.46–4.67)
All heart diseases				
Deaths (n)	105	167	29	35
Mortality rate[a]	1.3	2.3	4.9	6.4
HR (95% CI)[b]	1	1.06 (0.83–1.36)	1.78 (1.17–2.70)	2.07 (1.41–3.06)
CVD				
Deaths (n)	205	379	47	61
Mortality rate[a]	2.6	5.2	7.9	11.2
HR (95% CI)[b]	1	1.22 (1.03–1.45)	1.46 (1.06–2.01)	1.82 (1.37–2.43)
All causes				
Deaths (n)	665	976	107	163
Mortality rate[a]	8.5	13.4	18.0	29.8
HR (95% CI)[b]	1	1.07 (0.96–1.18)	1.13 (0.92–1.38)	1.63 (1.37–1.93)

Sex was included in the model, as the combined dataset of men and women was analysed

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these

[a] The mortality rate is the crude mortality rate per 1,000 person-years

[b] The HRs were adjusted for age, serum total cholesterol levels, BMI, hypertension, cigarette smoking categories, drinking categories and residential districts. p<0.001 for all trends

increased gradually in the high CBG groups ($p<0.01$ for trend; Table 3). PAFs of high CBG and borderline high CBG for CHD, all heart diseases, CVD and all-cause mortality were 12.0, 8.8, 4.9 and 3.5%, respectively, compared with normal CBG groups (CBG<7.77 mmol/l). PAFs of high CBG alone for CHD, all heart diseases, CVD and all-cause mortality were 7.0, 5.2, 3.3 and 3.1%, respectively. PAFs of the borderline high CBG alone for CHD, all heart diseases, CVD and all-cause mortality were 5.0, 3.6, 1.5 and 0.4%, respectively.

Discussion

In this study, we found that CBG levels predicted CHD mortality. The risk for CHD mortality increases with CBG levels, regardless of time since last meal. We also found that participants with borderline high CBG or high CBG had higher mortality due to CHD. Furthermore, the data showed that lower blood glucose levels led to lower HRs for CVD mortality, even within the normal blood glucose range.

Our cohort study was conducted with a representative sample from the Japanese population with a long-term follow-up period. The participants were randomly selected from across Japan. The participation rate and follow-up rate were high: more than 75 and 90%, respectively. Thus our data should be applicable to the general Japanese population. Due to our study's representative nature, we were able to assess the PAF of high CBG and borderline high CBG groups for CHD mortality.

Table 3 The number of deaths and multivariate-adjusted HRs for CVD according to CBG levels <7.77 mmol/l divided into five classes, for men and women combined

Cardiovascular diseases					
Baseline CBG (mmol/l)	*n*	Person-years	Deaths (*n*)	Mortality rate[a]	HR (95% CI)[b]
1.40–4.63	1,710	31,552	71	2.3	1
4.68–5.01	1,766	32,905	84	2.6	1.07 (0.78–1.47)
5.06–5.44	1,632	30,485	117	3.8	1.30 (0.97–1.75)
5.48–6.01	1,579	29,826	141	4.7	1.33 (1.00–1.78)
6.05–7.76	1,603	29,655	193	6.5	1.39 (1.06–1.83)

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents or any combination of these

The HRs were adjusted for age, sex, serum total cholesterol levels, BMI, hypertension, cigarette smoking categories, drinking categories and residential districts

[a] The mortality rate is the crude mortality rate per 1,000 person-years

[b] p for trend <0.01

The prevalence of diabetes mellitus in our data at baseline was comparable with that reported in other studies. Sairenchi et al. [23] reported that the diabetes prevalence in men aged 40–59 at baseline was 6.2% in those who survived, 8.4% in participants who died of CVD and 12.4% in those who died of non-CVD causes during a follow-up period of 9 years. The prevalence for women was 2.6, 11.4 and 5.4%, respectively. The corresponding prevalence in those aged 60–79 at baseline was 7.8, 11.4 and 10.7% for men and 5.2, 12.2 and 7.4% for women. The investigators collected non-fasting samples and defined diabetes mellitus as a plasma glucose level ≥7.0 mmol/l (fasting), ≥11.1 mmol/l (non-fasting) or treatment for diabetes mellitus. We believe that these results are consistent with ours. As expected, CHD mortality rates from our data were very low compared with those of other developed countries. Other papers have also pointed out the low CHD mortality in Japan [24, 25]. Although the reason is unclear, various hypotheses have been proposed, e.g. low serum cholesterol levels in Japanese in 1980 compared with westernised countries [11], as well as levels of fish [26] or green tea intake [27] among the Japanese.

In the present study, we were able to show that CBG potentially predicts future CVD mortality. Thus, in some settings, such as community screenings for CVD risk factors, where high participation rates are desired, as well as in clinics normally not visited in a fasting state, CBG could be a viable alternative to OGTT or fasting blood glucose. Our finding on prediction of CVD mortality was also consistent with previous reports. Based on the NIPPON DATA80, the probability of death over a 10 year period from CHD, stroke and CVD was calculated and displayed as colour charts [10]. These charts showed that participants with diabetes mellitus defined as CBG levels ≥11.1 mmol/l had higher CHD, stroke and CVD mortality risks than those without diabetes mellitus. Our results expanded on those results. Irie et al. [6] reported the relationship between CBG obtained in general health check-ups and CHD, CVD and all-cause mortality in a Japanese population. Their study had a large sample with a shorter follow-up period of 5 years. Similarly to our results, they found that the HRs for CHD, CVD and all-cause mortality were higher than the reference groups, even among participants in the borderline high CBG group.

It should, however, be emphasised that although CBG is a feasible way of assessing CVD risk factors in community screenings, it cannot be used for a definitive diagnosis of diabetes because of the difficulty in standardisation. Recently, diabetes risk scores incorporating age, sex, BMI, steroid or antihypertensive medication, family history,