Table 2. Sex- and Age-Adjusted HR and Multivariable HR of Intraparenchymal Hemorrhage According to Lipid Categories

	Lipid Categories					
	(Lower)					(Higher)
LDL cholesterol						
Range, mg/dL	<80	80–99	100–119	120–139	≥140	
Range, mmol/L	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62	
Person-years	85 071	164 778	225 619	201 327	221 685	
No. of events	46	56	56	53	53	
Sex- and age-adjusted HR	1.0	0.62 (0.42–0.91)	0.45 (0.30–0.66)	0.46 (0.31–0.69)	0.43 (0.28–0.64)	
P		0.02	<0.001	<0.001	<0.001	
Multivariable HR	1.0	0.65 (0.44–0.96)	0.48 (0.32–0.71)	0.50 (0.33–0.75)	0.45 (0.30–0.69)	
P		0.03	<0.001	<0.001	<0.001	
Total cholesterol						
Range, mg/dL	<160	160–179	180–199	200–219	220–239	≥240
Range, mmol/L	<4.13	4.13–4.64	4.65–5.16	5.17–5.67	5.68–6.19	≥6.20
Person-years	87 968	145 915	201 150	195 096	139 412	128 939
No. of events	39	58	53	50	35	29
Sex- and age-adjusted HR	1.0	0.95 (0.63–1.42)	0.62 (0.41–0.94)	0.61 (0.40–0.94)	0.59 (0.37–0.94)	0.55 (0.33–0.89)
P		0.80	0.03	0.02	0.03	0.02
Multivariable HR	1.0	0.97 (0.65–1.46)	0.63 (0.42–0.96)	0.62 (0.40–0.95)	0.59 (0.37–0.95)	0.55 (0.33–0.91)
P		0.89	0.03	0.03	0.03	0.02
HDL cholesterol						
Range, mg/dL	<40	40–49	50–59	60–69	≥70	
Range, mmol/L	<1.03	1.03–1.28	1.29–1.54	1.55–1.80	≥1.81	
Person-years	109 174	227 509	251 961	169 678	140 159	
No. of events	42	58	59	57	48	
Sex- and age-adjusted HR	1.0	0.72 (0.48–1.07)	0.71 (0.48–1.06)	1.07 (0.71–1.59)	1.11 (0.73–1.68)	
P		0.10	0.09	0.75	0.63	
Multivariable HR	1.0	0.71 (0.47–1.06)	0.68 (0.46–1.03)	0.99 (0.65–1.51)	0.98 (0.62–1.53)	
P		0.09	0.07	0.97	0.91	
Non-HDL cholesterol						
Range, mg/dL	<100	100–120	120–139	140–159	160–179	≥180
Range, mmol/L	<2.56	2.59–3.08	3.10–3.59	3.62–4.11	4.14–4.63	≥4.65
Person-years	69 361	131 645	190 428	196 428	149 260	161 359
No. of events	41	43	57	51	30	42
Sex- and age-adjusted HR	1.0	0.55 (0.36–0.84)	0.49 (0.32–0.73)	0.42 (0.27–0.63)	0.32 (0.20–0.51)	0.42 (0.27–0.65)
P		0.006	<0.001	<0.001	<0.001	<0.001
Multivariable HR	1.0	0.56 (0.36–0.86)	0.51 (0.34–0.77)	0.43 (0.28–0.66)	0.33 (0.20–0.54)	0.42 (0.26–0.68)
P		0.009	0.001	<0.001	<0.001	<0.001
Triglycerides						
Range, mg/dL	<100	100–149	150–199	200–249	250–299	≥300
Range, mmol/L	<1.12	1.12–1.68	1.69–2.24	2.25–2.81	2.82–3.37	≥3.38
Person-years	333 991	265 519	145 676	73 544	36 395	43 357
No. of events	98	90	35	18	9	14
Sex- and age-adjusted HR	1.0	1.04 (0.78–1.38)	0.74 (0.50–1.08)	0.76 (0.46–1.26)	0.80 (0.40–1.58)	1.16 (0.66–2.03)
P		0.80	0.12	0.29	0.52	0.61
Multivariable HR	1.0	1.06 (0.79–1.42)	0.76 (0.51–1.14)	0.77 (0.46–1.29)	0.81 (0.41–1.64)	1.13 (0.63–2.02)
P		0.70	0.19	0.32	0.56	0.69

Multivariable HR (95% CI) was adjusted for sex, age, and other cardiovascular risk factors.

Other cardiovascular risk factors included blood pressure categories, antihypertensive medication use, diabetes mellitus, lipid medication use, body mass index, γ-glutamyl transferase, smoking status, alcohol consumption, and kidney dysfunction.

Table 3. Multivariable HR and 95% CI of Intraparenchymal Hemorrhage at Extremely Low Levels of LDL Cholesterol

	LDL Cholesterol Categories						
Range, mg/dL	<60	60–69	70–79	80–99	100–119	120–139	≥140
Range, mmol/L	<1.55	1.55–1.80	1.81–2.05	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62
Person-years	18 379	23 312	43 380	164 778	225 619	201 327	221 685
No. of events	17	11	18	56	56	53	53
Multivariable HR		1.0 (Reference)		0.65 (0.44–0.96)	0.48 (0.32–0.71)	0.50 (0.33–0.75)	0.45 (0.30–0.69)
P				0.03	<0.001	<0.001	<0.001
Multivariable HR	1.0 (Reference)	0.50 (0.27–0.91)		0.40 (0.23–0.69)	0.29 (0.17–0.51)	0.30 (0.17–0.53)	0.28 (0.16–0.49)
P		0.02		0.001	<0.001	<0.001	<0.001
Multivariable HR	1.0 (Reference)	0.52 (0.24–1.12)	0.49 (0.25–0.94)	0.40 (0.23–0.69)	0.29 (0.17–0.51)	0.30 (0.17–0.53)	0.28 (0.16–0.49)
P		0.09	0.03	0.001	<0.001	<0.001	<0.001

Multivariable HR (95% CI) was adjusted for sex, age, and other cardiovascular risk factors.

0.92; $P=0.03$) in the time-dependent covariate Cox proportional hazard model. We also excluded persons with lipid medication use (n=2273) at baseline inquiry and confirmed that there were no differences in the association between LDL cholesterol and death due to intraparenchymal hemorrhage before and after such exclusion; the multivariable HR for highest versus lowest categories of LDL cholesterol was 0.45 (0.30 to 0.69; $P<0.001$) after this exclusion.

To examine the effect of extremely low levels of LDL cholesterol on death due to intraparenchymal hemorrhage, we subgrouped persons with LDL <80 mg/dL into those with <60 mg/dL, 60 to 69 mg/dL, and 70 to 79 mg/dL (Table 3). Compared with persons with <60 mg/dL of LDL cholesterol (number of events=17), the multivariable HR of death due to intraparenchymal hemorrhage was 0.52 (0.24 to 1.12; $P=0.09$) for those with LDL cholesterol 60 to 69 mg/dL (number of events=11); 0.49 (0.25 to 0.94; $P=0.03$) for 70 to 79 mg/dL (number of events=18); 0.40 (0.23 to 0.69; $P=0.001$) for 80 to 99 mg/dL; 0.29 (0.17 to 0.51; $P<0.001$) for 100 to 119 mg/dL; 0.30 (0.17 to 0.53; $P<0.001$) for 120 to 139 mg/dL; and 0.28 (0.16 to 0.49; $P<0.001$) for ≥140 mg/dL.

To examine the effect of competing risks, we also conducted sensitivity analysis (Table 4). The HR did not change substantially among each model of sensitivity analysis except

in worst-case scenario 1. Although the association in worst-case scenario 1 became weaker, the effect of low LDL cholesterol for increased risk of death due to intraparenchymal hemorrhage remained statistically significant.

The inverse association between LDL cholesterol and cardiovascular disease mortality was confined to intraparenchymal hemorrhage (Table 5). LDL cholesterol levels were positively associated with death due to coronary heart disease, and the multivariate hazard ratio was 1.50 (1.07 to 2.10; $P=0.02$) for the highest versus lowest LDL cholesterol level. When death due to intraparenchymal hemorrhage and coronary heart disease was combined, we found a U-shaped relationship between LDL cholesterol and mortality risk, with a nadir at LDL cholesterol levels of 120 to 139 mg/dL (3.10 to 3.61 mmol/L). There was no significant association of LDL cholesterol with death due to subarachnoid hemorrhage or ischemic stroke.

The inverse associations between LDL cholesterol and intraparenchymal hemorrhage were examined, stratified by sex, hypertension, fasting, smoking, and drinking status (Table 6). The associations did not vary by sex, hypertension, fasting, or smoking status. We observed an inverse association among current drinkers versus nondrinkers, although statistically significant associations were observed even among nondrinkers.

Table 4. Sensitivity Analysis of Multivariable HR and 95% CI of Intraparenchymal Hemorrhage

	LDL Cholesterol Categories, mmol/L				
	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62
Stratified Cox proportional hazard model	1.0	0.65 (0.44–0.97)	0.48 (0.32–0.72)	0.51 (0.34–0.76)	0.47 (0.31–0.71)
		$P=0.03$	$P<0.001$	$P=0.001$	$P<0.001$
Proportional hazard model for the subdistribution	1.0	0.67 (0.45–0.98)	0.49 (0.33–0.73)	0.52 (0.34–0.78)	0.47 (0.31–0.71)
		$P=0.04$	$P<0.001$	$P=0.002$	$P<0.001$
Worst-case scenario 1	1.0	0.84 (0.79–0.90)	0.78 (0.72–0.83)	0.73 (0.68–0.79)	0.76 (0.71–0.82)
		$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
Worst-case scenario 2	1.0	0.66 (0.45–0.99)	0.49 (0.33–0.74)	0.52 (0.34–0.78)	0.47 (0.31–0.72)
		$P=0.04$	$P<0.001$	$P=0.002$	$P<0.001$

Multivariable HR (95% CI) was adjusted for age, sex, and other cardiovascular risk factors.

Worst-case scenario 1: All subjects censored because of disease other than intraparenchymal hemorrhage or who moved out of the communities were assumed to have died of intraparenchymal hemorrhage instead. Worst-case scenario 2: All subjects censored because of disease other than intraparenchymal hemorrhage or who moved out of the communities were assumed to have survived as long as the longest survival time (until the end of 2003) observed in the present study.

Table 5. Crude Mortality Rate (per 100 000 Person-Years) and Multivariable HR and 95% CI of Intraparenchymal Hemorrhage and Other Cardiovascular Disease According to LDL Cholesterol Categories

	LDL Cholesterol Categories, mmol/L				
	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62
All-cause mortality					
No. of events	1049	1490	1727	1422	1456
Crude mortality rate	1233 .	904	765	706	657
Multivariable HR	1.0	0.81 (0.74–0.87)	0.72 (0.66–0.78)	0.67 (0.62–0.73)	0.66 (0.61–0.72)
P		<0.001	<0.001	<0.001	<0.001
Total cardiovascular disease					
No. of events	261	384	478	407	484
Crude mortality rate	307	233	212	202	218
Multivariable HR	1.0	0.80 (0.68–0.94)	0.76 (0.65–0.89)	0.72 (0.62–0.85)	0.82 (0.70–0.96)
P		<0.001	<0.001	<0.001	0.07
Total stroke					
No. of events	141	195	235	203	218
Crude mortality rate	166	118	104	101	98
Multivariable HR	1.0	0.73 (0.59–0.91)	0.67 (0.54–0.83)	0.65 (0.52–0.81)	0.67 (0.54–0.84)
P		<0.001	<0.001	<0.001	<0.001
Hemorrhagic stroke					
No. of events	70	93	103	92	96
Crude mortality rate	82	56	46	46	43
Multivariable HR	1.0	0.70 (0.51–0.95)	0.56 (0.41–0.77)	0.54 (0.39–0.75)	0.51 (0.37–0.71)
P		0.02	<0.001	<0.001	<0.001
Subarachnoid hemorrhage					
No. of events	24	37	47	39	43
Crude mortality rate	28	22	21	19	19
Multivariable HR	1.0	0.79 (0.47–1.33)	0.73 (0.44–1.20)	0.64 (0.38–1.08)	0.62 (0.37–1.05)
P		0.38	0.22	0.10	0.07
Intraparenchymal hemorrhage					
No. of events	46	56	56	53	53
Crude mortality rate	54	34	25	26	24
Multivariable HR	1.0	0.65 (0.44–0.96)	0.48 (0.32–0.71)	0.50 (0.33–0.75)	0.45 (0.30–0.69)
P		0.03	<0.001	<0.001	<0.001
Ischemic stroke					
No. of events	71	102	132	111	122
Crude mortality rate	83	62	59	55	55
Multivariable HR	1.0	0.75 (0.55–1.02)	0.77 (0.58–1.04)	0.75 (0.55–1.02)	0.85 (0.62–1.15)
P		0.07	0.09	0.07	0.29
Coronary heart disease					
No. of events	48	96	130	109	156
Crude mortality rate	56	58	58	54	70
Multivariable HR	1.0	1.14 (0.81–1.62)	1.19 (0.85–1.67)	1.11 (0.78–1.57)	1.50 (1.07–2.10)
P		0.45	0.31	0.57	0.02
Intraparenchymal hemorrhage and coronary heart disease					
No. of events	94	152	186	162	209
Crude mortality rate	110	92	82	80	94
Multivariable HR	1.0	0.90 (0.70–1.17)	0.84 (0.65–1.08)	0.81 (0.62–1.05)	0.97 (0.75–1.26)
P		0.43	0.17	0.11	0.83

Crude mortality rate was described as number of deaths per 100 000 person-years.

Multivariable HR (95% CI) was adjusted for age, sex, and other cardiovascular risk factors. For cause-specific analyses, persons who died of other causes were treated as censored.

Table 6. Multivariable HR and 95% CI of Intraparenchymal Hemorrhage According to LDL Cholesterol Categories, Stratified by Sex and Other Related Variables

	LDL Cholesterol Categories, mmol/L					
	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	≥3.62	P for Interaction
Men						
No. of events	34	29	31	17	14	
Multivariable HR	1.0	0.57 (0.34–0.94)	0.52 (0.32–0.86)	0.39 (0.21–0.71)	0.41 (0.21–0.77)	
P		0.03	0.01	0.002	0.006	
Women						
No. of events	12	27	25	36	39	
Multivariable HR	1.0	0.88 (0.45–1.74)	0.50 (0.25–1.00)	0.67 (0.35–1.30)	0.57 (0.30–1.10)	0.18
P		0.71	0.05	0.24	0.09	
Nonhypertensive						
No. of events	13	18	13	16	10	
Multivariable HR	1.0	0.68 (0.33–1.39)	0.36 (0.16–0.78)	0.50 (0.23–1.06)	0.31 (0.13–0.72)	
P		0.29	0.01	0.07	0.007	
Hypertensive*						
No. of events	33	38	43	37	43	
Multivariable HR	1.0	0.62 (0.39–0.99)	0.51 (0.32–0.82)	0.48 (0.29–0.78)	0.51 (0.31–0.82)	0.42
P		0.05	0.005	0.003	0.006	
Nonfasting						
No. of events	43	50	51	46	44	
Multivariable HR	1.0	0.62 (0.41–0.94)	0.48 (0.32–0.73)	0.49 (0.32–0.76)		
P		0.02	<0.001	0.001	<0.001	
Fasting†						
No. of events	3	6	5	7	9	
Multivariable HR	1.0	0.94 (0.23–3.83)	0.45 (0.10–1.97)	0.63 (0.15–2.56)	0.54 (0.13–2.18)	0.99
P		0.93	0.29	0.52	0.38	
Nonsmoker						
No. of events	28	44	43	41	44	
Multivariable HR	1.0	0.72 (0.45–1.17)	0.48 (0.30–0.78)	0.48 (0.29–0.78)	0.45 (0.28–0.73)	
P		0.19	0.003	0.003	0.001	
Current smoker						
No. of events	18	12	13	12	9	
Multivariable HR	1.0	0.50 (0.24–1.04)	0.50 (0.24–1.04)	0.62 (0.29–1.33)	0.57 (0.24–1.35)	0.94
P		0.06	0.06	0.22	0.20	
Nondrinker						
No. of events	24	31	36	41	48	
Multivariable HR	1.0	0.53 (0.31–0.91)	0.41 (0.24–0.69)	0.47 (0.28–0.79)	0.47 (0.28–0.77)	
P		0.02	<0.001	0.004	0.003	
Current drinker						
No. of events	22	20	19	11	5	
Multivariable HR	1.0	0.68 (0.37–1.25)	0.57 (0.30–1.07)	0.47 (0.22–0.99)	0.27 (0.10–0.72)	0.07
P		0.21	0.08	0.05	0.01	

Multivariable HR (95% CI) was adjusted for age, sex, and other cardiovascular risk factors except stratified factors.
*Hypertensive was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or as use of medication for hypertension.
†Fasting was defined as having a blood sample taken ≥8 hours after the last meal.

Discussion

In the large population-based prospective study of Japanese reported here, we observed a significant association between low LDL cholesterol levels and increased risk of death due to intraparenchymal hemorrhage. These associations were not altered substantially after adjustment for known risk factors, the use of time-dependent covariates, the exclusion of persons with hypertriglyceridemia, or by stratification by sex, hypertension, fasting, smoking, and drinking status.

To examine the potential effect of competing risks, we conducted sensitivity analysis. We found a statistically significant association between low LDL cholesterol and increased risk of death due to intraparenchymal hemorrhage among all models of the sensitivity analysis, which suggests that the effect of competing risks may be small.

Arteriolosclerosis is characterized by angionecrosis of smooth muscles cells and an increase in basement membrane–like substance in the outer layer of smooth muscle cells of intracerebral arteries in the basal ganglia, thalamus, and brain stem.[2,3] A hypercholesterolemic diet reduces angionecrosis and prevents occurrence of hemorrhagic stroke among spontaneously hypertensive rats,[4] and higher intake of saturated fat, which leads to higher LDL cholesterol concentrations, was shown to be associated with reduced risk of intraparenchymal hemorrhage for both Japanese and Americans.[32] Furthermore, low LDL cholesterol concentrations were associated with multifocal signal loss lesion detected on T2*-weighted gradient-echo (GE) MRI,[33] which was a predictor of intraparenchymal hemorrhage.[34] Moreover, a recent randomized clinical trial for LDL cholesterol lowering with high-dose atorvastatin after stroke or transient ischemic attack demonstrated a reduction of risk for overall fatal stroke but an increase in risk of hemorrhagic stroke.[35] The mean LDL cholesterol level among patients receiving atorvastatin during the trial was 73 mg/dL.[35] Although it is difficult to confirm the causality between low LDL cholesterol and increased risk of intraparenchymal hemorrhage through the present observational study only, the consistency of epidemiological and experimental evidence stated above also supports a causal relationship.

Many previous population-based cohort studies,[5–20] but not all,[17,21] revealed a similar association between low total cholesterol, but not LDL cholesterol, and increased risk of intraparenchymal hemorrhage. In the present study, the association with total cholesterol was weaker than that with LDL cholesterol, probably due to surrogate dilution bias.[36] We also observed an association between high LDL cholesterol and increased risk of death due to coronary heart disease, consistent with the large body of evidence from previous cohort studies.[22,36]

There was a U-shaped relationship between LDL cholesterol and combined death due to intraparenchymal hemorrhage and coronary heart disease, with a nadir at LDL cholesterol levels of 120 to 139 mg/dL (3.10 to 3.61 mmol/L), because these 2 outcomes have an opposite direction in the association with LDL cholesterol. On the other hand, we observed inverse associations of LDL cholesterol with death due to total cardiovascular disease and all-cause mortality, because the Japanese population had high rates of death due to total stroke, with a high proportion of intraparenchymal hemorrhage, and low rates of death due to coronary heart disease compared with Americans. A previous study of Americans showed a U-shaped relationship between LDL cholesterol and all-cause mortality, with a nadir at LDL cholesterol levels of 160 to 189 mg/dL (4.14 to 4.90 mmol/L) for men and 130 to 159 mg/dL (3.36 to 4.12 mmol/L) for women.[37] Because the present study population had a lower mean level of LDL cholesterol (119 mg/dL [3.09 mmol/L])

and lower mortality rate due to coronary heart disease (60 per 100 000 person-years), it was difficult to identify the effect of high LDL cholesterol on increased risk of all-cause mortality.

We found no significant association of low LDL cholesterol with death due to subarachnoid hemorrhage, probably because the pathological mechanism in subarachnoid hemorrhage differs from that in intraparenchymal hemorrhage.[3] On the other hand, we observed a significant association with death due to hemorrhagic stroke, more specifically intraparenchymal hemorrhage.

A limitation of the present study is that we estimated LDL cholesterol levels using the Friedewald formula, which cannot be used for specific metabolic conditions such as hypertriglyceridemia and which was constructed based on fasting subjects.[28] However, there was no change in the association between LDL cholesterol and intraparenchymal hemorrhage after the exclusion of persons with hypertriglyceridemia at the baseline survey and after stratification by fasting status. Second, we used mortality data based on death certificate diagnoses; however, validation studies have shown that death certificate diagnosis with regard to stroke and its subtypes is valid because of the high use of CT scans and MRIs in general hospitals in Japan.[29] Third, we had no incidence data; thus, it remains unclear whether LDL cholesterol may be associated with increased risk of nonfatal intraparenchymal hemorrhage. Fourth, because drinking status was ascertained by interview survey, nondrinkers could be contaminated with drinkers; however, only 5.2% of nondrinkers designated themselves as current drinkers 5 years after the baseline survey (3.8% as occasional drinkers and only 0.02% as heavy drinkers). Thus, the potential effect of misclassification is unlikely to be large. Fifth, we could not obtain data on hepatic cirrhosis and its indicators (eg, international normalized ratio of prothrombin time) in the baseline inquiry; however, the prevalence of hepatic cirrhosis was only 0.03% (1 of 2917 persons) in community-based samples from Ibaraki prefecture,[29] which suggests that the effect of residual confounding by the existence of hepatic cirrhosis would be small. Moreover, although it was difficult to examine the effect of extremely low levels of LDL cholesterol on death due to intraparenchymal hemorrhage because of the small sample size, we observed a consistent inverse association between LDL cholesterol and death due to intraparenchymal hemorrhage among persons with LDL <100 mg/dL, which includes the target LDL cholesterol level for prevention of coronary heart disease.[38] Finally, extrapolation of the results to the general population must be done carefully. The study subjects were selected from the general population, but the participation rate was only 36.4%. However, the standard mortality ratio did not differ from that in the total Japanese population,[24] which suggests that the potential selection bias is small.

The strength of the present study is that we had standardized lipid measurement values in a single laboratory, which in turn was standardized by the CDC-NHLBI Lipid Standardized Program.[26] This justifies our assumption that misclassification bias due to lipid measurement errors has been reduced appropriately and that the resultant accuracy of lipid

measurement has led to comparable results with previous well-standardized studies.

In conclusion, the present study provides epidemiological evidence that low LDL cholesterol levels are associated with increased risk of death due to intraparenchymal hemorrhage. Low LDL cholesterol may be an independent risk factor for intraparenchymal hemorrhage.

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CLINICAL PERSPECTIVE

Previous studies have suggested that low total cholesterol levels are associated with an increased risk of intraparenchymal hemorrhage. The present study extends the evidence of an association between low total cholesterol levels and hemorrhage risk. We showed an association between low low-density lipoprotein cholesterol (<80 mg/dL [<2.06 mmol/L]) and increased risk of death due to intraparenchymal hemorrhage in the general population. The basic pathology of intraparenchymal hemorrhage is arteriolosclerosis, characterized by angionecrosis (destruction) of smooth muscle cells in intracerebral small arteries, as opposed to atherosclerosis (plaque formation) in medium to large arteries. Low-density lipoprotein cholesterol may have an opposite effect on development of intraparenchymal hemorrhage than on coronary heart disease. The present finding suggests that low low-density lipoprotein cholesterol may be an independent risk factor for intraparenchymal hemorrhage.

The Complex Relationship Between Cholesterol and Brain Hemorrhage

Larry B. Goldstein, MD

In this issue of *Circulation*, Noda et al[1] report an association between low levels of low-density lipoprotein cholesterol (LDL-C) and an increase in the risk of fatal intraparenchymal intracerebral hemorrhage in a Japanese population-based cohort. The relationship between lipid levels and stroke is complex. The Prospective Studies Collaboration conducted a meta-analysis evaluating the association between blood cholesterol and vascular mortality based on data from 61 prospective cohort studies including nearly 900 000 persons free of vascular disease at baseline (11.6 million person-years at risk).[2] Lower levels of usual total cholesterol were strongly associated with lower risk of fatal ischemic heart disease; every 1 mmol/L lower cholesterol was associated with a 56% reduction (hazard ratio [HR], 0.44; 95% CI, 0.42 to 0.48) in those 40 to 49 years of age, a 34% reduction (HR, 0.66; 95% CI, 0.65 to 0.68) in those 50 to 69 years of age, and a 17% reduction (HR, 0.83; 95% CI, 0.81 to 0.85) in those 70 to 89 years of age. In contrast to death resulting from ischemic heart disease, there was only a weak relationship between usual total cholesterol and death caused by stroke in those 40 to 59 years of age (HR, 0.90; 95% CI, 0.84 to 0.97 for every 1 mmol/L lower cholesterol) and no relationship for older age groups after accounting for blood pressure. An analysis combing the data for the Prospective Studies Collaboration with data from the Multiple Risk Factors Intervention Trial (MRFIT) also found that lower usual total cholesterol was associated with a lower risk of fatal stroke in those 40 to 49 years of age (HR, 0.87; 95% CI, 0.76 to 1.00 per 1 mmol/L lower total cholesterol), with similar reductions in those 50 to 59 (HR, 0.91; 95% CI, 0.85 to 0.97) and 60 to 69 (HR =0.93; 95% CI 0.89 to 0.97) years of age but no reductions in those >70 years of age.[2] There was no relationship between non–high-density lipoprotein cholesterol and stroke risk at any age. Data for analyses based on stroke subtype were limited because many of the studies did not verify whether a stroke was due to ischemia or hemorrhage with neuroimaging. The MRFIT included an analysis of the relationship between total cholesterol and fatal brain hemorrhage.[3] Intracranial hemorrhage was 3 times more common (*P*=0.05) in men with serum cholesterol levels

<160 mg/dL compared with those with higher levels, whereas higher levels were associated with an increased risk of ischemic stroke (*P*=0.007). Although there were too few deaths for meaningful analysis, there was no apparent relationship between non–high-density lipoprotein cholesterol and stroke subtype.

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The Prospective Studies Collaboration meta-analysis was based primarily on studies conducted in North America and Western Europe, and MRFIT was done in the United States. The study by Noda et al was carried out in Japan. The Asia-Pacific Cohort collaborators analyzed combined data from 29 regional studies.[4] There was a 25% (95% CI, 13 to 40) increased risk of fatal ischemic stroke but a 20% (95% CI, 8 to 30) decreased risk of fatal hemorrhagic stroke for every 4.5-mg/dL increase in total cholesterol. Therefore, in both Western and Asian populations, the relationship between usual total cholesterol and overall stroke may be at least partially obscured by competing risks; higher levels of total cholesterol tend to be associated with an increased risk of ischemic stroke, with lower levels associated with an increased risk of hemorrhagic stroke.

Consistent with the previously cited reports, after multivariable adjustment, the present study identified a lower risk of parenchymal brain hemorrhage associated with higher total cholesterol (HR, 0.55; 95% CI, 0.33 to 0.91; *P*=0.02 for total cholesterol >240 versus <160 mg/dL) but, in addition, found a somewhat stronger relationship with LDL-C (HR, 0.45; 95% CI, 0.30 to 0.69; *P*<0.001 for LDL-C >140 versus <80 mg/dL). The 95% CIs for the point estimates based on these 2 lipid indexes overlap and therefore do not differ significantly. The observation suggesting a relationship between LDL-C and brain hemorrhage supports the findings from a pooled cohort of the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS).[5] Multivariable analysis found that older age, black ethnicity, hypertension, lower LDL-C, and lower triglycerides were independently associated with an increased risk of intracerebral hemorrhage. Although uncontrolled hypertension was the strongest risk factor for hemorrhage, the relative rate for the highest compared with the lowest quartile of LDL-C was 0.52 (95% CI, 0.31 to 0.88; *P*=0.008). The relationship between low, usual LDL-C and brain hemorrhage is further supported by a Korean study using T2*-weighted gradient-echo magnetic resonance imaging to detect "micobleeds," areas of old extravasation of blood thought to be associated with an increased risk of intracerebral hemorrhage.[6] Both total cholesterol and LDL-C levels were lower in those with

compared with those without such magnetic resonance imaging findings.

Although low, usual total cholesterol and LDL-C levels in persons free of cardiovascular disease or stroke appear to be associated with a higher risk of brain hemorrhage, this does not mean that treating patients with vascular disease with lipid-lowering medications increases risk. A meta-analysis of data from 90 056 participants in 14 randomized trials of statins found that treatment was associated with a 12% reduction in all-cause mortality per 1-mmol/L reduction in LDL-C (rate ratio [RR], 0.88; 95% CI, 0.84 to 0.91; $P<0.0001$) and reductions in myocardial infarction or coronary death (RR, 0.77; 95% CI, 0.74 to 0.80; $P<0.0001$) and in fatal or nonfatal stroke (RR, 0.83; 95% CI, 0.78 to 0.88; $P<0.0001$).[7] There was no increase in brain hemorrhage with treatment (RR, 1.05; 95% CI, 0.78 to 1.41). This is consistent with another meta-analysis that found no relationship between statin therapy and the risk of hemorrhagic stroke (n=54 334; RR, 0.94; 95% CI, 0.68 to 1.30).[8] The same lack of relationship between lipid lowering with statins and hemorrhagic stroke risk appears to be true in Japanese primary prevention populations.[9] Even achieving very low levels of LDL-C (ie, <40 mg/ dL[10] or <64 mg/dL[11]) with statins in patients with coronary heart disease is not associated with an increased risk of brain hemorrhage.

The situation is somewhat more complicated in patients with a prior history of stroke. Secondary analysis of data from the subgroup of patients enrolled in the Heart Protection Study with prior cerebrovascular disease found a nonstatistically significant increase in hemorrhagic stroke in those treated with simvastatin 40 mg/d versus placebo (n=21 [1.3%] versus n=11 [0.7%]).[12] There was, however, statistical heterogeneity between those with and without a prior stroke history for the risk of brain hemorrhage (P=0.03). The Stroke Prevention With Aggressive Reduction of Cholesterol Levels (SPARCL) trial cited by Noda et al in their discussion was a pure secondary cerebrovascular prevention trial.[13] Subjects with a stroke or transient ischemic attack within the preceding 1 to 6 months, an LDL-C between 100 and 190 mg/dL, and no known coronary heart disease were randomized to atorvastatin 80 mg/d or placebo. The overall treatment-related benefit in reducing the risk of the primary end point (fatal or nonfatal stroke; adjusted HR, 0.84; 95% CI, 0.71 to 0.99; P=0.03; unadjusted P=0.05) was partially attenuated by a treatment-related increase in brain hemorrhage (HR, 1.66; 95% CI, 1.08 to 2.55). Thus, the relationship between statin therapy and the risk of brain hemorrhage may be different in patients with a history of cerebrovascular disease (who overall still benefit from statin treatment) compared with those without such a history.

Noda et al[1] write, "Although it is difficult to confirm the causality between low LDL cholesterol and increased risk of intraparenchymal hemorrhage through the present observational study only, the consistency of epidemiological and experimental evidence [referring to the SPARCL trial in which the average on-treatment LDL-C was 73 mg/dL] ... supports a causal relationship" (p 2143).

Although the epidemiological data based on usual total cholesterol and LDL-C levels suggest an association between

low levels and increased risk of brain hemorrhage, as reviewed above, there is no evidence of a relationship between cholesterol levels and bleeding risk in patients with coronary heart disease whose lipid levels have been lowered medically. Furthermore, exploratory analyses of SPARCL trial data found that the risk of hemorrhage was independently related to treatment assignment, age, sex, a baseline hemorrhage, and uncontrolled hypertension.[14] The risk of hemorrhage was unrelated to LDL-C levels in statin-treated subjects.[14] Regardless of treatment assignment, there were no increase in hemorrhagic stroke in those who had the greatest reductions in LDL-C (HR, 1.04; 95% CI, 0.61 to 1.78; P=0.8864) and no LDL-C threshold below which the risk of brain hemorrhage was increased.[15]

Establishing causality based on statistical associations from observational studies is always hazardous. In the general population, having low, usual total cholesterol and LDL-C appears to be associated with a higher risk of brain hemorrhage. In contrast, there is no evidence of a similar relationship in persons whose total cholesterol and LDL-C levels have been lowered therapeutically. This suggests no causal relationship between total cholesterol and LDL-C and bleeding risk.

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Disclosures

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Correspondence

Letter by Noda and Iso Regarding Article, "Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study"

To the Editor:

We reported an association between low low-density lipoprotein (LDL) cholesterol and increased death due to intraparenchymal hemorrhage in the general Japanese population aged 40 to 79 years in the April 28, 2009, issue of *Circulation*.[1] In his accompanying editorial, Dr Goldstein pointed out that the results were inconsistent between observational studies and randomized clinical trials (RCTs) and concluded, "This suggests no causal relationship between total cholesterol and LDL-C and bleeding risk," based on the previous RCTs.[2] However, the previous RCTs had several limitations and do not necessarily support a conclusion of no causal relationship between low-LDL cholesterol and risk of intraparenchymal hemorrhage.

First, our observational study showed a nonlinear association between LDL cholesterol and risk of intraparenchymal hemorrhage: We observed a negative dose–response association for LDL cholesterol levels <100 mg/dL, whereas the risk plateaued for LDL cholesterol levels >100 mg/dL.[1] Therefore, any increased risk during intervention may depend on the LDL cholesterol levels achieved during the follow-up. The RCTs that showed no associations had inadequate statistical power (generally, ≤36%) to detect such associations. Even the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, in which participants had relatively low LDL cholesterol, had only 51% statistical power. The post hoc analyses in the SPARCL trial also had low statistical power.

The second limitation is the short intervention period (≈5 years) of these RCTs. A previous meta-analysis of cholesterol-lowering RCTs for coronary heart disease prevention showed that the trials with longer intervention periods had a larger difference between intervention and control groups than did those with shorter periods,[3] probably because of the long-term effect of cholesterol lowering. Inasmuch as an effect of low LDL cholesterol on development of intraparenchymal hemorrhage is expected to appear in the long term (ie, over several decades), previous short-term RCTs likely underestimated the association.

Third, the previous RCTs did not discriminate intraparenchymal hemorrhage from subarachnoid hemorrhage. Because the low cholesterol effect is thought to be confined to intraparenchymal hemorrhage,[4] which constitutes only 37% of hemorrhagic stroke in Western populations,[5] the nondiscrimination of hemorrhagic strokes may have resulted in underestimating the association.[1]

Finally, the progression of physiological conditions in observational and intervention studies may be different. Observational studies deal with initially low LDL cholesterol levels, whereas intervention studies usually deal with initially high LDL cholesterol, which is reduced to moderate-to-low LDL cholesterol levels during intervention. Furthermore, statins used in the RCTs may have pleiotropic effects (eg, antiinflammatory and antithrombotic effects) rather than cholesterol-lowering effects, which make any causal inference complex.

Whereas RCTs are useful for establishing causal inference, especially where relatively short-term change affects risk, RCTs that are not designed to examine the relationship between low LDL cholesterol and risk of intraparenchymal hemorrhage are not always superior to observational studies. The effect of cholesterol lowering to low levels for a long period has not been tested in previous RCTs, to our knowledge, so only the observational studies are available for this judgment. We need to carefully weigh results from both observational and intervention studies in order to draw causal inferences.

Disclosures

None.

Hiroyuki Noda, MD
Harvard Center for Population and Development Studies
Harvard School of Public Health
Cambridge, Mass

Hiroyasu Iso, MD
Public Health
Department of Social and Environmental Medicine
Osaka University, Graduate School of Medicine
Osaka, Japan

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Correspondence

Letter by Drinka Regarding Article, "Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study"

To the Editor:

Noda et al[1] reported that reduced low-density lipoprotein levels were associated with an elevated risk of death due to intraparenchymal hemorrhage. Lesions of the penetrating branches of cerebral arteries cause lacunar infarcts and hemorrhagic stroke. Fisher examined serial sections from the parent artery through the lacunae.[2,3] He found atheroma and thrombosis in some and obstructing lipohyalin degeneration in others. Atheroma involved arteries 400 to 900 μ in diameter, whereas lipohyalin degeneration involved arteries <200 μ in diameter. Lipohyalin degeneration produced a thinned wall composed of connective tissue shreds. In some patients this resulted in false aneurysm resembling the Charcot-Bouchard aneurysms of brain hemorrhage. The location of lesions in the penetrating arteries (ie, proximal atheromas versus distal lipohyalin degeneration) may explain an inverse relationship between cholesterol and hemorrhagic stroke. Perhaps atheromatous proximal flow restriction facilitated by elevated low-density lipoproteins protects the distal artery from hypertension, lipohyalin degeneration, false aneurysm formation, and hemorrhagic rupture.

Disclosures

None.

Paul Drinka, MD
Medical College of Wisconsin
Milwaukee, Wis

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Response to Letter Regarding Article, "Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study"

We thank Dr Drinka for his interest in our study[1] and the opportunity to clarify several issues. Dr Drinka presented one possible causal pathway that might link reduced low-density lipoprotein (LDL) cholesterol with the development of arteriolosclerosis and increased risk of intraparenchymal hemorrhage. This hypothesis asserts that distal lipohyalin degeneration (destruction: arteriolosclerosis) may be protected against by proximal atheromatous degeneration (plaque formation: atherosclerosis) through the flow restriction and consequent lower blood pressure in the distal penetrating artery. The lower risk of intraparenchymal hemorrhage associated with higher LDL cholesterol levels may be explained in part by his flow restriction hypothesis. Although we consider the proposed causal pathway to be plausible, we do not consider this explanation to be the major one involving low LDL cholesterol for the following reasons.

First, if it were true that atheromatous degeneration prevents the development of arteriolosclerosis, increased risk of intraparenchymal hemorrhage should be observed at levels of LDL cholesterol at which the risk of coronary heart disease decreases. However, in our study the increased risk of death from intraparenchymal hemorrhage was observed at a level of LDL cholesterol <100 mg/dL, whereas death from coronary heart disease plateaued in this range. Second, low high-density lipoprotein cholesterol and high triglycerides, which may lead to atheromatous degeneration, were not associated with reduced death from intraparenchymal hemorrhage.

Our finding supports Konishi's osmotic fragility hypothesis[2] that very low levels of serum cholesterol in the intimal cell membranes of intracerebral arteries contribute to plasma insudation into the intima because of reduced osmotic resistance, which leads to the destruction of smooth muscle cells in the media and increased risk of intraparenchymal hemorrhage.[3] This hypothesis was also supported by a community-based pathology study.[4] An in vivo study suggested the hypothesis, showing that low sarcolemmal cholesterol content in neonatal cardiomyocytes enhanced sarcolemmal fluidity and anoxial-induced cell damage.[5] Moreover, other in vivo studies showed that cellular cholesterol depletion may induce apoptosis.[6] Further studies are necessary to explore pathological mechanisms.

Disclosures

None.

Hiroyuki Noda, MD
Hiroyasu Iso, MD
Osaka University Graduate School of Medicine
Department of Social and Environmental Medicine
Osaka, Japan

Fujiko Irie, MD
Yoko Izumi, MD
Mikio Doi, MD
Ibaraki Prefectural Office
Department of Health and Social Services
Ibaraki, Japan

Toshimi Sairenchi, PhD
Dokkyo Medical University School of Medicine
Department of Public Health
Tochigi, Japan

Emiko Ohtaka
Hitoshi Ohta, MD
Ibaraki Health Service Association
Ibaraki Prefectural Health Plaza
Ibaraki, Japan

References

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Associations Between Metabolic Syndrome and Mortality From Cardiovascular Disease in Japanese General Population, Findings on Overweight and Non-Overweight Individuals
—— Ibaraki Prefectural Health Study ——

Fujiko Irie, MD; Hiroyasu Iso, MD*; Hiroyuki Noda, MD*; Toshimi Sairenchi, PhD**;
Emiko Otaka†; Kazumasa Yamagishi, MD††; Mikio Doi, MD;
Yoko Izumi, MD; Hitoshi Ota, MD†

Background: The impact of being overweight, as a component of the metabolic syndrome (MetS), for cardiovascular disease (CVD) mortality was investigated and compared with the predictive value of MetS by 2 different definitions.
Methods and Results: A 12-year prospective study of 30,774 Japanese men and 60,383 women aged 40–79 years was conducted. The multivariate hazard ratio (HR; 95% confidence interval) of total CVD mortality for overweight subjects with ≥2 additional risk factors with reference to subjects with 0 of 4 MetS components was 1.83 (1.41–2.38) for men and 1.90 (1.45–2.49) for women, and for non-overweight subjects with ≥2 additional risk factors 1.75 (1.38–2.24) and 1.97 (1.52–2.55), respectively. The proportion of excess CVD deaths in the latter group was 1.5-fold higher than that in the former group. Multivariate HRs of coronary heart disease and total CVD mortality for MetS by the modified criteria of the American Heart Association/National Heart, Lung, and Blood Institute were 1.62 (1.31–2.00) and 1.23 (1.09–1.39), respectively, for men and 1.32 (1.05–1.65) and 1.12 (1.00–1.25), respectively, for women. The respective HRs for MetS by the International Diabetic Federation definition did not reach statistical significance, except for coronary heart disease in men.
Conclusions: Non-overweight individuals with metabolic risk factors, as well as overweight individuals with such factors, should be targeted to reduce the CVD burden in the general population. (*Circ J* 2009; 73: 1635–1642)

Key Words: Cardiovascular disease; Follow-up studies; Metabolic syndrome; Mortality; Risk factors

The metabolic syndrome (MetS) is known as an important risk factor for cardiovascular disease (CVD) and mortality in Western populations.[1–3] Several cohort studies of Asians have also shown that MetS according to the Adult Treatment Panel III guideline of the National Cholesterol Education Program (NCEP/ATPIII) definition is positively associated with CVD events and mortality.[4–7] Different clinical criteria for MetS have been developed over the past decade. The NCEP expert panel and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) considers that each metabolic factor has the same importance, whereas the International Diabetes Federation (IDF) and Japanese Society of Internal Medicine requires central obesity as an essential component of the diagnosis for MetS.[8–11] A recent report of a Japanese cohort study showed that clustering of metabolic risk factors is related to CVD mortality, irrespective of being overweight.[6] Thus, it is uncertain whether overweight as a component of MetS has a significant contribution in identifying a high-risk subgroup of CVD among Japanese people, who are characterized by a low prevalence of obese individuals, lower mortality from ischemic heart disease and higher mortality from stroke, compared with Western populations.

We investigated the impact of being overweight as a component of MetS for CVD mortality in the Japanese general population, and compared the prevalence and predictive value of MetS using the AHA/NHLBI and IDF definitions.

Table 1. Diagnostic Criteria for the 4 Definitions of MetS

	NCEP/ATPIII	AHA/NHLBI	IDF	Japanese Society of Internal Medicine
	≥3 of the following 5 risk factors:	≥3 of the following 5 risk factors:	Central obesity plus any 2 risk factors:	Central obesity plus any 2 risk factors:
Central obesity (waist circumference)	≥102cm in men, ≥88cm in women	≥102cm in men, ≥88cm in women (for Asian Americans ≥90cm in men, ≥80cm in women)	≥94cm in men, ≥80cm in women (for Asians ≥90cm in men, ≥80cm in women)	≥85cm in men, ≥90cm in women
TG	≥150mg/dl	≥1.7mmol/L (150mg/dl) or drug treatment	≥1.7mmol/L (150mg/dl) or drug treatment	≥1.7mmol/L (150mg/dl) or drug treatment and/or*
HDL-C	<40mg/dl in men, <50mg/dl in women	<40mg/dl in men, <50mg/dl in women or drug treatment	<1.03mmol/L (40mg/dl) in men, <1.29mmol/L (50mg/dl) in women or drug treatment	<1.03mmol/L (40mg/dl) in men and women or drug treatment
BP	SBP ≥130mmHg or DBP ≥85mmHg	SBP ≥130mmHg or DBP ≥85mmHg or drug treatment	SBP ≥130mmHg or DBP ≥85mmHg or drug treatment	SBP ≥130mmHg or DBP ≥85mmHg or drug treatment
Fasting glucose	≥110mg/dl	≥100mg/dl or drug treatment	≥5.6mmol/L (100mg/dl) or previously diagnosed type 2 diabetes	≥110mg/dl or drug treatment

*In the definition of the Japanese Society of Internal Medicine, triglycerides and HDL-C are combined into 1 component of dyslipidemia.
MetS, metabolic syndrome; NCEP/ATPIII, National Cholesterol Education Program-Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; TG, triglycerides; HDL, high-density lipoprotein; BP, blood pressure (S, systolic; D, diastolic).

Methods

Study Population

The surveyed population comprised 96,433 persons (32,915 men, 63,518 women) aged 40–79 years living in Ibaraki Prefecture, Japan, who participated in annual community-based health checkups in 1993 (Ibaraki Prefectural Health Study). The health examinations were conducted by municipalities under the legal requirement for health and medical services for the aged. Because we excluded employees who had their annual health checkups conducted by their employers under the Industrial Safety and Health Law, the number of female participants exceed that of males. Of 85 communities, 38 were included in this study. The participating communities entrusted their health examinations to the Ibaraki Health Service Association and also the management of the basic resident register to the Ibaraki Accounting Center. The communities were distributed evenly across the prefecture because 5–11 communities participated from each of the middle, northern, southern, eastern, and western areas. The participation rate for health checkups was 36.4% in these areas, and was similar to the rate for Ibaraki prefecture in 1993 (35.8%). Persons with a history of stroke (n=935) or heart disease (n=4,433) were excluded, and the data of the remaining 91,157 persons (30,774 men, 60,383 women) were used for the analysis. The study protocol was approved by the Ethics Committee of the Ibaraki Prefectural Office.

Mortality Surveillance

Mortality surveys were conducted by systematic review of the death certificates and resident registrations, with the cooperation of public health centers and municipal government offices. The underlying causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9, 1993–1994) and 10th revision (ICD-10, 1995–2005). Follow-up was conducted until the end of 2005. Persons who moved out of the communities during the follow-up numbered 3,226 (3.5%), and 9,282 persons

(10.2%) died. Such individuals were censored at the date of moving or of death. The median follow-up period for all participants was 12.0 years. Cause-specific mortality was also determined individually in terms of total stroke (ICD-9 codes 430–438; ICD-10 codes I60–I69), hemorrhagic stroke (codes 431–432; I60–I61, I69.0, I69.1), ischemic stroke (codes 433–434, 437.7A, 437.7B; I63, I69.3), coronary heart disease (codes 410–414; I20–I25), and total CVD (codes 393–459; I00–I99).

Measurement of Risk Factors

At baseline survey, body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Height in stocking feet and weight in light clothing were measured. The proportion of obesity (BMI ≥30kg/m^2) was only 1.7% in men and 3.4% in women. Serum triglyceride (TG) and serum total cholesterol (TC) levels were measured with enzyme methods using an RX-30 device (JEOL Ltd, Tokyo, Japan). High-density lipoprotein-cholesterol (HDL-C) was measured with a phosphotungstic acid magnesium method using an MTP-32 device (Corona Electric, Ibaraki, Japan). The measurement of these lipids in the laboratory of the Ibaraki Health Service Association was standardized by the laboratory of the Osaka Medical Center for Health Science and Promotion under the laboratory network program of the US Centers for Disease Control and Prevention (Atlanta, GA, USA).[12] Blood pressure (BP) was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Plasma glucose levels were measured with a glucose oxidase electrode method using a GA1140 device (ARKRAY, Inc, Kyoto, Japan). Fasting was not required. The time since the last meal was <2h (25%), 2h (25%), 3–7h (33%) and ≥8h (17%).

An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual weekly intake of alcohol in "go" units (a Japanese traditional unit of volume corresponding to 23g ethanol), which was converted to grams of ethanol per day, and histories of stroke and heart

disease. Histories of CVD were also determined by inter-
view in which the subjects were asked if they had been
diagnosed as stroke and/or heart disease. Symptoms typical
of stroke and coronary heart disease or findings on brain
imaging studies and/or ECG were not taken into account.

Definitions of MetS

The components of MetS were defined as: (1) over-
weight: BMI ≥25 kg/m², (2) elevated TGs: ≥1.69 mmol/L
(150 mg/dl), (3) reduced HDL-C: <1.03 mmol/L (40 mg/dl)
for men and <1.29 mmol/L (50 mg/dl) for women, (4) ele-
vated BP: ≥130/85 mmHg and/or antihypertensive medica-
tion use, and (5) elevated glucose: ≥5.55 mmol/L (100 mg/dl)
fasting or ≥7.22 mmol/L (130 mg/dl) non-fasting, and/or
on treatment for diabetes mellitus. Because waist circum-
ference was not measured in our study, BMI ≥25 kg/m² was
used as the criterion for being overweight for the analyses;
this BMI level is reported to correspond well to the Asian
criterion for high waist circumference ≥90 cm in men and
≥80 cm in women.[13] Non-fasting plasma glucose was also
used as a criterion for glucose intolerance, because the
fasting plasma glucose level was not measured in four-fifths
of the participants. We defined elevated glucose as glucose
≥5.55 mmol/L (100 mg/dl) in fasting blood samples and
≥7.22 mmol/L (130 mg/dl) in non-fasting ones.

As shown in **Table 1**, MetS was defined as the presence
of 3 or more of the components (overweight, elevated TGs,
reduced HDL-C, elevated BP and elevated glucose) accord-
ing to the modified criteria of AHA/NHLBI, and the pres-
ence of 2 or more of the same cardiovascular risk factors
(elevated TGs, reduced HDL-C, elevated BP and elevated
glucose) among overweight persons according to the modi-
fied criteria of the IDF. The AHA/NHLBI definition included
non-overweight people with 3 or 4 abnormalities of TGs,
HDL-C, BP and glucose, who would not be classified as
MetS by the IDF criteria.

Statistical Analysis

Sex-specific hazard ratios (HRs) of CVD mortality and the
corresponding 95% confidence intervals (95%CI) were
calculated with reference to the risk for individuals without
each of MetS components or with none of the components,
or without MetS, using the Cox proportional hazards model.
Elevated TC was defined as ≥5.69 mmol/L (220 mg/dl). We
adjusted for age at baseline (years), and for other potential
confounding factors including cigarette smoking (never-
smokers, ex-smokers, current smokers of 1–19, 20–29 and
≥30 cigarettes/day), usual alcohol intake (never, former,
current <23 g/day, 23–45, 46–68 and ≥69 g/day ethanol),
time since last meal (<2, 2, 3–7 and ≥8 h) and sex-specific
quartiles of serum TC levels.

Participants were stratified into categories according to
the number of metabolic risk factors (BMI< or ≥25 kg/m²
plus 0, 1, 2, 3 or more (≥3), or 2 or more (≥2) of additional
risk factors except being overweight). The HRs and corre-
sponding 95%CI of death were calculated with reference to
persons with 0 of 4 MetS components. We conducted tests
for trend across the categories of the number of metabolic
risk factors by assigning median values for each category
(0, 1, 2 and ≥3) and testing the significance of this variable.
The HRs of mortality for MetS according to the IDF and
AHA/NHLBI definitions were also calculated with refer-
ence to individuals without MetS. P values for statistical
tests were 2-tailed and P<0.05 was regarded as statistically
significant. The SAS statistical package (version 9.1; SAS

Institute Inc, Cary, NC, USA) was used for the analyses.
We also calculated population attributable fractions (PAF)
to examine the contribution of the MetS and its components
to the risk of CVD mortality, using multivariate HRs of
statistical significance and the proportion of cases in each
category. PAF was estimated as $[p(HR\text{-}1)]/[1+p(HR\text{-}1)]$,
where p is the proportion of cases falling into the category
and HR is the HR in the category.[14]

Results

During the 12-year follow-up, there were 9,282 deaths
(5,124 for men; 4,158 for women), comprising 1,317 deaths
from total stroke, 569 from hemorrhagic stroke, 716 from
ischemic stroke, 704 from coronary heart disease, and 2,674
from total CVD.

Table 2 presents the sex-specific HRs (95%CI) for mor-
tality from hemorrhagic stroke, ischemic stroke and coro-
nary heart disease according to metabolic risk factors. Age-
adjusted HR for mortality from hemorrhagic stroke was 1.9
in both sexes in the presence of elevated BP. Age-adjusted
HRs for mortality from ischemic stroke ranged from 1.3
to 1.5 in the presence of elevated BP and reduced HDL-C
in men, and were between 1.5 and 1.7 in the presence of
elevated BP and glucose levels in women. Age-adjusted
HRs of mortality from coronary heart disease ranged from
1.4 to 1.6 in the presence of elevated BP, elevated glucose
and reduced HDL-C in men, and were between 1.4 and 1.9
in the presence of elevated BP and glucose levels in women.
Age-adjusted HRs for mortality from total CVD ranged
from 1.2 to 1.6 in the presence of elevated BP, elevated
glucose and reduced HDL-C in men, and were between 1.4
and 1.7 in the presence of elevated BP and glucose levels
in women. Elevated TC was associated with increased mor-
tality from coronary heart disease in men, but not in women.
Smoking was associated with increased mortality from
hemorrhagic stroke in women, and coronary heart disease
and total CVD in both sexes. These associations remained
statistically significant after adjustment for confounding
factors. Associations between being overweight and diseases
outcomes were generally weak and only significant for coro-
nary heart disease in men.

The PAFs of these 4 outcomes were approximately 20–
40% for elevated BP in both sexes, whereas the PAFs of
coronary heart disease and total CVD were approximately
10–20% for elevated glucose in both sexes, and approxi-
mately 20–25% for smoking in men.

Table 3 presents the multivariate HRs for mortality from
ischemic stroke, coronary heart disease and total CVD
according to the number of metabolic risk factors stratified
by BMI. In both men and women, a dose–response relation-
ship was found between the number of metabolic risk
factors and the HR of mortality from each endpoint for both
non-overweight and overweight subgroups. The multi-
variate HR (95%CI) of total CVD was 1.75 (1.38–2.24) in
non-overweight persons with ≥2 risk factors (components
of MetS except for overweight) and 1.83 (1.41–2.38) in
overweight persons with ≥2 risk factors in men. The respec-
tive HRs were 1.97 (1.52–2.55) and 1.90 (1.45–2.49) in
women. The HRs of mortality from total CVD for over-
weight individuals with ≥2 risk factors were similar to
those for non-overweight persons with ≥2 other MetS com-
ponents in both men and women. The PAF in the former
category was 10%, and 15% in the latter among both men
and women. Furthermore, we also calculated age-specific

Table 2. Sex-Specific HRs (95%CI) of Cardiovascular Disease Mortality According to Metabolic Risk Factors

	No. of persons	Person-years	Hemorrhagic stroke No. of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF %	Ischemic stroke No. of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF %	Coronary heart disease No. of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF %	Total cardiovascular disease No. of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF %
Men																		
Non-overweight	22,362	250,754	171	1.00	1.00		336	1.00	1.00		268	1.00	1.00		1,033	1.00	1.00	
Overweight	8,412	96,790	42	0.75 (0.54–1.06)	0.81 (0.58–1.15)		68	0.72 (0.56–0.94)*	0.77 (0.59–1.01)		112	1.34 (1.07–1.67)*	1.39 (1.11–1.75)†	10	299	0.96 (0.85–1.10)	1.02 (0.90–1.17)	
Normal TGs	19,366	216,800	159	1.00	1.00		284	1.00	1.00		238	1.00	1.00		911	1.00	1.00	
Elevated TGs	11,408	130,745	54	0.68 (0.50–0.93)*	0.74 (0.54–1.02)		120	0.99 (0.80–1.23)†	1.01 (0.81–1.26)		142	1.25 (1.01–1.54)*	1.20 (0.96–1.49)		421	1.01 (0.90–1.13)	1.03 (0.91–1.16)	
Normal HDL-C	25,033	283,144	170	1.00	1.00		317	1.00	1.00		282	1.00	1.00		1,046	1.00	1.00	
Reduced HDL-C	5,741	64,401	43	1.17 (0.84–1.63)	1.11 (0.78–1.57)		87	1.34 (1.06–1.70)*	1.32 (1.03–1.68)*	6	98	1.62 (1.29–2.04)†	1.49 (1.17–1.89)†	8	286	1.29 (1.14–1.48)†	1.24 (1.09–1.42)†	4
Normal BP	8,438	97,546	28	1.00	1.00		53	1.00	1.00		55	1.00	1.00		182	1.00	1.00	
Elevated BP	22,336	249,998	185	1.87 (1.25–2.79)†	1.91 (1.27–2.86)†	40	351	1.52 (1.14–2.03)†	1.52 (1.13–2.03)†	27	325	1.58 (1.19–2.11)†	1.67 (1.25–2.23)†	33	1,150	1.59 (1.36–1.86)†	1.61 (1.38–1.89)†	31
Normal glucose	21,299	241,841	138	1.00	1.00		267	1.00	1.00		233	1.00	1.00		853	1.00	1.00	
Elevated glucose	9,475	105,704	75	1.19 (0.89–1.57)	1.23 (0.92–1.66)		137	1.13 (0.92–1.39)	1.14 (0.92–1.41)		147	1.37 (1.12–1.69)†	1.43 (1.15–1.78)†	12	479	1.23 (1.10–1.37)†	1.24 (1.11–1.40)†	7
Normal TC	24,551	276,423	185	1.00	1.00		340	1.00	1.00		286	1.00	1.00		1,091	1.00	1.00	
Elevated TC	6,223	71,121	28	0.66 (0.44–0.98)*	0.69 (0.46–1.02)		64	0.87 (0.66–1.13)	0.95 (0.72–1.24)		94	1.45 (1.15–1.84)†	1.53 (1.21–1.94)†	10	241	0.99 (0.86–1.14)	1.05 (0.92–1.21)	
Never smoked	6,824	78,402	50	1.00	1.00		79	1.00	1.00		73	1.00	1.00		269	1.00	1.00	
Ex-smokers	8,120	91,694	56	0.87 (0.60–1.28)	0.88 (0.60–1.29)		103	1.02 (0.76–1.37)	1.01 (0.75–1.36)		84	0.89 (0.65–1.22)	0.89 (0.65–1.22)		334	0.96 (0.82–1.13)	0.94 (0.80–1.11)	
Current smoker	15,830	177,449	107	1.06 (0.76–1.48)	0.99 (0.70–1.40)		222	1.65 (1.28–2.14)†	1.60 (1.23–2.08)†	24	223	1.56 (1.20–2.04)†	1.63 (1.25–2.14)†	25	729	1.45 (1.26–1.66)†	1.41 (1.22–1.63)†	18
Women																		
Non-overweight	42,014	488,250	242	1.00	1.00		214	1.00	1.00		217	1.00	1.00		901	1.00	1.00	
Overweight	18,369	215,468	114	0.97 (0.78–1.22)	1.00 (0.80–1.25)		98	0.98 (0.78–1.25)	0.99 (0.78–1.26)		107	1.03 (0.81–1.29)	1.03 (0.82–1.30)		441	1.02 (0.91–1.14)	1.03 (0.92–1.16)	
Normal TGs	41,654	485,071	234	1.00	1.00		190	1.00	1.00		192	1.00	1.00		845	1.00	1.00	
Elevated TGs	18,729	218,646	122	0.92 (0.74–1.15)	0.92 (0.74–1.16)		122	1.11 (0.89–1.40)	1.13 (0.89–1.43)		132	1.19 (0.95–1.48)	1.18 (0.93–1.48)		497	1.01 (0.91–1.13)	1.01 (0.90–1.14)	
Normal HDL-C	40,891	475,864	221	1.00	1.00		201	1.00	1.00		196	1.00	1.00		831	1.00	1.00	
Reduced HDL-C	19,492	227,854	135	1.09 (0.88–1.36)	1.02 (0.83–1.27)		111	0.96 (0.76–1.21)	0.95 (0.75–1.21)		128	1.15 (0.92–1.43)	1.12 (0.89–1.40)		511	1.08 (0.96–1.20)	1.04 (0.93–1.17)	
Normal BP	22,973	268,516	54	1.00	1.00		37	1.00	1.00		54	1.00	1.00		190	1.00	1.00	
Elevated BP	37,410	435,202	302	1.85 (1.37–2.49)†	1.93 (1.43–2.60)†	37	275	1.66 (1.17–2.34)†	1.68 (1.19–2.37)†	30	270	1.36 (1.01–1.84)*	1.41 (1.04–1.89)*	20	1,152	1.63 (1.39–1.90)†	1.67 (1.43–1.96)†	29
Normal glucose	48,477	565,684	266	1.00	1.00		213	1.00	1.00		203	1.00	1.00		939	1.00	1.00	
Elevated glucose	11,906	138,034	90	1.13 (0.89–1.44)	1.15 (0.89–1.48)		99	1.45 (1.14–1.84)†	1.48 (1.16–1.91)†	9	121	1.92 (1.53–2.40)†	2.01 (1.59–2.56)†	17	403	1.38 (1.23–1.55)†	1.42 (1.25–1.60)†	8
Normal TC	39,507	461,260	240	1.00	1.00		189	1.00	1.00		199	1.00	1.00		837	1.00	1.00	
Elevated TC	20,876	242,459	116	0.75 (0.60–0.94)*	0.76 (0.61–0.95)*	8	123	1.01 (0.80–1.26)	1.01 (0.80–1.27)		125	0.96 (0.77–1.21)	0.96 (0.77–1.21)		505	0.93 (0.83–1.03)	0.93 (0.83–1.04)	
Never smoked	56,980	665,764	321	1.00	1.00		295	1.00	1.00		288	1.00	1.00		1,227	1.00	1.00	
Ex-smoker	441	4,880	2	–	–		3	1.52 (0.49–4.75)	1.60 (0.51–5.00)		1	–	–		10	1.27 (0.68–2.37)	1.30 (0.70–2.43)	
Current smoker	2,962	33,074	33	2.62 (1.83–3.74)†	2.70 (1.87–3.90)†	8	14	1.20 (0.70–2.05)	1.19 (0.70–2.05)		35	3.14 (2.21–4.46)†	3.19 (2.23–4.57)†	10	105	2.22 (1.82–2.70)†	2.22 (1.81–2.72)†	6

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
Multivariate HR adjusted for age, serum TC level, cigarette smoking, alcohol intake category, time since last meal.
HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction; TC, total cholesterol. Other abbreviations see in Table 1.

Table 3. Multivariate HRs (95% CIs) of Cause-Specific Mortality According to Metabolic Risk Factors, Stratified by BMI in Men and Women Aged 40–79 Years

	No. at risk	Person-years	Ischemic stroke			Coronary heart disease			Total cardiovascular disease		
			No. of deaths	Multivariate HR‡ (95%CI)	PAF %	No. of deaths	Multivariate HR‡ (95%CI)	PAF %	No. of deaths	Multivariate HR‡ (95%CI)	PAF %
Men No. of metabolic factors											
BMI <25											
0	3,468	40,033	23	1.00		20	1.00		76	1.00	
1	9,010	100,661	152	1.67 (1.08–2.60)*	13	111	1.64 (1.02–2.64)*	10	448	1.63 (1.28–2.08)‡	12
2	6,986	77,785	106	1.58 (1.01–2.49)*	9	82	1.60 (0.98–2.61)	–	344	1.67 (1.30–2.15)‡	9
≥3	2,898	32,275	55	2.07 (1.27–3.38)‡	7	55	2.49 (1.48–4.16)‡	8	165	1.97 (1.49–2.58)‡	6
P for trend				0.026			0.002			<0.001	
≥2	9,884	250,754	161	1.72 (1.11–2.66)*	16	137	1.86 (1.16–2.99)*	15	509	1.75 (1.38–2.24)‡	15
BMI ≥25											
0	434	5,154	0	1.00		1	–	–	4	0.59 (0.21–1.60)	–
1	2,232	25,717	17	1.10 (0.58–2.05)	–	26	2.02 (1.12–3.62)*	4	69	1.36 (0.98–1.88)	–
2	3,155	36,338	19	0.95 (0.52–1.75)	–	37	2.09 (1.21–3.61)‡	6	103	1.55 (1.15–2.08)‡	4
≥3	2,591	29,582	32	1.92 (1.12–3.30)*	5	48	3.08 (1.82–5.21)‡	10	123	2.17 (1.62–2.89)‡	6
P for trend				0.011			0.009			<0.001	
≥2	5,746	96,790	51	1.38 (0.84–2.27)	–	85	2.54 (1.55–4.15)‡	16	226	1.83 (1.41–2.38)‡	10
Women No. of metabolic factors											
BMI <25											
0	10,850	125,746	11	1.00		14	1.00		65	1.00	
1	15,698	183,286	81	2.03 (1.08–3.82)*	14	77	1.87 (1.06–3.31)*	12	335	1.70 (1.30–2.22)†	11
2	9,983	115,736	77	2.41 (1.28–4.55)‡	12	68	2.12 (1.19–3.79)*	10	311	2.02 (1.54–2.65)‡	10
≥3	5,483	63,483	45	2.19 (1.13–4.26)*	6	58	2.73 (1.51–4.92)‡	8	190	1.89 (1.42–2.51)‡	5
P for trend				0.025			0.001			<0.001	
≥2	15,466	488,250	122	2.33 (1.25–4.33)‡	18	126	2.35 (1.35–4.10)‡	19	501	1.97 (1.52–2.55)‡	15
BMI ≥25											
0	1,668	19,694	2	–	–	1	–	–	9	1.00 (0.50–2.00)	–
1	5,465	64,163	17	1.30 (0.61–2.78)	–	27	1.93 (1.01–3.69)*	5	110	1.66 (1.22–2.26)‡	4
2	5,685	66,842	37	2.43 (1.24–4.76)*	7	30	1.81 (0.96–3.42)	–	130	1.66 (1.23–2.24)‡	4
≥3	5,551	64,769	42	2.32 (1.19–4.51)*	6	49	2.55 (1.40–4.64)‡	8	192	2.11 (1.59–2.81)‡	6
P for trend				0.104			0.047			0.008	
≥2	11,236	215,468	79	2.37 (1.26–4.46)‡	13	79	2.20 (1.24–3.89)†	12	322	1.90 (1.45–2.49)‡	10

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
‡Adjusted for age, serum TC level, cigarette smoking, alcohol intake category, time since last meal.
BMI, body mass index. Other abbreviations see in Tables 1,2.

HRs of mortality from total CVD according to the number of metabolic risk factors stratified by BMI (<25, ≥25 kg/m²), and found similar associations in both age subgroups. For example, the PAF of total CVD among men was 17% for overweight individuals with ≥2 risk factors and 17% for non-overweight ones with ≥2 other MetS components in the age subgroups of 40–64 years, and 6% and 16%, respectively, for the older subgroups of 65–79 years. The respective PAFs among women were 10%, 23%, 12% and 16% (not shown in **Table 3**).

Non-overweight individuals with ≥3 risk factors also had a considerable contribution to CVD mortality, even though they were not classified as MetS by the IDF definition. PAF

in this category was 6% in men and 5% in women for total CVD mortality. Similar associations were observed for ischemic stroke and coronary heart disease.

Figure shows sex-specific multivariate HRs of mortality from total CVD according to the number of metabolic risk factors stratified by BMI. Although the HR for non-overweight individuals with ≥2 MetS components other than being overweight was similar to that for overweight persons with ≥2 risk factors; the proportion of subjects in the former category was approximately 1.5–2-fold higher than that in the latter. Thus, the number of total CVD deaths for non-overweight individuals with ≥2 MetS components exceeded substantially that for overweight persons with ≥2 risk factors.
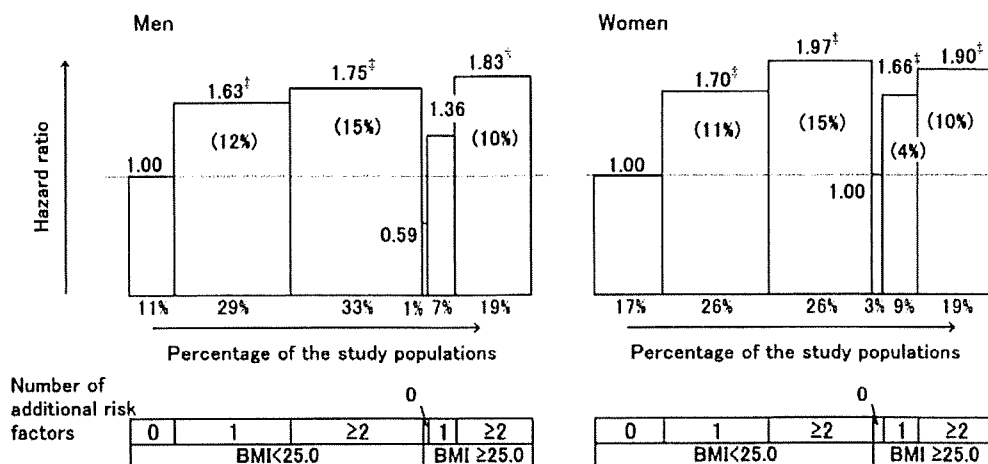
Figure. Sex-specific multivariable hazard ratios for mortality from total cardiovascular disease according to the number of metabolic risk factors, stratified by body mass index (BMI) for men and women aged 40–79 years. The population attributable fractions are shown in parentheses. ‡P<0.001.

Table 4. Prevalence of MetS and Multivariate HRs (95%CIs) of Cause-Specific Mortality According to 2 Definitions

	No. at risk	Person-years	Proportion at risk, %	Ischemic stroke			Coronary heart disease			Total cardiovascular disease		
				No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %
Men												
MetS by IDF definition												
No	25,028	81%	281,625	353	1.00	0	295	4.00	0	1,106	1.00	0
Yes	5,746	19%	65,920	51	0.88 (0.66–1.19)	–	85	1.51 (1.18–1.93)*	9	226	1.15 (1.00–1.34)	–
MetS by AHA/NHLBI definition												
No	22,130	72%	249,350	298	1.00	0	240	1.00	0	941	1.00	0
Yes	8,644	28%	98,195	106	1.12 (0.89–1.40)	–	140	1.62 (1.31–2.00)*	15	391	1.23 (1.09–1.39)*	6
Women												
MetS by IDF definition												
No	49,147	81%	572,107	233	1.00	0	245	1.00	0	1,020	1.00	0
Yes	11,236	19%	131,611	79	1.20 (0.93–1.55)	–	79	1.12 (0.86–1.44)	–	322	1.10 (0.97–1.25)	–
MetS by AHA/NHLBI definition												
No	43,664	72%	508,624	188	1.00	0	187	1.00	0	830	1.00	0
Yes	16,719	28%	195,094	124	1.19 (0.95–1.49)	–	137	1.32 (1.05–1.65)*	8	512	1.12 (1.00–1.25)	–

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
§Adjusted for age, serum TCl level, cigarette smoking, alcohol intake category, time since last meal.
Abbreviations see in Tables 1,2.

Similar results were observed for mortality from other end-points.

Table 4 presents the prevalence of MetS and HRs of CVD mortality for MetS according to the 2 definitions. The prevalence of MetS was 26% according to the AHA/NHLBI criteria and 19% according to the IDF definition in either men or women. Multivariate HRs (95%CI) of mortality from coronary heart disease and total CVD for MetS based on the AHA/NHLBI with reference to individuals without MetS were 1.62 (1.31–2.00) and 1.23 (1.09–1.39), respectively, in men, and 1.32 (1.05–1.65) and 1.12 (1.00–1.25), respectively, in women. The respective HRs for MetS by the IDF definition did not reach statistical significance, except for coronary heart disease in men. The PAF for MetS based on the AHA/NHLBI criteria was 15% for coronary heart disease and 6% for total CVD in men and 8% for coronary heart disease in women. The PAF for MetS based on the IDF criteria was 9% for coronary heart disease in men.

Discussion

In this large prospective study of the Japanese general population, we showed that contribution of overweight per se to CVD mortality is not obvious compared with elevated glucose and BP. The excess risk of mortality from total CVD and other endpoints was similar for overweight and non-overweight persons with ≥2 metabolic components in both men and women. Because of the 2-fold higher proportion of non-overweight high-risk individuals, the excess proportion of death was obviously larger for non-overweight persons with ≥2 metabolic components than for persons with Mets by the IDF definition.

It is controversial whether central obesity defined by waist circumference or BMI is essential in the diagnosis

of MetS. Previous studies show that central obesity is an important component of MetS, but a large proportion of individuals with normal waist circumference are also characterized by multiple cardiovascular risk factors and increased risk of mortality.[15,16] Nilsson et al reported that the IDF definition was not superior to the NCEP/ATPIII or EGIR (European Group for the Study of Insulin Resistance) definition for the prediction of total CVD events, and that MetS according to the NCEP/ATPIII definition was most predictive.[17] In our study, the prevalence of MetS and the HR of CVD mortality for MetS by the AHA/NHLBI definition was higher than that for MetS by the IDF criteria, because of the considerable contribution of non-overweight individuals with ≥3 risk factors who were not classified as MetS by the IDF definition. Persons with MetS by the AHA/NHLBI definition had a 1.2-fold higher mortality from total CVD than person without MetS, and the contribution of MetS to total CVD was 6%. However, that contribution was one-fifth that of elevated BP for men.

The magnitude of the HRs of MetS for total CVD mortality was somewhat smaller in our study than previously reported.[2,3,17–19] Two large meta-analyses in Western countries indicated that the pooled HRs of total CVD deaths for MetS ranged from 1.7 to 1.9.[2,3] The lower prevalence of obese individuals, lower mortality from ischemic heart disease and higher mortality from hemorrhagic stroke in the Japanese population compared with Western populations may explain the smaller contribution of MetS to CVD, even for middle-aged men, in the present study.

Among the cardiovascular risk factors, elevated BP had the largest impact on mortality from CVD. The PAF of elevated BP ranged from 20% to 40%, which was far larger than that of other metabolic risk factors. Our study also confirmed that the impact of each metabolic risk factor varied among the cardiovascular outcomes. Although elevated BP was strongly associated with mortality from hemorrhagic stroke,[20,21] elevated glucose level was associated with mortality from coronary heart disease[22,23] in both sexes. In men, reduced HDL[24,25] and being overweight[26] were also associated with mortality from coronary heart disease.

In our study, serum TC tended to be inversely associated with mortality from hemorrhagic stroke, whereas elevated TC was associated with mortality from coronary heart disease, which was consistent with results from recent studies in the Asia–Pacific region.[27,28] Being overweight was associated with mortality from coronary heart disease, but not from hemorrhagic or ischemic stroke, which was also consistent with previous Japanese studies.[29–33]

The strengths of our study include the long term follow-up, sufficient number of deaths, complete follow-up of subjects using basic resident registers and systematic review of death certificates, and gender-specific analysis. To our knowledge, this study is the first large-scale prospective study of the Japanese general population to evaluate the gender-specific impact of each metabolic risk factor to mortality from CVD, stratified by BMI.

Study Limitations

First, the subjects of this study were participants in health checkups for residents with a response rate of 36.4%. Further, male participants were resident non-employees, so it is uncertain whether the findings in men can be generalized. However, the potential selection bias may be small because the rate of all-cause mortality was similar for the study subjects and the total Japanese population. The standard mor-

tality ratio of all-cause mortality for the study participants was 95 (95%CI: 86, 103) for men and 100 (95%CI: 89, 110) for women compared with the total Japanese population in 2000.[34,35] Second, we used death certificate diagnoses rather than medical records or autopsy findings. Validation studies have been performed to evaluate the accuracy of death certificate diagnosis between the mid-1980s and the 1990s in Japan.[36–41] The positive predictive value and sensitivity for stroke diagnosis were 95% and 87%, respectively.[36] Moreover, previous studies have shown that the diagnosis on death certificates with regard to total stroke and its subtypes is valid because of the widespread use of CT scanning and MRI in Japanese hospitals.[42,43] As for coronary heart disease, the positive predictive value was lower than that for stroke, ranging from 50% to 78%, but the sensitivity was similar to that for stroke, ranging from 72% to 91%.[36–41] Third, we used BMI to define central obesity because waist circumference was not measured at the baseline examination. BMI has been used to diagnose overweight in many epidemiological studies and is considered to closely correlate with waist circumference.[13] Fourth, non-fasting blood samples were used for four-fifths of the participants at the baseline examination, which may cause misclassification of participants with elevated plasma glucose or elevated TGs.

In conclusion, non-overweight subjects with metabolic risk factors are at high risk of CVD mortality, as well as overweight subjects with such factors, and the excess mortality was 1.5-fold larger in the former than in the latter. The prevention and control of metabolic risk factors other than being overweight may therefore be important to reduce the burden of CVD in the general population.

Disclosure

None.

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