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γ-Glutamyltransferase and mortality risk from heart disease and stroke in Japanese men and women: NIPPON DATA90

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Summary
Background: Studies have shown that baseline serum γ-glutamyltransferase (GGT) is independently associated with cardiovascular disease (CVD) risk in men and women. However, less is known whether GGT is similarly associated with both stroke and heart disease (HD) risk in Asia. We examined an association between serum GGT and deaths from stroke and HD in Japanese men and women.

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Methods: From 1990 to 2005, we followed 7488 adults (3089 men) randomly selected from 300 districts throughout Japan, aged 30–95 with no history of coronary disease nor stroke at baseline. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) according to sex-specific GGT strata.
Results: During the study period, observed deaths from HD and stroke were 165 (83 men), and 135 (66 men), respectively. After adjustment for confounding factors, HRs of HD death for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT stratum were 1.61, 2.28, 2.48, and 4.59 in women (P for trend = 0.001), and 0.90, 0.74, 1.42, and 1.56 in men (P for trend = 0.250). The corresponding HRs of total stroke death were 1.52, 0.95, 1.22, and 1.34 in women (P for trend = 0.785), and 0.75, 0.91, 1.26, and 1.02 in men (P for trend = 0.642). Results were similar when analysis was limited to never-drinkers.
Conclusion: This cohort study of representative Japanese men and women suggested that baseline GGT independently predicts future HD mortality risk, especially in women, but not stroke mortality risk in Asian.

Introduction

Elevated serum γ-glutamyltransferase (GGT) level has been shown to predict cardiovascular diseases (CVD) incidence [1,2] and mortality [3] but less is known whether GGT is independently associated with both heart disease (HD) and stroke mortalities. For example, a meta-analysis that pooled prospective cohorts showed that GGT was associated with both incident coronary heart disease (CHD) and incident stroke [4], but many of the enrolled studies [2,3,5,6] did not take into account effect of alcohol consumption. Furthermore, current evidence on association between GGT and CVD risk is largely based on US and/or European populations. Asian populations are far less studied for association of GGT with risk of HD and stroke [7]. Although we previously reported an independent association between GGT and CVD death [8], we felt that events were too few to study an association with HD and stroke separately. In this study with extended follow-up period, we investigated whether serum GGT level at baseline is independently associated with long-term mortality from HD and stroke in both men and women in Japan. The question is of particular importance because stroke is more common in Asia compared to Europe and US. In addition, mortalities from CHD and ischemic stroke were examined as our secondary outcomes. We studied a cohort of representative Japanese men and women that has been followed up for 15 years.

Methods

Study participants

The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged (NIPPON DATA) consists of two ongoing cohorts that are based on two national surveys conducted in Japan. Detailed methods in constructing the cohorts were described elsewhere [9–11]. In brief, they were constructed upon the National Survey of Circulatory Disorder conducted in 1980, and in 1990, which become the bases of "NIPPON DATA80" [9] and "NIPPON DATA90" [10], respectively. Both surveys included physical examination, laboratory tests, and self-administered questionnaire on lifestyle and medical information. The present study was based only on NIPPON DATA90 because the baseline survey of NIPPON DATA80 did not contain measurement of serum GGT level.

We followed a total of 8383 community residents (3504 men and 4879 women; age 30 or older) from 300 randomly selected districts across the nation until November 15, 2005. The overall population of ⩾30-year-old in all the districts was 10,956, and the participation rate in the survey was 76.5%. Of the 8383 participants, we excluded 895 participants for the following reasons; no baseline GGT measurement (n = 662), those with CHD and/or stroke at baseline (n = 222), and with missing pertinent covariates (n = 11), leaving 7488 individuals for analysis (3089 men, 4399 women). We utilized the National Vital Statistics to ascertain the cause of death. In accordance with Japan's Family Registration Law, all death certificates, issued by a physician, are to be forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residency. The cause of death is then coded for the National Vital Statistics. The 9th International Classification for Disease (ICD9) was used for deaths occurring up to the end of 1994, and the 10th International Classification for Disease (ICD10) for deaths occurring thereafter. Permission was obtained from the Management and Coordination Agency of the Japanese Government for use of pertinent information from the National Vital Statistics. The respective codes for ICD9 and 10 used were as follows: heart disease (HD), 393–429 (ICD9), I01–I09, I11, I13, I20–I50 (ICD10); stroke, 430–438 (ICD9), I60–I69 (ICD10); coronary heart disease (CHD), 410–414 (ICD9), I20–I25 (ICD10); ischemic stroke 433, 434, 437.8a, 437.8b (ICD9), I63, I69.3 (ICD10). The study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17–21, 2005).

Measurement

The baseline survey was conducted by a public health center in each area. Blood pressure was measured by a trained staff member using a standard mercury sphygmomanometer over the right arm of a seated participant after at least 5 min-rest. Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meter. From the self-administered questionnaire, the following information

was obtained; physician-diagnosed diseases [Yes, No, Unknown] (stroke, myocardial infarction), status of clinical visit for the corresponding medical condition, and use of medication. Alcohol intake was first categorized into [Never, Current, Former], then further asked amount (''*go*'', the traditional Japanese unit for *sake*, per day; 1*gou* (180 mL) of *sake* contains 23 g of alcohol) of consumption for those who responded as ''current''. Based on these questions, we used three categories (never, past, current) in main analysis, and six categories (never, past, current <23 g of alcohol/day, current 23 g to <46 g/day, current 46 g to <69 g/day, and current ⩾69 g/day) in sensitivity analysis. Smoking status was categorized into three groups; never-smoker, ex-smoker, and current-smoker. Exercise status was grouped into three categories; ''unable to exercise due to a health related reason'', ''unable to exercise due to a non-health related reason'', and ''exercise regularly''. Public health nurses confirmed information on smoking, drinking habits, and medical history.

Non-fasting blood samples were obtained and serum was separated and centrifuged immediately after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. Serum GGT was measured using 3-carboxyl-4-nitroanilide substrate methods based on International Federation of Clinical Chemistry and Laboratory Medicine with Hitachi 736-60 (Hitachi Ltd., Tokyo, Japan). Glutamyl oxaloacetic transaminase (GOT; also known as aspartate aminotransferase, AST) and glutamyl pyruvic transaminase (GPT; also known as alanine aminotransferase, ALT) were measured using ultraviolet methods. Serum total cholesterol and triglycerides (TG) as well as plasma glucose were measured enzymatically. High-density lipoprotein (HDL) cholesterol was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control/National Heart, Lung and Blood Institute. Diabetes mellitus was defined as serum glucose ⩾200 mg/dL and/or presence of self-reported history. All samples were shipped to the central laboratory (SRL, Tokyo, Japan) for measurement.

Statistical analysis

Because the relationship between GGT and CVD mortality was different by gender in our previous study [8], all analyses were performed separately in men and women. For main analysis, GGT level was categorized into five groups using sex-specific cut-off points of the 25th, 50th, 75th, and 90th percentiles computed over the each gender group, following previous works by Lee and the colleagues [1,12,13]. In estimating mortality risk, we first calculated crude total mortality rates according to the GGT strata. Then, multivariate-adjusted hazard ratios (HRs) were estimated using Cox proportional hazards model. Because distributions for GOT, GPT, and TG were right-skewed, values were natural log-transformed (ln-GOT, ln-GPT, ln-TG) when entering models as well as upon calculating linear trend across baseline GGT strata. Model 1 was adjusted for age only. Model 2 was further adjusted for systolic blood pressure (mmHg), BMI (kg/m^2), smoking status, regular exercise status, and total and HDL cholesterol (mg/dL), ln-TG, and diabetes mellitus at baseline. In Model 3, we further adjusted for alcohol intake. Model 4 further included ln-GOT and ln-GPT. We conducted a parallel procedure on the subgroup who reported as a never-drinker. To avoid instability in estimation, we used 25th and 50th percentiles combined as a reference group for secondary outcomes (CHD, ischemic stroke) due to their fewer events. Trends across the GGT strata were tested by regression with a median value used for a corresponding GGT stratum. All the statistical tests were two-tailed, and values of $P < 0.05$ were considered significant. Statistical analyses were conducted with SAS release 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the participants at baseline are shown in Table 1. Median age (years) at baseline was 51 for women and 52 for men. Median BMI (kg/m^2) was 22.5 for women and 22.9 for men. Only less than 7% of the women reported as a current-drinker whereas more than a half (59%) of the men did so. Majority (92%) of the women reported as a never-drinker. The 25th, 50th, 75th, and 90th percentile levels of GGT were 8, 12, 17, 26, and 52 U/L for women, and 15, 24, 41, 76, and 158 U/L for men. There was a clear gender difference in age distribution across GGT strata. As GGT level increased, the median age increased in women, whereas it decreased in men (P for trend < 0.001 for both). Despite such difference in age distribution, many cardiovascular risk factors were similarly associated with GGT level in both sexes; as GGT increases, BMI, total cholesterol, TG, systolic and diastolic blood pressure levels increased in both men and women (P for trend < 0.001 for all those variables in both sexes). The proportions of current-drinker and current-smoker were higher in higher GGT strata for both men and women, but there was a striking gender difference in absolute proportions such that both current-drinker and current-smoker were much fewer in women than in men even in the highest GGT group.

During the mean follow-up of 13.7 years, we observed 165 HD deaths (83 men), and 135 stroke deaths (66 men). Deaths due to CHD and ischemic stroke were 65 (40 men), and 83 (men 42), respectively. Estimated crude mortality rate, adjusted hazard ratios (HRs) for deaths from HD, CHD, total and ischemic stroke according to GGT strata are shown in Table 2 for women and in Table 3 for men.

In women, crude mortality rates (per 1000 person-years) were similar between HD and total stroke; 1.34, and 1.13, respectively (Table 2). By Cox regression models, we observed a significant graded positive association between GGT and HD mortality in women. After multivariate adjustment, the HRs of HD death of 25th, 50th, 75th, 90th GGT strata were 1.61, 2.28, 2.48, and 4.59 in reference to the lowest GGT group (Model 4, P for trend = 0.001). The association pattern of CHD death was similar to, and with apparently greater strength than HD (Table 2). In contrast, we observed no clear association between GGT and neither total stroke nor ischemic stroke death throughout the models.

In men, crude mortality rates (per 1000 person-years) were 2.00 for HD, and 1.59 for stroke, respectively (Table 3). In Models 3 and 4, we observed an apparent

J-shaped trend between GGT levels and HD death. The adjusted HRs for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT group were 0.90, 0.74, 1.42, and 1.56, respectively (Model 4, *P* for trend = 0.250). The J-shape association was more evident in CHD deaths with adjusted HRs for 50th, 75th, and 90th GGT percentiles being 0.47, 1.98, and 2.68. Similar to women, we observed no clear association between GGT and neither total nor ischemic stroke death throughout the models.

Table 1 Characteristics of the participants at baseline.

	Sex-specific GGT[a]					Total	
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th		
Women							
No.	960	1138	1124	719	458	4399	
Age (years)	45	49	52	56	56	51	(41–62)
BMI (kg/m^2)	21.5	21.9	22.8	23.6	23.9	22.5	(20.5–24.8)
Total cholesterol (mg/dL)	192	200	206	214	220	203	(179–231)
HDL-C (mg/dL)	57	57	55	55	53	56	(46–66)
Triglycerides (mg/dL)	82	95	103	116	130	101	(71–145)
GOT (U/L)	18	19	20	22	27	20	(17–24)
GPT (U/L)	12	14	16	20	28	16	(12–22)
SBP (mmHg)	126	128	132	138	140	130	(118–146)
DBP (mmHg)	76	78	80	82	82	80	(70–88)
Use of antihypertensives (%)	12.5	16.0	21.4	29.1	31.2	20.3	
Diabetes mellitus (%)	2.1	3.0	3.7	6.5	7.9	4.1	
Smoking							
Never (%)	91.9	88.4	87.5	86.2	83.4	88.1	
Former (%)	1.9	3.6	2.5	2.1	2.4	2.6	
Current (%)	6.3	8.0	10.0	11.7	14.2	9.4	
Drinking							
Never (%)	96.7	93.7	92.1	90.4	84.1	92.4	
Former (%)	0.4	1.1	1.1	1.3	0.9	1.0	
Current (%)	2.9	5.2	6.9	8.3	15.1	6.7	
Regular exercise							
Not, for health (%)	5.8	6.0	6.0	8.3	9.4	6.7	
Not, for other reason (%)	78.1	74.3	75.6	71.8	71.8	74.8	
Yes (%)	16.0	19.7	18.3	19.9	18.8	18.5	
Men							
No.	681	831	795	472	310	3089	
Age (years)	56	55	51	49	49	52	(41–63)
BMI (kg/m^2)	21.4	22.4	23.4	24.2	24.0	22.9	(20.8–24.9)
Total cholesterol (mg/dL)	182	194	200	203	204	195	(174–221)
HDL-C (mg/dL)	48	48	48	47	51	48	(40–58)
Triglycerides (mg/dL)	93	108	132	154	172	119	(83–181)
GOT (U/L)	20	22	24	27	34	24	(19–29)
GPT (U/L)	16	19	24	31	42	22	(16–32)
SBP (mmHg)	132	132	136	140	138	136	(124–150)
DBP (mmHg)	80	80	84	88	88	84	(76–90)
Use of antihypertensives (%)	14.5	17.8	16.5	20.3	17.1	17.1	
Diabetes mellitus (%)	6.2	6.4	6.9	8.9	9.4	7.2	
Smoking							
Never (%)	26.3	21.8	20.0	17.4	12.6	20.7	
Former (%)	22.9	25.5	23.6	21.6	18.7	23.2	
Current (%)	50.8	52.7	56.4	61.0	68.7	56.1	
Drinking							
Never (%)	57.1	42.7	28.4	15.5	10.0	34.8	
Former (%)	6.8	8.2	5.9	4.7	3.5	6.3	
Current (%)	36.1	49.1	65.7	79.9	86.5	59.0	

Table 1 *(continued)*

	Sex-specific GGT[a]					Total
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th	
Regular exercise						
Not, for health (%)	5.0	5.3	4.5	4.9	1.3	4.6
Not, for other reason (%)	71.2	72.0	72.8	75.8	76.8	73.1
Yes (%)	23.8	22.7	22.6	19.3	21.9	22.3

Values are expressed in median unless otherwise specified. Numbers in parenthesis are inter-quartile ranges.
Abbreviations: GGT, γ-glutamyltransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
[a] Cut-off GGT values (U/L) for 25th, 50th, 75th, and 90th percentile were 8, 12, 17, 26 and 52 in women and 15, 24, 41, 76 and 158 in men, respectively.

Table 2 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in women.

GGT category (value in U/L)	<25th (1–10)	25 to <50th (11–14)	50 to <75th (15–21)	75 to <90th (22–36)	⩾90th (37–385)	Total
Person-years	13,467	15,933	15,698	9844	6072	61,012
Heart disease death						
No.	10	16	21	19	16	82
Crude rate (per 1000 person-years)	0.74	1.00	1.34	1.93	2.64	1.34
						P for trend
Model 1	1	1.44	1.90	2.15	3.52	<0.001
Model 2	1	1.61	2.31	2.54	4.81	<0.001
Model 3	1	1.61	2.31	2.57	4.88	<0.001
Model 4	1	1.61	2.28	2.48	4.59	0.001
CHD death						
No.	5		7	7	6	25
Crude rate (per 1000 person-years)	0.17		0.45	0.71	0.99	0.41
						P for trend
Model 1	1		2.72	3.39	5.66	0.005
Model 2	1		3.27	4.40	7.95	0.001
Model 3	1		3.35	4.46	7.59	0.002
Model 4	1		3.56	5.01	10.31	0.002
Total stroke death						
No.	14	22	13	13	7	69
Crude rate (per 1000 person-years)	1.04	1.38	0.83	1.32	1.15	1.13
						P for trend
Model 1	1	1.40	0.84	1.06	1.10	0.890
Model 2	1	1.48	0.94	1.14	1.27	0.881
Model 3	1	1.50	0.93	1.15	1.32	0.819
Model 4	1	1.52	0.95	1.22	1.34	0.785
Ischemic stroke death						
No.	27		4	7	3	41
Crude rate (per 1000 person-years)	0.92		0.25	0.71	0.49	0.67
						P for trend
Model 1	1		0.30	0.64	0.57	0.298
Model 2	1		0.33	0.68	0.66	0.455
Model 3	1		0.32	0.67	0.69	0.483
Model 4	1		0.32	0.70	0.67	0.552

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.
Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Table 3 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in men.

GGT category (value in U/L)	<25th (1–18)	25 to <50th (19–30)	50 to <75th (31–57)	75 to <90th (58–110)	⩾90th (111–1803)	Total
Person-years	8939	11,114	10,862	6488	4140	41,542
Heart disease death						
No.	30	24	14	10	5	83
Crude rate (per 1000 person-years)	3.36	2.16	1.29	1.54	1.21	2.00
						P for trend
Model 1	1	0.72	0.53	0.84	0.80	0.754
Model 2	1	0.81	0.62	1.02	1.08	0.704
Model 3	1	0.87	0.69	1.30	1.43	0.324
Model 4	1	0.90	0.74	1.42	1.56	0.250
CHD death						
No.	25		4	7	4	40
Crude rate (per 1000 person-years)	1.62		0.37	1.08	0.97	0.96
						P for trend
Model 1	1		0.38	1.39	1.49	0.343
Model 2	1		0.41	1.52	2.05	0.134
Model 3	1		0.46	1.97	2.74	0.048
Model 4	1		0.47	1.98	2.68	0.060
Total stroke death						
No.	20	16	16	10	4	66
Crude rate (per 1000 person-years)	2.24	1.44	1.47	1.54	0.97	1.59
						P for trend
Model 1	1	0.72	0.97	1.41	1.13	0.380
Model 2	1	0.76	0.96	1.35	1.16	0.440
Model 3	1	0.77	0.98	1.40	1.23	0.398
Model 4	1	0.75	0.91	1.26	1.02	0.642
Ischemic stroke death						
No.	24		13	4	1	42
Crude rate (per 1000 person-years)	1.20		1.20	0.62	0.24	1.01
						P for trend
Model 1	1		1.47	1.16	0.59	0.839
Model 2	1		1.45	0.97	0.52	0.616
Model 3	1		1.59	1.15	0.65	0.845
Model 4	1		1.64	1.19	0.65	0.794

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.

Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

The results were virtually unchanged when detailed categorization for alcohol intake was used in the models (data not shown). For subgroup analysis on never-drinker, observed number of death from HD and from stroke were 79 and 68 in women ($n = 4064$), and 41 and 24 in men ($n = 1074$), respectively. Estimated patterns of association were similar to the main analysis except that no J-shaped trend was observed between GGT and HD in men. The adjusted HRs for HD death of 25th, 50th, 75th, 90th GGT strata were 1.56, 2.36, 2.36, and 5.46 in women (P for trend < 0.001), 0.56, 0.79, 0.30, and 0.77 in men (P for trend = 0.564); the corresponding HRs for stroke death were 1.54, 0.98, 1.24, and 1.45 in women (P for trend = 0.679), 1.00, 0.70, 1.58, and 0.00 in men (P for trend = 0.815. No events in the highest group) (data not tabulated).

Discussion

In this 15-year follow-up study, we examined whether baseline GGT is independently associated with both HD and stroke deaths in Japanese men and women. We observed positive associations of GGT with the risk of total HD mortality and of CHD mortality in women. For men, there seemed to be a non-significant J-shaped trend of HD, especially CHD. In contrast, we did not observe a clear association between GGT and stroke mortality in either sexes.

Previous studies indicated that elevated GGT is associated with increased risk for CVD, but less is clear whether GGT is independently associated with both HD and stroke mortality. For example, Fraser and colleagues conducted a

meta-analysis pooling prospective cohorts, and showed that GGT was associated with both incident CHD and incident stroke [4]. However, many studies including those in the meta-analysis did not adjust for alcohol intake [2,3,5, 6,14], which left a possibility of confounding by alcohol effect. We dealt with this issue by both statistical adjustment and by restriction to never-drinkers, and the results from both approaches seemed similar. Another uncertainty is regarding a potential ethnic difference. Current evidence on association between GGT and CVD risk is largely based on US/European population, and Asians are far less studied. Since stroke is more common in east-Asia [15] compared to the US/European population, it is important to examine disease-specific association of GGT.

In our study population, stroke death rate was higher than that of CHD. Thus, it is unlikely that the observed null association with stroke risk is attributable to fewer deaths in light of positive association with CHD risk in women. However, the null association with stroke is not consistent with some studies including one from Japan that reported a positive association with incident stroke [7]. Although the exact reason for this inconsistency is unclear, we speculate followings reasons. First, stroke includes etiologically heterogenous conditions with different fatality risk [16,17]. Therefore, factors that affect stroke incidence may be different from those of stroke death. Second, prevalence of stroke subtype can be different between Asians and Caucasians [18], which could lead to difference in association.

We observed sex-difference in association of GGT with HD and CHD; not significant in men, whereas significant and monotonic in women. Similar sex-difference in association of GGT with incident stroke was reported from a Japanese population [7]. Such difference might be explained by the fact that GGT level is affected not only by alcohol consumption, but also obesity (through visceral and hepatic fat [19]), as well as smoking in the presence of alcohol [20]. Most women in our study were never-drinker, never-smoker, and young female tended to have lower BMI. In contrast, among our male group, both alcohol intake and smoking habit were common especially in the young who tended to have greater BMI. In a population such as our male group, the association of GGT may be obscured despite the attempt to deconfound. A larger sample size for never-drinking men is needed to examine this issue.

GGT has other potentially important determinants that can be even stronger than liver function or alcohol consumption [21]. Biological mechanism in explaining the link between elevated GGT and CVD mortalities is not fully understood. Serum GGT is considered to be a marker for insulin resistance [22], as well as for oxidative stress and inflammation which may lead to cardiovascular diseases [23,24]. Another mechanism has been suggested by histochemical analyses showing GGT activity expressed by macrophage-derived foam cells within human atheromas [25] co-localizing with oxidized LDL [26]. Furthermore, GGT is shown to mediate LDL oxidation [27], indicating that GGT is a potential marker for the preclinical atherosclerosis.

Major strengths of the study include prospective study design with longitudinal ascertainment of deaths, length of follow-up, and enrollment of both sexes with a broad age range based on the National Survey on randomly sampled areas nationwide, which made our cohort representative of the Japanese population. Several limitations should be mentioned. First, we did not have incidence data for CHD and stroke. Thus we were unable to examine potential difference between incidence and mortality. Second, we did not have information pertinent to hepatic conditions, such as chronic viral hepatitis, although we believe this limitation is less likely to distort our inference because our main outcomes are CVD mortalities, not hepatic/gastrointestinal or total mortalities.

Conclusion

We found that baseline GGT level was independently associated with long-term risk of HD mortality, especially in women, but not with stroke mortality in a representative sample of Japanese population.

Conflict of interest statement

None declared.

Role of funding source

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(3) 日本における循環器疾患死亡の喫煙とメタボリックシンドロームの人口寄与危険割合 -NIPPON DATA90-

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【背景】

喫煙やメタボリックシンドロームは循環器疾患リスクとして知られている。アジアにおいて、肥満の割合が増加しており、男性の喫煙率も依然として高い。本研究では喫煙とメタボリックシンドローム(あるいは肥満)の組み合わせによる循環器疾患の過剰死亡に寄与する割合についてNIPPON DATA90をもちいて検討した。

【方法】

1990年に日本全国からランダムに抽出された300地区の調査協力者のうち、30歳から70歳の男女で循環器疾患の既往のない6650名(男性2752名、女性3898名)を対象とした。メタボリックシンドロームは本邦の診断基準に準じ、血圧高値は血圧≥130/85mmHgまたは降圧薬治療中、高血糖は血中グルコース濃度≥110mg/dlまたは糖尿病治療中、脂質異常は中性脂肪≥150mg/dl、またはHDLコレステロール<40mg/dlまたは脂質異常症にて治療中を、またBMI25以上を肥満ありとした。喫煙とメタボリックシンドローム(あるいは肥満)の組み合わせによる循環器疾患死亡の多変量調整ハザード比(HR)をCOX比例ハザードモデルを用いて解析を行った。非喫煙、非肥満あるいは非メタボリックシンドロームのものをリファレンスとした。さらに循環器疾患の過剰死亡、人口寄与危険割合(PAF)について計算した。人口寄与危険割合（PAF）は$pd\times$

(HR-1)/HR で計算した（*pd* はそれぞれのカテゴリでの死亡した人の割合)。

【結果】
追跡期間中に男性 87 名、女性 61 名の循環器疾患死亡が確認された。非肥満の喫煙者の循環器疾患死亡の PAF component は男性が 36.8%、女性が 11.3%で肥満の喫煙者より高い割合を示した(男性が 9.1%、女性が 5.2%)。循環器疾患死亡の PAF component は喫煙者でメタボリックシンドロームがない男性では 40.9%、女性は 11.9%で、喫煙者でメタボリックシンドロームがある者(男性は 7.1%、女性は 3.9%)と比較して高い割合を示した。

【結論】
本研究の結果は循環器疾患過剰死亡は非肥満あるいは、メタボリックシンドロームでない喫煙者で、特に男性で高い割合を示した。この結果は、メタボリックシンドロームの有無にかかわらず喫煙者への介入がアジア諸国において循環器疾患の予防のために重要であることを示唆している。

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RESEARCH ARTICLE Open Access

Population Attributable Fraction of Smoking and Metabolic Syndrome on Cardiovascular Disease Mortality in Japan: a 15-Year Follow Up of NIPPON DATA90

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Abstract

Background: Smoking and metabolic syndrome are known to be related to cardiovascular diseases (CVD) risk. In Asian countries, prevalence of obesity has increased and smoking rate in men is still high. We investigated the attribution of the combination of smoking and metabolic syndrome (or obesity) to excess CVD deaths in Japan.

Methods: A cohort of nationwide representative Japanese samples, a total of 6650 men and women aged 30-70 at baseline without history of CVD was followed for 15 years. Multivariate-adjusted hazard ratio for CVD death according to the combination of smoking status and metabolic syndrome (or obesity) was calculated using Cox proportional hazard model. Population attributable fraction (PAF) of CVD deaths was calculated using the hazard ratios.

Results: During the follow-up period, 87 men and 61 women died due to CVD. The PAF component of CVD deaths in non-obese smokers was 36.8% in men and 11.3% in women, which were higher than those in obese smokers (9.1% in men and 5.2% in women). The PAF component of CVD deaths in smokers without metabolic syndrome was 40.9% in men and 11.9% in women, which were also higher than those in smokers with metabolic syndrome (7.1% in men and 3.9% in women).

Conclusion: Our results indicated that a large proportion of excess CVD deaths was observed in smokers without metabolic syndrome or obesity, especially in men. These findings suggest that intervention targeting on smokers, irrespective of the presence of metabolic syndrome, is still important for the prevention of CVD in Asian countries.

Background

Obesity and clustering of its related factors, now called as metabolic syndrome, have been widely reported as important risk factors for cardiovascular diseases (CVD) [1-6], and, also in Asian countries including Japan, obesity has emerged as a new health problem [5]. The National Health and Nutrition Survey in Japan in 2005 showed that 22.4% of adult men and 10.8% of adult women were diagnosed as having metabolic syndrome [7]. Therefore, it is expected that metabolic syndrome or obesity would contribute to a large part of excess CVD events in Japan.

On the other hand, cigarette smoking is an established risk factor for CVD [8-12] and one of the biggest health problems in Asian countries including Japan [9,12,13]. In Asian countries, smoking rate in men is still high at 40 to 50% [14]. In Japan, smoking rate in 2005 was also high at 39.3% in men [15]. Therefore, smoking has largely contributed to increase CVD events in Asia, and it was reported that up to 30% of cardiovascular deaths was attributed by smoking in Asia Pacific region [16].

However, there have been few reports on the attribution of the combination of smoking status and metabolic syndrome (or obesity) to CVD deaths in Asian countries.

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Several previous studies also reported that CVD risk was high in both smokers and non-smokers with clustering of metabolic risk factors [17]. Therefore, it is important to elucidate the attribution of obesity, metabolic syndrome, and smoking to CVD mortality in Asia, where obesity is still less common compared with Western countries.

The purpose of this report is to examine excess CVD deaths and population attributable fractions on CVD deaths by the combination of smoking and metabolic syndrome (or obesity) in a 15-year cohort study of randomly selected representative Japanese samples from the National Survey on Circulatory Disorders of Japan.

Methods

Participants and follow-up

Cohort studies of the National Survey on Circulatory Disorders of Japan comprise the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA). Baseline surveys for the cohort of this report were performed in 1990 (NIPPON DATA90) [18,19]. We analyzed the 15-year follow-up data of NIPPON DATA90 in this report.

A total of 8383 men and women aged ≥ 30 years from 300 randomly selected districts were participated in the survey in 1990. The baseline surveys were carried out at local public health centers. The participation rate in the baseline survey was 76.5%. The present study was for 7329 participants aged 30 to 70 years at baseline. From these participants, we excluded 379 participants who had a history of coronary heart disease or stroke (n = 249) or who had missing information in the baseline survey (n = 130). Thus, 6650 participants (2752 men and 3898 women) were eligible for the analyses.

NIPPON DATA90 has completed follow-up surveys until 2005. We used the National Vital Statistics data to indentify the cause of death. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from 1995. Deaths from any CVD were identified by ICD-9 codes (393-459) and ICD-10 codes (I00-I99). The details of the classification are described elsewhere [18,19]. The Institutional Review Board of Shiga University of Medical Science (NO.12-18, 2000) approved the study.

Biochemical and physical examinations

Public health nurses obtained data including smoking habit, as well as current health status and medical history. Public health nurses asked all participants about current smoking status (current smoking, past smoking and never-smoking), the number of cigarettes per day and the duration of smoking. Smoking habit was categorized into non-smoker, past smoker and current smoker. Drinking habit was categorized into non-drinker, past drinker, occasional drinker and daily drinker. Body mass index was calculated as weight divided by height squared (kg/m^2).

Non-fasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to one laboratory (SRL, Tokyo, Japan) for blood measurements. Plasma glucose was measured enzymatically. Serum triglycerides and total cholesterol were also measured enzymatically, and high density lipoprotein (HDL) cholesterol was measured after heparin-calcium precipitation [20].

We defined metabolic risk factors using the Japanese criteria of the metabolic syndrome [21,22] as follow: obesity as body mass index ≥ 25 kg/m^2; high blood pressure: BP ≥ 130/85 mm Hg or on treatment for hypertension; high blood glucose: serum glucose ≥ 110 mg/dl or on treatment for diabetes; dyslipidemia: serum triglyceride ≥ 150 mg/dl, HDL cholesterol < 40 mg/dl or on treatment for dyslipidemia. We defined the metabolic syndrome as having obesity (defined as body mass index ≥ 25 kg/m^2) and two or more other metabolic risk factors; the definition was modified from the Japanese criteria [22] where the presence of obesity is essential. We defined metabolic risk factors clustering as having two or more metabolic risk factors.

Statistical analysis

Multivariate-adjusted hazard ratios (HR) of all CVD deaths for each component of metabolic risk factors including BMI, systolic BP (SBP), triglyceride, glucose, HDL cholesterol were calculated using Cox proportional hazards models. Multivariate-adjusted HR for all CVD deaths according to metabolic risk factors and smoking categories were calculated using Cox proportional hazards models adjusted for age and drinking. Non-smokers without metabolic syndrome or obesity were set as the reference group.

Population attributable fractions (PAF) for CVD deaths due to the combination of smoking and metabolic syndrome (or obesity) were calculated based on hazard ratios assessed by proportional hazards models [23,24]. PAF was estimated as $pd \times (HR-1)/HR$ where pd is the proportion of death cases arising from the each categories. All analyses were performed by SAS 9.1 (Statistical Analysis System, Cary, NC).

Results

Baseline characteristics are shown in Table 1. Mean age at baseline was 49.9 years in men and 49.0 years in women. Mean body mass index was 23.1 kg/m^2 in men and 22.9 kg/m^2 in women. Smoking rate was 58.0% in men and

Table 1: Baseline characteristics of study population. NIPPON DATA90, men and women aged 30 to 70 years in 1990.

	Men		Women	
Number (N)	2752		3898	
Age (year)	49.9	±11.2	49.0	±11.3
BMI (kg/m^2)	23.1	±3.0	22.9	±3.3
SBP (mmHg)	136.2	±19.5	131.3	±19.9
DBP (mmHg)	83.8	±11.7	79.4	±11.8
Total cholesterol (mg/dl)	199.6	±36.6	205.5	±38.0
HDL cholesterol (mg/dl)	50.4	±15.0	57.5	±14.9
Triglyceride (mg/dl)	151.8	±108.8	119.1	±79.8
Blood glucose (mg/dl)	102.0	±33.4	101.1	±28.9
Drinking				
Non drinker	921	33.5%	3572	91.6%
Ex-drinker	141	5.1%	39	1.0%
Current drinker	1690	61.4%	287	7.4%
Smoking				
Never smoker	556	20.2%	3431	88.0%
Ex-smoker	601	21.8%	94	2.4%
Current smoker	1595	58.0%	373	9.6%
Obesity	689	25.1%	912	23.4%
High blood pressure	1840	66.9%	2119	54.4%
High blood glucose	578	21.0%	829	21.3%
Dyslipidemia	1280	46.5%	1094	28.1%

Values are number, %, or mean ± SD.
High blood pressure, BP ≥ 130/85 mmHg or on treatment of hypertension; high blood glucose, blood glucose≥ 110 mg/dl or on treatment of diabetes; dyslipidemia as triglyceride≥ 150 mg/dl or high density lipoprotein < 40 mg/dl or on treatment of dyslipidemia. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein.

Table 2: Adjusted HR for 1 standard deviation increasing in the continuous variables and sex, smoking and drinking habits for mortality from cardiovascular diseases.

	Adjusted hazard ration (95%CI)		
Current -smoker	3.45	(2.12	-5.60)
Past-smoker	2.04	(1.11	-3.75)
Body mass index (1 SD increasing)	0.99	(0.83	-1.18)
Systolic blood pressure (1 SD increasing)	1.32	(1.13	-1.54)
Triglyceride (1 SD increasing)*	0.85	(0.69	-1.04)
High density lipoprotein cholesterol (1 SD increasing)	0.93	(0.76	-1.11)
Glucose (1 SD increasing)	1.10	(1.00	-1.24)
Female	1.00	(0.61	-1.64)

This Cox model also includes age, and drinking habit.
* The variable was tested after log-transferred.

9.6% in women. The prevalence of hypertension and obesity were 66.9% and 25.1% in men and 54.4% and 23.4% in women.

During 15 years of follow-up, 87 men and 61 women died due to CVD (37 men and 22 women died due to stroke and 30 men and 8 women died due to coronary heart disease). Table 2 shows HRs of CVD death for each component of metabolic risk factors including all factors in a model, simultaneously. It showed that current smoking, past-smoking, SBP and glucose were significant risk factors of CVD mortality. Table 3 shows adjusted HRs and PAFs for CVD deaths according to the combination of obesity and smoking status. Irrespective of obesity, smoking and CVD mortality in both men and women were positively related. HRs (95% confidence interval [CI]) for non-obese smokers was 3.13 (1.33 to 7.36) in men and 4.32 (1.99 to 9.37) in women compared with non-obese, non-smokers. Estimated numbers of excess CVD deaths (and PAF component) in the non-obese smokers and obese smokers were 32.0 (36.8%), and 7.9 (9.1%) in men and 6.9 (11.3%) and 3.2 (5.2%) in women. The sum of the estimated number of excess CVD deaths (PAF) due to smoking and/or obesity was 49.3 (56.9%) in men and 15.3 (25.1%) in women.

Table 4 shows adjusted HRs and PAF components due to combination of smoking status and metabolic syndrome. Compared to non-smokers without metabolic syndrome, adjusted HRs (95% CI) for CVD deaths was higher in smokers with and without metabolic syndrome (HR 3.19 [1.13 to 9.03] and 3.47 [1.48 to 8.12] in men; 4.94 [1.52 to 16.09] and 3.63 [1.75 to 7.50] in women, respectively). PAFs for CVD mortality in smokers with and without metabolic syndrome were 7.1% and 40.9% in men and 3.9% and 11.9% in women, respectively. The sum of PAF components due to smoking and/or metabolic syndrome was 60.4% in men and 17.0% in women.

Table 5 shows adjusted HRs and PAF components due to the combination of smoking status and clustering of metabolic risk factors. Compared to non-smokers without metabolic risk factor clustering, adjusted HRs (95% CI) for CVD death in smokers with and without metabolic risk factor clustering were 5.85 (1.40 to 24.38) and 4.17 (0.98 to 17.71) for men, and 5.86 (2.41 to 14.23) and 4.56 (1.62 to 12.87) for women, respectively. PAF components for CVD mortality in non-smokers with metabolic risk factors clustering, smokers without metabolic risk factors clustering and smokers with metabolic risk factors clustering were 2.8%, 20.1% and 34.3% for men, and 18.7%, 6.4% and 10.9% for women, respectively.

Table 3: Hazard ratio and population attributable fraction for cardiovascular disease deaths according to the combination of smoking status and obesity*: NIPPON DATA90

		Number of participants	Person-years of follow-up	CVD deaths (n)	CVD mortality rate (per 1,000 person-years)	Adjusted hazard ratio (95% CI)†	Estimated excess CVD deaths (n)	PAF component for CVD deaths (%)
Men								
Non smoker	Non-obese	420	5938	6	1.01	1.00		
	Obese	136	1988	1	0.50	0.67 (0.08 -5.53)	–	–
Past smoker	Non-obese	431	6116	16	2.62	1.93 (0.75 -4.96)	7.7	8.8
	Obese	170	2414	5	2.07	1.52 (0.46 -4.99)	1.7	2.0
Smoker	Non-obese	1212	16780	47	2.80	3.13 (1.33 -7.36)	32.0	36.8
	Obese	383	5277	12	2.27	2.92 (1.09 -7.82)	7.9	9.1
Women								
Non smoker	Non-obese	2,638	37960	29	0.76	1.00		
	Obese	793	11256	17	1.51	1.34 (0.74 -2.45)	4.3	7.1
Past smoker	Non-obese	66	843	1	1.19	1.43 (0.19 -10.61)	0.3	0.5
	Obese	28	383	1	2.61	2.46 (0.33 -18.09)	0.6	1.0
Smoker	Non-obese	282	3889	9	2.31	4.32 (1.99 -9.37)	6.9	11.3
	Obese	91	1224	4	3.27	4.74 (1.66 -13.58)	3.2	5.2

*Obesity was defined as body mass index ≥ 25 kg/m^2.
†Hazard ratios were adjusted for age and drinking.
CVD, cardiovascular diseases; PAF, population attributable fraction; CI, confidence interval.

Table 4: Hazard ratio and population attributable fraction for cardiovascular disease deaths according to the combination of smoking status and metabolic syndrome: NIPPON DATA90.

	Metabolic syndrome*	Number of participants	Person-years of follow-up	CVD deaths (n)	CVD mortality rate (per 1,000 person-years)	Adjusted hazard ratio(95% CI) †		Estimated excess CVD deaths (n)	PAF component for CVD deaths (%)
Men									
Non smoker	-	480	6817	6	0.88	1.00			
	+	76	1109	1	0.90	1.32	(0.16 -10.97)	0.2	0.3
Past smoker	-	494	7036	18	2.56	2.13	(0.84 - 5.39)	9.5	11.0
	+	107	1494	3	2.01	1.49	(0.37 - 6.01)	1.0	1.1
Smoker	-	1343	18620	50	2.69	3.47	(1.48 - 8.12)	35.6	40.9
	+	252	3437	9	2.62	3.19	(1.13 - 9.03)	6.2	7.1
Women									
Non smoker	-	3,034	43585	38	0.87	1.00			
	+	397	5631	8	1.42	0.83	(0.38 - 1.78)	–	–
Past smoker	-	81	1042	1	0.96	1.06	(0.15 - 7.81)	0.05	0.1
	+	13	184	1	5.45	2.98	(0.41 -21.79)	0.6	1.1
Smoker	-	336	4627	10	2.16	3.63	(1.75 - 7.50)	7.2	11.9
	+	37	486	3	6.17	4.94	(1.52 -16.09)	2.4	3.9

*Metabolic syndrome were defined as follows: obesity (body mass index ≥ 25 kg/m^2) plus any two of the following three factors: high blood pressure as blood pressure ≥ 130/85 mmHg or on treatment of hypertension, high blood glucose as blood glucose ≥ 110 mg/dl or on treatment of diabetes, dyslipidemia as triglyceride ≥ 150 mg/dl or high density lipoprotein cholesterol <40 mg/dl or on treatment of dyslipidemia.

†Hazard ratios were adjusted for age and drinking.

CVD, cardiovascular diseases; PAF, population attributable fraction; CI, confidence interval.

Table 5: Hazard ratio and population attributable fraction for cardiovascular disease deaths according to the combination of smoking status and clustering of metabolic risk factors: NIPPON DATA90.

	Clustering of metabolic risk factors*	Number of participants	Person-years of follow-up	CVD deaths (n)	CVD mortality rate (per 1,000 person-years)	Adjusted hazard ratio (95% CI) †			Estimated excess CVD deaths (n)	PAF component for CVD deaths (%)
Men										
Non smoker	0 or 1	281	4002	2	0.50	1.00				
	2 ≤	275	3924	5	1.27	1.94	(0.38	-10.00)	2.4	2.8
Past smoker	0 or 1	282	4084	7	1.71	2.41	(0.50	-11.65)	4.1	4.7
	2 ≤	319	4446	14	3.15	3.37	(0.76	-14.96)	9.8	11.3
Smoker	0 or 1	819	11465	23	2.01	4.17	(0.98	-17.71)	17.5	20.1
	2 ≤	776	10592	36	3.40	5.85	(1.40	-24.38)	29.8	34.3
Women										
Non smoker	0 or 1	2,117	30554	14	0.46	1.00				
	2 ≤	1314	18661	32	1.71	1.55	(0.82	-2.95)	11.4	18.7
Past smoker	0 or 1	54	698	0	--			--	--	--
	2 ≤	40	527	2	3.79	3.08	(0.69	-13.81)	1.4	2.2
Smoker	0 or 1	222	3098	5	1.61	4.56	(1.62	-12.87)	3.9	6.4
	2 ≤	151	2016	8	3.97	5.86	(2.41	-14.23)	6.6	10.9

*Metabolic risk factors were any of the following four factors: obesity (body mass index ≥ 25 kg/m^2), high blood pressure as blood pressure ≥ 130/85 mmHg or on treatment of hypertension, high blood glucose as blood glucose ≥ 110 mg/dl or on treatment of diabetes, dyslipidemia as triglyceride ≥ 150 mg/dl or high density lipoprotein cholesterol < 40 mg/dl or on treatment of dyslipidemia.
†Hazard ratios were adjusted for age and drinking.
CVD, cardiovascular diseases; PAF, population attributable fraction; CI, confidence interval.

Discussion

The present report of a representative Japanese cohort showed that the majority of excess CVD deaths were observed in smokers without metabolic syndrome. The PAF component of CVD deaths in smokers without metabolic syndrome were 5 times higher than those in participants with metabolic syndrome in men (40.9% vs. 8.5%). The HR of CVD deaths in smokers without metabolic syndrome were also higher than non-smokers without metabolic syndrome, and it was similar to the HR in smokers with metabolic syndrome (3.47 vs. 3.19).

In Asian countries including Japan, there has been a rise in metabolic syndrome [7,25]. In these areas, prevalence of smoking has been higher than that in Western countries and smoking rates has been still increasing in younger women [14]. Previous studies have reported that obesity and smoking are risk factors for CVD [5,6,10,11]. The association of clustering of metabolic risk factors, including hyperglycemia, dyslipidemia, and hypertension, with CVD risk has also been widely reported [1,4,17,18]. Furthermore, a previous study from Japan reported that the effect of risk factor accumulation on CVD incidence was more evident among smokers than non smokers [17]. However, these previous reports did not show the attribution of the combination of smoking and metabolic syndrome (or obesity) to CVD events. To our knowledge, this is the first report showing that the majority of excess CVD deaths occurred in smokers without metabolic syndrome in a Asian population. A strength of our report is that the study was conducted in a 15-year cohort of nationwide representative Japanese samples.

In Japan, new health checkups and healthcare advice focusing on the metabolic syndrome to prevent CVD began in April 2008 through health insurance providers [7]. Our results support the necessity of intervention for people with metabolic syndrome because these people appear to be at higher CVD risk; however, PAF component in men and in women with metabolic syndrome were only 8.5% and 5.0%, respectively. On the other hand, the present study indicated that PAFs among smokers without metabolic syndrome were 40.9% in men and 11.9% in women; who are not the target population of the new health educational program in Japan. Moreover, not only PAF but also HR of smokers without metabolic syndrome was substantially higher. Thus the program might overlook a large population at an increased risk of CVD. Activities of smoking cessation for non-obese people would be still important for the prevention of CVD in Japan.

In the present study, we examined the association between each component of metabolic risk factors and CVD death. We conformed that current and past smoking, SBP and glucose were significant risk factors of CVD mortality in our study participants. Several previous reports revealed that clustering of metabolic risk factors increases CVD risk, irrespective of the presence of obesity [17,18]. When obesity was dealt with one of metabolic risk factors (not an essential factor) in the present study (Table 5), the PAF in smokers with metabolic risk factor clustering got larger in men (34.3%). However, even for smokers without metabolic risk factors clustering in the present study, PAF was 20.1% in men. This finding indicated that even if obesity is not essential for the diagnostic criteria of metabolic syndrome like the National Cholesterol Education Program (NCEP) [26], an intervention for smokers without clustering of metabolic risk factors would be also important for the prevention of CVD.

This study has several limitations. First, we used non-fasting blood samples and thus we might have misclassified several individuals with diabetes and dyslipidemia. Second, we used body mass index ≥ 25 kg/m^2 to define obesity and thus we might have misclassified individuals with abdominal obesity with higher waist circumference. However, this limitation would be ignorable because the correlation between BMI and waist circumstance is usually high enough. The cut-off point of body mass index for Japanese [21] is different from that for Asia-Pacific Region in the WHO definition (body mass index ≥ 23 kg/m^2) [27], which may underestimate the PAF in Asian people. Third, we did not adjust for socioeconomic status in this study. However, all Japanese are covered by the national health insurance program and socioeconomic status would not limit access to treatment in Japan. Fourth, in this study, we used information on smoking habit from self-reported smoking history; this may cause recall and information biases. Fifth, the numbers of participants or CVD events were not enough to analyze according to the number of cigarettes per day; therefore, we did not consider the intensity of smoking in this paper.

Conclusions

In conclusion, this long-term cohort study of representative Japanese samples indicated that CVD mortality in smokers without metabolic syndrome or without obesity was substantially high and a large proportion of excess deaths were observed in these groups. These findings suggest that intervention targeting on smokers, irrespective of the presence of metabolic syndrome (or obesity), is still important for the prevention of CVD death in relatively lean Japanese population with high smoking rate. This could apply to other Asian populations with high smoking rate but with lower prevalence of obesity compared with Western populations.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed to the concept, design, analysis, interpretation of data, and preparation of the manuscript. All authors read and approved the final manuscript.

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(4) やせていない日本人における境界域代謝性危険因子の集積と循環器疾患死亡リスクとの関連：NIPPON DATA90 15年追跡結果における検討

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【目的】メタボリックシンドロームの診断基準項目は正常高値血圧や糖尿病境界型等の従来要観察とされていた者から要医療とされた者を含む。本研究では従来要観察とされていた正常高値血圧や糖尿病境界型等の境界域代謝性危険因子の集積と循環器疾患死亡リスクの関連を検討した。

【方法】全国300箇所から無作為抽出された30歳以上の男女8384人NIPPON DATA90コホートから循環器疾患既往を持つ者やデータ欠損およびBMI 18.5未満のやせの者を除いた6758人を15年間追跡した。Cox比例ハザードモデルを用いて境界域代謝性危険因子の集積数による循環器疾患死亡ハザード比(HR)ならびに95%信頼区間（95%CI）を算出した。境界域代謝性危険因子は血圧高値130/85以上かつ140/90mmHg未満，随時血糖高値140mg/dl以上かつ200mg/dl未満，脂質異常は中性脂肪150mg/dl以上かつ/または男性HDL40mg/dl未満，女性HDL50mg/dl未満，肥満BMI25kg/m^2以上とした。なお、治療中の者は境界域代謝性危険因子の保有者には含まず、確立された要医療域の代謝性危険因子の保有者として扱った。年齢、性別、喫煙習慣、飲酒習慣、総コレステロール値を調整因子とした。また、境界域代謝性危険因子の集積による循環器疾患死亡の人口寄与危険割合(PAF)を算出した。

【結果】15年の追跡期間中、282人の循環器疾患死亡が確認された。対象者の34%に境界域代謝性危険因子集積を認めた。一方、要医療域の危険因子は47%であった。境界域代謝性危険因子の集積数（以下、危険因子数 1,2,3 以上）による循環器疾患死亡