≥1 cup/d). To correct the estimate for socioeconomic status, the models were adjusted for years of education. Time spent walking was used as an indicator of physical activity because it is the most common type of physical activity among middle-aged and older individuals in Japan. The validity and re-producibility of the question on time spent walking has been reported previously (18). Before including the above variables into the multivariate models, interactions between green tea consumption and confounders were tested through the addition of cross-product terms to the multivariate model.

We conducted stratified analyses by age, physical function status, and smoking status. We stratified by age (<70 y or ≥70 y), because death from pneumonia increases with age (19, 20). We also stratified by physical function status, because we considered that the participants with limited physical function (MOS score of 0–1) would be at high risk of aspiration pneumonia. In addition, stratified analysis by smoking status was conducted, because smoking is a risk factor for pneumonia (4, 5). For stroke, our previous study found an inverse association between green tea consumption and death from stroke (15). Therefore, to

TABLE 1
Baseline characteristics of men according to green tea consumption (n = 19,079)

| Characteristics | Green tea consumption | | | | P value[1] |
	<1 cup/d (n = 5775)	1–2 cups/d (n = 4313)	3–4 cups/d (n = 3897)	≥5 cups/d (n = 5094)	
Age (y)	57.2 ± 10.7[2]	57.3 ± 10.8	59.8 ± 10.3	61.4 ± 9.9	<0.0001
Years of education [n (%)]					<0.0001
<10 y	3460 (62.6)	2356 (56.6)	2206 (58.5)	3041 (61.6)	
≥10 y	2067 (37.4)	1808 (43.4)	1564 (41.5)	1894 (38.4)	
BMI [n (%)]					<0.006
<18.5 kg/m²	179 (3.3)	138 (3.4)	103 (2.7)	193 (3.9)	
18.5–24.9 kg/m²	3824 (69.6)	2929 (71.0)	2713 (72.2)	3489 (71.3)	
≥25.0 kg/m²	1489 (27.1)	1056 (25.6)	942 (25.1)	1215 (24.8)	
Time spent walking [n (%)]					<0.006
<1 h/d	2676 (49.9)	2062 (51.0)	1960 (53.7)	2443 (51.4)	
≥1 h/d	2685 (50.1)	1979 (49.0)	1693 (46.3)	2308 (48.6)	
Physical function status [n (%)]					<0.0001
Able to perform vigorous or moderate activity	4663 (83.0)	3579 (85.2)	3258 (85.6)	4251 (85.3)	
Capable of light activity	627 (11.1)	411 (9.8)	388 (10.2)	527 (10.6)	
Capable of self-care or unable to do anything	329 (5.9)	210 (5.0)	160 (4.2)	203 (4.1)	
History of hypertension [n (%)]					<0.0001
Yes	1238 (21.4)	1003 (23.3)	986 (25.3)	1248 (24.5)	
No	4537 (78.6)	3310 (76.7)	2911 (74.7)	3846 (75.5)	
History of diabetes mellitus [n (%)]					0.09
Yes	386 (6.7)	284 (6.6)	304 (7.8)	371 (7.3)	
No	5389 (93.3)	4029 (93.4)	3593 (92.2)	4723 (92.7)	
History of gastric ulcer [n (%)]					0.002
Yes	1102 (19.1)	848 (19.7)	794 (20.4)	1116 (21.9)	
No	4673 (80.9)	3465 (80.3)	3103 (79.6)	3978 (78.1)	
History of tuberculosis [n (%)]					<0.0001
Yes	205 (3.5)	151 (3.5)	206 (5.3)	307 (6.0)	
No	5570 (96.5)	4162 (96.5)	3691 (94.7)	4787 (94.0)	
Smoking status [n (%)]					<0.0001
Never	1151 (21.7)	804 (20.4)	722 (19.9)	824 (17.5)	
Former	1289 (24.3)	964 (24.4)	1022 (28.2)	1349 (28.6)	
Current, <20 cigarettes/d	930 (17.6)	713 (18.0)	650 (17.9)	898 (19.1)	
Current, ≥20 cigarettes/d	1926 (36.4)	1471 (37.2)	1230 (34.0)	1640 (34.8)	
Alcohol consumption [n (%)]					<0.0001
Never	931 (16.5)	615 (14.6)	563 (14.8)	918 (18.5)	
Former	540 (9.6)	379 (9.0)	372 (9.8)	547 (11.1)	
Current	4161 (73.9)	3214 (76.4)	2865 (75.4)	3490 (70.4)	
Total energy intake (kcal/d)	1783 ± 612.5	1812 ± 603.3	1852 ± 587.7	1901 ± 591.3	<0.0001
Daily dietary consumption					
Miso (soybean paste) soup [n (%)]	4914 (85.1)	3807 (88.3)	3504 (89.9)	4633 (91.0)	<0.0001
Soybean products (g/d)	47 ± 28.7	50 ± 28.3	53 ± 27.7	57 ± 26.9	<0.0001
Total fish (g/d)	55 ± 35.5	58 ± 34.8	61 ± 34.3	67 ± 34.6	<0.0001
Green or yellow vegetables (g/d)	62 ± 42.9	67 ± 43.2	72 ± 43.3	78 ± 45.9	<0.0001
Coffee, ≥1 cup/d [n (%)]	2357 (44.3)	1892 (50.9)	1415 (42.5)	1513 (35.7)	<0.0001

[1] ANOVA or chi-square test.
[2] Mean ± SD (all such values).

The American Journal of Clinical Nutrition

distinguish the relation between green tea consumption and pneumonia risk and that between green tea consumption and stroke risk, we conducted a sensitivity analysis with the use of a subset of data that was restricted to participants with a very low risk of stroke, who had no history of hypertension, and had never smoked.

To minimize the possibility that diet or lifestyle factors had changed in response to subclinical disease, we repeated all analyses after excluding participants who had died in the first 3 y

of follow-up. To ensure that the estimates were not biased by multicollinearity, the age-adjusted HRs for the green tea consumption categories were also calculated and compared with the multivariate-adjusted HRs.

RESULTS

Baseline characteristics of the participants according to green tea consumption category are shown in **Table 1** and **Table 2**.

TABLE 2
Baseline characteristics of women according to green tea consumption (n = 21,493)

| Characteristics | Green tea consumption | | | | |
	<1 cup/d (n = 4877)	1–2 cups/d (n = 4458)	3–4 cups/d (n = 4950)	≥5 cups/d (n = 7208)	P value[1]
Age (y)	58.5 ± 10.8[2]	59.6 ± 10.5	61.2 ± 9.7	62.2 ± 9.2	<0.0001
Years of education [n (%)]					<0.0001
<10 y	2683 (58.9)	2288 (54.3)	2545 (54.0)	3980 (58.0)	
≥10 y	1689 (41.1)	1926 (45.7)	2167 (46.0)	2877 (42.0)	
BMI [n (%)]					0.003
<18.5 kg/m²	209 (4.6)	158 (3.7)	192 (4.1)	252 (3.7)	
18.5–24.9 kg/m²	2942 (64.3)	2770 (65.3)	3096 (65.5)	4,335 (62.9)	
≥25.0 kg/m²	1422 (31.1)	1317 (31.0)	1438 (30.4)	2301 (33.4)	
Time spent walking [n (%)]					0.0006
<1 h/d	2444 (55.7)	2295 (56.1)	2670 (59.2)	3836 (58.7)	
≥1 h/d	1941 (44.3)	1794 (43.9)	1843 (40.8)	2703 (41.3)	
Physical function status [n (%)]					<0.0001
Able to perform vigorous or moderate activity	3171 (67.1)	2963 (68.6)	3313 (68.4)	4925 (70.0)	
Capable of light activity	936 (19.8)	859 (19.9)	1039 (21.4)	1482 (21.1)	
Capable of self-care or unable to do anything	621 (13.1)	496 (11.5)	494 (10.2)	624 (8.9)	
History of hypertension [n (%)]					<0.0001
Yes	1203 (24.7)	1212 (27.2)	1413 (28.5)	2157 (29.9)	
No	3674 (75.3)	3246 (72.8)	3537 (71.5)	5051 (70.1)	
History of diabetes mellitus [n (%)]					0.06
Yes	252 (5.2)	204 (4.6)	264 (5.3)	413 (5.7)	
No	4625 (94.8)	4254 (95.4)	4686 (94.7)	6795 (94.3)	
History of gastric ulcer [n (%)]					0.70
Yes	531 (10.9)	510 (11.4)	545 (11.0)	774 (10.7)	
No	4346 (89.1)	3948 (88.6)	4405 (89.0)	6434 (89.3)	
History of tuberculosis [n (%)]					0.0002
Yes	123 (2.5)	102 (2.3)	161 (3.2)	253 (3.5)	
No	4754 (97.5)	4356 (97.7)	4789 (96.8)	6955 (96.5)	
Smoking status [n (%)]					<0.0001
Never	3370 (87.5)	3231 (91.6)	3654 (92.9)	5062 (89.3)	
Former	112 (2.9)	84 (2.4)	91 (2.3)	152 (2.7)	
Current, <20 cigarettes/d	236 (6.1)	138 (3.9)	146 (3.7)	316 (5.6)	
Current, ≥20 cigarettes/d	136 (3.5)	73 (2.1)	44 (1.1)	140 (2.4)	
Alcohol consumption [n (%)]					<0.0001
Never	2883 (70.7)	2697 (73.0)	3092 (74.9)	4341 (72.4)	
Former	220 (5.4)	146 (3.9)	159 (3.9)	248 (4.1)	
Current	977 (23.9)	853 (23.1)	876 (21.2)	1407 (23.5)	
Total energy intake (kcal/d)	1188 ± 365.9	1231 ± 347.9	1268 ± 329.8	1310 ± 330.4	<0.0001
Daily dietary consumption					
Miso (soybean paste) soup [n (%)]	4004 (82.1)	3886 (87.2)	4409 (89.1)	6395 (88.7)	<0.0001
Soybean products (g/d)	43 ± 24.2	47 ± 23.1	50 ± 22.0	51 ± 21.5	<0.0001
Total fish (g/d)	47 ± 30.6	50 ± 30.3	54 ± 29.0	57 ± 29.7	<0.0001
Green or yellow vegetables (g/d)	72 ± 47.0	81 ± 47.4	85 ± 46.6	89 ± 48.4	<0.0001
Coffee, ≥1 cup/d [n (%)]	1829 (42.2)	1783 (47.0)	1599 (39.1)	1715 (29.4)	<0.0001

[1] ANOVA or chi-square test.
[2] Mean ± SD (all such values).

Men and women with higher green tea consumption were significantly older and had a history of hypertension and tuberculosis, but they were less likely to have time spent walking. They were also more likely to have a higher energy intake and to consume individual foods such as miso soup, soybean products, total fish, and total green or yellow vegetables. No apparent associations were observed between green tea consumption categories and years of education and alcohol consumption. Men were more likely to have a history of gastric ulcer, but they were less likely to be obese and to have never smoked. Women were more likely to be obese and to have a history of diabetes mellitus.

Over 12 y of follow-up (406,824 person-years), we documented 406 deaths from pneumonia. A total of 6033 participants were lost to follow-up during the study period because of withdrawal from the NHI system, and the follow-up rate was 85.1%. The association between green tea consumption and the HRs and associated 95% CIs of death from pneumonia are shown in Table 3. We found inverse associations between green tea consumption and death from pneumonia in women but not in men. In women, the multivariate HRs of death from pneumonia associated with different frequencies of green tea consumption were 1.00 (reference) for <1 cup/d, 0.59 (95% CI: 0.36, 0.98) for 1–2 cups/d, 0.55 (95% CI: 0.33, 0.91) for 3–4 cups/d, and 0.53 (95% CI: 0.33, 0.83) for ≥5 cups/d (P for trend: 0.008). Comparison between the age-adjusted model and the multivariate model suggested that the estimates were not biased by multicollinearity. The multivariate HRs of death from pneumonia according to the 5 categories of green tea consumption, without combining the lower 2 categories, were 1.00 (reference) for never, 0.56 (95% CI: 0.30, 1.02) for occasional, 0.41 (95% CI: 0.22, 0.76) for 1–2 cups/d, 0.38 (95% CI: 0.21, 0.70) for 3–4 cups/d, and 0.36 (95% CI: 0.21, 0.65) for ≥5 cups/d (P for trend: 0.002). When we excluded the 47 participants who died within the first 3 y of follow-up, the results did not change substantially.

We also tested the interaction between green tea consumption and confounders through the addition of cross-product terms to the multivariate model. Interaction between green tea consumption and sex was statistically significant (P = 0.01), but no interaction between green tea consumption and the other variables was observed.

The multivariate HRs of death from pneumonia according to green tea consumption stratified by age, physical function status, and smoking status in women are shown in Table 4. Among participants aged <70 y and participants aged ≥70 y, the point estimates of the HRs for death from pneumonia were below unity. In contrast, in men, no apparent association was observed between green tea consumption and HRs of death from pneumonia among participants aged <70 y and those aged ≥70 y. Although we additionally conducted stratified analyses by age at 65 y and 75 y, the results also did not change substantially. For physical function status, in men, no apparent association was observed between green tea consumption and the HRs of death from pneumonia in all subgroups. In women, in all subgroups, the point estimates of the HRs for death from pneumonia were below unity, although the trend test showed no statistically significant relations. Among never smokers in women, green tea consumption was substantially associated with a low risk of death from pneumonia. Because the number of deaths from pneumonia in former smokers and current smokers was insufficient for separate analysis, we combined the data of the former smokers and current smokers. In contrast, for men, no apparent association was observed between green tea consumption and the HRs of death from pneumonia among the participants in all subgroups.

When analysis was restricted to the 13,735 participants with a low risk of stroke, who had no history of hypertension and had never smoked, the point estimates of the HRs for death from pneumonia were below unity. The multivariate HRs were 1.00

TABLE 3
Hazard ratios (HRs) of death from pneumonia according to green tea consumption in Japan[1]

	Green tea consumption				
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	P for trend
Men (n = 19,079)					
Person-years	57,481	42,963	38,830	51,309	
No. of deaths	75	52	55	93	
Age-adjusted HR[2]	1.00 (referent)	0.90 (0.63, 1.28)	0.81 (0.57, 1.15)	0.91 (0.67, 1.23)	0.49
Multivariate HR[2,3]	1.00 (referent)	0.98 (0.69, 1.41)	1.02 (0.71, 1.45)	1.15 (0.83, 1.59)	0.38
Multivariate HR[2–4]	1.00 (referent)	0.97 (0.65, 1.45)	1.07 (0.73, 1.56)	1.21 (0.86, 1.71)	0.24
Women (n = 21,493)					
Person-years	47,426	44,411	50,528	73,879	
No. of deaths	43	24	26	38	
Age-adjusted HR[2]	1.00 (referent)	0.54 (0.33, 0.89)	0.48 (0.30, 0.78)	0.44 (0.29, 0.68)	0.0004
Multivariate HR[2,3]	1.00 (referent)	0.59 (0.36, 0.98)	0.55 (0.33, 0.91)	0.53 (0.33, 0.83)	0.008
Multivariate HR[2–4]	1.00 (referent)	0.65 (0.39, 1.09)	0.56 (0.33, 0.94)	0.50 (0.31, 0.81)	0.005

[1] HRs were calculated by Cox proportional hazard regression analysis.

[2] 95% CIs in parentheses.

[3] Adjusted for age (continuous variable); years of education (<10 or ≥10 y); BMI (in kg/m²; <18.5, 18.5–24.9, or ≥25.0); time spent walking (<1 or ≥1 h/d); physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of gastric ulcer (yes or no); history of tuberculosis (yes or no); smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d); alcohol consumption (never, former, or currently drinking); daily total energy intake (continuous variables); daily consumption of miso (soybean paste) soup (yes or no); daily consumption of soybean products, total fish, and total green or yellow vegetables (for each food, continuous variable); and daily consumption of coffee (<1 or ≥1 cup).

[4] Participants who died in the first 3 y of follow-up were excluded from this analysis.

TABLE 4
Stratified analysis of the association between green tea and death from pneumonia in women[1]

	Green tea consumption					
	<1 cup/d	1–2 cups/d	3–4 cups/d	≥5 cups/d	P for trend	P for interaction
Age						0.15
<70 y (n = 17,235)						
Person-years	39,752	36,582	40,865	58,538		
No. of deaths	11	7	5	8		
Multivariate HR[2,3]	1.00 (referent)	0.69 (0.26, 1.82)	0.38 (0.13, 1.13)	0.42 (0.16, 1.10)	0.05	
≥70 y (n = 4258)						
Person-years	7673	7829	9662	15,341		
No. of deaths	32	17	21	30		
Multivariate HR[2]	1.00 (referent)	0.56 (0.31, 1.02)	0.61 (0.35, 1.08)	0.57 (0.34, 0.96)	0.06	
Physical function status						0.32
Able to perform vigorous or moderate activity (n = 14,372)						
Person-years	31,638	30,038	34,326	51,240		
No. of deaths	11	4	9	12		
Multivariate HR[3,4]	1.00 (referent)	0.33 (0.10, 1.05)	0.52 (0.20, 1.31)	0.46 (0.20, 1.11)	0.18	
Capable of light activity (n = 4316)						
Person-years	8976	8499	10,603	15,049		
No. of deaths	11	12	3	12		
Multivariate HR[3,4]	1.00 (referent)	1.00 (0.43, 2.35)	0.23 (0.06, 0.84)	0.58 (0.24, 1.36)	0.07	
Capable of self-care or unable to do anything (n = 2235)						
Person-years	5350	4564	4634	5844		
No. of deaths	21	7	13	12		
Multivariate HR[3,4]	1.00 (referent)	0.38 (0.16, 0.92)	0.62 (0.30, 1.30)	0.45 (0.22, 0.95)	0.07	
Smoking status						0.31
Never (n = 15,317)						
Person-years	32,973	32,321	37,575	52,132		
No. of deaths	26	21	21	25		
Multivariate HR[3,5]	1.00 (referent)	0.81 (0.45, 1.46)	0.67 (0.37, 1.21)	0.56 (0.32, 0.99)	0.04	
Former (n = 439) or current (n = 1229)						
Person-years	4682	2880	2751	6124		
No. of deaths	7	1	0	3		
Multivariate HR[3,5]	1.00 (referent)	0.11 (0.01, 1.09)	—	0.13 (0.02, 0.67)	0.01	

[1] Hazard ratios (HRs) were calculated by Cox proportional hazard regression analysis and were adjusted for age (continuous variable); years of education (<10 or ≥10 y); BMI (in kg/m²; <18.5, 18.5–24.9, or ≥25.0); time spent walking (<1 or ≥1 h/d); history of hypertension (yes or no); history of diabetes mellitus (yes or no); history of gastric ulcer (yes or no); history of tuberculosis (yes or no); alcohol consumption (never, former, or currently drinking); daily total energy intake (continuous variables); daily consumption of miso (soybean paste) soup (yes or no); daily consumption of soybean products, total fish, and total green or yellow vegetables (for each food, continuous variable); and daily consumption of coffee (<1 or ≥1 cup).

[2] Additionally adjusted for physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything) and smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d).

[3] 95% CIs in parentheses.

[4] Additionally adjusted for smoking status (never, former, currently smoking <20 cigarettes/d, or currently smoking ≥20 cigarettes/d).

[5] Additonally adjusted for physical function status (those able to perform vigorous or moderate activity, those capable of light activity, or those capable of self-care or unable to do anything).

(reference) for <1 cup/d, 0.65 (95% CI: 0.30, 1.40) for 1–2 cups/d, 0.80 (95% CI: 0.41, 1.57) for 3–4 cups/d, and 0.77 (95% CI: 0.41, 1.43) for ≥5 cups/d (P for trend: 0.52).

DISCUSSION

This is the first prospective cohort study to have investigated the association between green tea consumption and death from pneumonia. Our study showed an inverse association between green tea consumption and death from pneumonia in women. This finding was consistent with in vitro and animal studies that have shown activities of catechins against a variety of infectious agents (9–13).

Our study showed a discrepancy between men and women for the association between green tea consumption and risk of death from pneumonia. We first considered that this discrepancy might be attributable to the effect of cigarette smoking, because the smoking rate was higher in men than in women. However, inverse associations were observed among never smokers in women (Table 4), and no apparent associations were observed for any smoking status among men. In addition, no interaction between green tea consumption and smoking status was observed. We therefore secondly considered that catechin activities might differ between men and women. It has been reported that tea catechins may have estrogenic activity, which might partly account for the discrepancy between men and women

(21). However, the reasons for the discrepancy remain largely uncertain.

Our previous study also indicated an inverse association between green tea consumption and death as a result of cardiovascular disease, and this inverse association was stronger in women (15). Therefore, the present results could be interpreted as not only an effect of green tea in preventing pneumonia, but also as an effect of green tea in preventing other diseases that are associated with pneumonia risk, such as stroke. We did not follow the incidence of stroke that had occurred after the baseline survey. However, the results of sensitivity analysis of participants with a low risk of stroke, who had no history of hypertension and had never smoked, showed an inverse association between green tea consumption and risk of death from pneumonia. In Japan, primary cause of death has been determined according to the rules for selecting the underlying cause of death in the ICD-10. Therefore, death from pneumonia associated with previous stroke was classified as stroke, and pneumonia unrelated to previous stroke was classified as pneumonia. The present results might therefore be interpreted as an effect of green tea against infection.

The observed inverse associations between green tea consumption and death from pneumonia might be mediated by health and comorbidities that lead to aspiration pneumonia. However, we limited deaths from influenza and pneumonia (J10–J18), and we did not include aspiration pneumonia (J69). We also statistically controlled for a variety of potential confounding factors in the multivariate-adjusted model and conducted analyses after excluding participants who had died in the first 3 y of follow-up. In addition, we conducted a stratified analysis by age, because death from pneumonia increases with age (19, 20). The inverse association between green tea consumption and risk of death from pneumonia was consistently observed in women, irrespective of whether they were aged <70 y or aged ≥70 y. We also conducted a stratified analysis by physical function status, because we considered that participants with limited physical function would be at higher risk of aspiration pneumonia. The inverse association between green tea consumption and risk of death from pneumonia was consistently observed, irrespective of whether participants were able to perform vigorous or moderate activity, light activity, or merely self-care or unable to do anything unaided. The finding that their 95% CIs were not significant might have been due to lack of statistical power. Therefore, the observed inverse associations between green tea consumption and death from pneumonia might not be mediated by health and comorbidities that lead to aspiration pneumonia.

Our finding of an inverse association between green tea consumption and death from pneumonia appeared to be a threshold effect. In women, the multivariate HRs of death from pneumonia compared with <1 cup/d were 0.59 for 1–2 cups/d, 0.55 for 3–4 cups/d, and 0.53 for ≥5 cups/d. The results of analysis according to the 5 categories, without combining the lower 2 categories of green tea consumption, also showed a threshold effect. In other words, persons consuming ≥1 cup/d might receive the benefit from the beverage. There may be differences in dietary intake and health characteristics besides green tea consumption between the lowest fourth and the highest three-fourths of the distribution. However, in our models we adjusted for various potential confounders, and the estimates did not change substantially from the age-adjusted estimates. Further-

more, a previous study showed that higher intakes of fruit and vegetables were associated with lower risk of death from all causes, cancer, and cardiovascular disease, and that the association appeared to be a threshold effect (22). Taken together, the results might indicate that polyphenols, contained in fruit and vegetables as well as green tea, might operate through a threshold effect.

Our study had several limitations. First, we collected the information on green tea consumption only once before the follow-up period. Therefore, measurement error caused by changes in green tea consumption over time among the subjects could have distorted our results. However, this misclassification may be nondifferential and would tend to result in underestimation of the effect of green tea consumption. Second, we had no information about the cause of pneumonia. Of 406 deaths from pneumonia, 96% were classified as organism unspecified (J18) because such information was not provided on the death certificates. However, the causative agent responsible for pneumonia is rarely identified, even in rigorous epidemiologic studies of pneumonia (23, 24). Third, although we statistically controlled for a variety of potential confounding factors in the multivariate-adjusted model, conducted analyses after excluding participants who had died in the first 3 y of follow-up, and conducted a stratified analysis by age and physical function status, we were unable to eliminate residual confounding. In addition, we were unable to fully exclude the possibility that the death from pneumonia might have included pneumonia associated with previous stroke, although the primary cause of death was determined according to the rules for selecting the underlying cause of death in the ICD-10. Aspiration pneumonia also might have been coded as death from pneumonia, although we limited deaths from pneumonia (J10–J18), and we did not include aspiration pneumonia (J69). Therefore, clinical trials are ultimately necessary to confirm the protective effect of green tea on death from pneumonia.

In conclusion, this prospective cohort study has shown an inverse association between green tea consumption and death from pneumonia among Japanese women. Our data showed the effect of green tea consumption against pneumonia and support the possibility that green tea components exert antiviral and antimicrobial activities against a variety of infectious agents.

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Mild metabolic abnormalities, abdominal obesity and the risk of cardiovascular diseases in middle-aged Japanese men

Running title: Mild metabolic abnormalities and CVD

Wataru Hirokawa[1], Koshi Nakamura[1], Masaru Sakurai[1], Yuko Morikawa[1], Katsuyuki Miura[2], Masao Ishizaki[3], Katsushi Yoshita[4], Teruhiko Kido[5], Yuchi Naruse[6], and Hideaki Nakagawa[1]

1. Department of Epidemiology and Public Health, Kanazawa Medical University, Uchinada, Japan
2. Department of Health Science, Shiga University of Medical Science, Otsu, Japan
3. Department of Social and Environmental Medicine, Kanazawa Medical University, Uchinada, Japan
4. Nutritional Epidemiology Program, National Institute of Health and Nutrition, Tokyo, Japan
5. School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan
6. Department of Human Science and Fundamental Nursing, Toyama University School of Nursing, Toyama, Japan

Aim: We investigated the individual and population impacts of mild abnormalities associated with the metabolic syndrome (blood pressure, lipids and glucose) and abdominal obesity, to which lifestyle modification is initially applicable, on cardiovascular disease risk. **Methods:** Using a cohort study of 2,685 Japanese men aged 35 to 59 years with an 11-year follow-up period, we calculated relative risks for cardiovascular diseases due to mild metabolic abnormalities that included at least one of the following three conditions: 1) systolic blood pressure 130-139 mmHg and/or diastolic blood pressure 85-89 mmHg; 2) triglycerides 150-299 mg/dl and/or high-density lipoprotein cholesterol 35-39 mg/dl; and 3) fasting plasma glucose 110-125 mg/dl and/or abdominal obesity. Participants with a mild metabolic abnormality were compared to participants with no metabolic abnormality or abdominal obesity. The population attributable fraction of these abnormalities for cardiovascular diseases was also estimated. **Results:** At baseline, 9.8% and 21.8% of the total population had a mild metabolic abnormality with or without abdominal obesity, respectively, while 7.5% had isolated abdominal obesity without any metabolic abnormality. A mild metabolic abnormality with or without abdominal obesity and isolated abdominal obesity increased the risk of cardiovascular disease by 2.68-fold, 1.49-fold, and 2.36-fold, respectively. Approximately 20% of cardiovascular diseases in the total population were attributable to either mild metabolic abnormalities or isolated abdominal obesity. **Conclusion:** The importance of lifestyle modification should be acknowledged especially in cases with a mild metabolic abnormality and/or abdominal obesity, who may contribute to approximately 20% of the population burden for cardiovascular diseases.

Keywords: abdominal obesity, blood pressure, cardiovascular diseases, glucose, lipids

Corresponding author: Koshi Nakamura
Department of Epidemiology and Public Health, Kanazawa Medical University
1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan
Tel: +81-76-218-8093 Fax: +81-76-286-3728 Email: knaka@kanazawa-med.ac.jp

[**Introduction**]

Cardiovascular risk factors such as elevated blood pressure, abnormal lipid profiles and disordered glucose metabolism have a graded linear relationship with the risk of cardiovascular diseases including coronary heart disease and stroke [1-5]. On the basis of this evidence, more rigorous intervention is applicable to a worse condition. Thus, individuals with moderate-to-severely abnormal findings are generally required to be under medical control. Individuals with only mildly abnormal findings are usually encouraged to improve these abnormalities, using non-pharmacological therapy, in health checkups and healthcare advice, even though the individuals may have several mildly abnormal findings.

In 2008, the Japanese national government introduced a nationwide public health strategy to reduce the burden of cardiovascular diseases due to abdominal obesity and associated metabolic disorders, mainly elevated blood pressure, high triglycerides, low high-density lipoprotein (HDL) cholesterol, and disordered glucose metabolism [6-8]. In this strategy which is influenced by the Japanese concept and diagnostic criteria of the metabolic syndrome [9], priority is given to obese individuals who have metabolic disorders, with the concept that such individuals should modify their lifestyle in order to decrease accumulation of abdominal fat, which in turn may lead to control of blood pressure and lipid and glucose levels. In addition, the severity of metabolic disorders is also considered to determine whether individuals should be treated first using pharmacological or non-pharmacological therapies. Although non-obese individuals with a metabolic abnormality are not prior candidates in this strategy, appropriate healthcare advice should be provided for such non-obese individuals. Non-obese individuals with a mild metabolic abnormality are also in need of non-pharmacological therapy initially, but this therapy is, at least partially, different from what is required for obese individuals with a mild metabolic abnormality. There is therefore a need to examine the risk of developing cardiovascular diseases, taking into account the above situations as they apply to the Japanese population. It is particularly important for public health purposes such as medical checkups and healthcare advice, to estimate the population burden of cardiovascular diseases due to a mild metabolic abnormality with and without abdominal obesity, to which appropriate non-pharmacological therapy should be applicable, depending on the presence or absence of abdominal obesity. To the best of our knowledge, little is known on the risk of developing cardiovascular diseases due to mild metabolic abnormalities associated with the metabolic syndrome and/or abdominal obesity in the Japanese population, as previous studies have mainly examined the association between metabolic disorders (or morbid conditions pursuant to this syndrome) and the risk of these diseases, without considering the severity of the metabolic disorders and excluding individuals who are taking medication for metabolic disorders [10-18]. We used a cohort study in middle-aged Japanese men to investigate the individual and population impacts of mild abnormalities associated with the metabolic syndrome and/or abdominal obesity on the risk of cardiovascular diseases.

[**Participants and Methods**]

Study design and participants

The study population consisted of Japanese men who worked for a metal products factory in Toyama prefecture, Japan. The Industrial Safety and Health Law in Japan requires employers to conduct annual health examinations for all employees. Details of this study population have been reported previously [15,19,20]. A total of 2,952 male employees aged 35 to 59 years, who underwent a health examination in 1996, were enrolled in the study, with subsequent follow-up for 11 years until March 2007. The present cohort study was approved by the Institutional Review Committee of Kanazawa Medical University for Ethical Issues.

Of the 2,952 participants, 267 were excluded due to either a history of previous cardiovascular disease (n = 11), taking medications for either hypertension, hypercholesterolemia, hypertriglyceridemia and/or diabetes (n = 211), missing information at the time of the baseline survey (n = 12), or failure to obtain information in the follow-up survey (n = 33). The remaining 2,685 participants were included in the analyses.

Baseline examination
Data collected at study entry included age, medical history, smoking and alcohol drinking habits, leisure-time physical activity, anthropometric indices including waist circumference, blood pressure, serum total cholesterol, HDL cholesterol, triglycerides and fasting plasma glucose. Fasting blood samples were obtained by cubital venipuncture and then shipped to one laboratory (BML, Inc., Toyama, Japan) for analysis. Plasma glucose levels were measured enzymatically using an automatic analyzer. Total cholesterol and triglyceride levels were measured by enzyme assay using another automatic analyzer, while HDL cholesterol levels were measured by a direct determination method. A single blood pressure measurement was carried out by trained staff using a mercury sphygmomanometer after the participants had rested for five minutes in the seated position. Waist circumference was measured above the iliac crest and below the lowest rib margin during minimal respiration in the standing position. Medical history, cigarette smoking and alcohol drinking habits, and leisure-time physical activity were evaluated using a self-administered questionnaire.

Definition of the absence or presence of mild or moderate-to-severe metabolic abnormalities and abdominal obesity
Abnormalities in blood pressure, lipids (triglycerides and/or HDL cholesterol) and glucose were defined using the criteria of the Japanese Society of Internal Medicine on behalf of the Japanese Committee to Evaluate Diagnostic Standards for Metabolic Syndrome [9]. Each abnormality was then classified further as being either mildly or moderate-to-severely abnormal, using the criteria adopted by the Japanese health checkups and healthcare advice, with particular focus on the metabolic syndrome ("*Tokutei Kenshin Tokutei Hoken Shidou*") [6-8]. Mildly abnormal blood pressure, lipids (triglycerides and/or HDL cholesterol) and glucose were defined as meeting the criteria where individuals need support to modify their undesirable lifestyle in order to improve metabolic disorders accounting to the criteria of the *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on the

metabolic syndrome). Moderately-to-severely abnormal blood pressure, lipids and glucose were defined as meeting the criteria where individuals should be advised to consult a physician. Details of this classification are shown in Table 1. The lower cut-off value for mildly abnormal glucose was set as 110 mg/dl which represents the Japanese metabolic syndrome criteria [9] and not 100 mg/d, the criteria used in the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on the metabolic syndrome) [6-8].

The study participants were diagnosed as having no, a mild or moderate-to-severe metabolic abnormality after comprehensive evaluation of blood pressure, lipids, and glucose (Table 2). Participants who did not have abnormal blood pressure, lipid profile or glucose levels were classified as having "no metabolic abnormality". Participants who had at least one mild abnormality in either blood pressure, lipids or glucose without moderate-to-severely abnormal blood pressure, lipids or glucose were classified as having a "mild metabolic abnormality". Participants who had at least one moderate-to-severe abnormality in either blood pressure, lipids or glucose were classified as having a "moderate-to-severe metabolic abnormality".

Abdominal obesity, defined as a waist circumference ≥ 85 cm, was treated separately from abnormal blood pressure, lipids and glucose, as the criteria for the Japanese metabolic syndrome regards it as a mandatory element [9].

Follow-up survey

Vital status and the incidence of cardiovascular diseases were ascertained at March 2007, representing a follow-up period of over 11 years. For participants who stayed in the target factory, questionnaires on medical history in the annual health checkups and medical certifications for sickness absence were used to obtain information on cardiovascular disease history during the follow-up period. For retired participants, questionnaires on cardiovascular disease history were sent annually by mail. In the case of deceased participants, information was obtained from family members. The medical records of every participant who was considered as having a history of cardiovascular disease from this procedure were reviewed to confirm the diagnosis, without knowledge of the variables at baseline. In some deceased cases, death certifications were referenced. If a participant died or a retired participant did not reply to the questionnaire on cardiovascular disease history, follow-up was stopped at that point.

The diagnostic criteria for myocardial infarction were modified from those of the MONItoring trends and determinants of CArdiovascular disease (MONICA) project conducted by the World Health Organization [21]. Myocardial infarction was defined as suffering typical chest pain with findings of abnormal and persistent Q or QS waves on an electrocardiogram and/or changes in cardiac enzyme activity. Sudden cardiac death was defined as death within one hour of onset, a witnessed cardiac arrest or abrupt collapse. Angina pectoris was also included as a coronary heart disease event in cases who underwent coronary artery angioplasty or bypass surgery. Stroke was defined as suffering a focal neurological disorder with

rapid onset, which persisted for at least 24 hours or until death, with supporting evidence from imaging examinations such as computed tomography or magnetic resonance imaging. The diagnosis of stroke subtype was classified on the basis of the imaging examinations.

Outcome used in the present study was a first-ever incident event of all cardiovascular diseases that included coronary heart disease and stroke. The former included myocardial infarction, sudden cardiac death, and angina pectoris requiring an intervention to the coronary arteries, while the latter included cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and unspecified stroke.

Statistical analysis

The three metabolic abnormality groups (ie, no, mild or moderate-to-severe metabolic abnormality) defined in the previous section (Table 2) were stratified further according to the presence or absence of abdominal obesity. This yielded the following six groups: 1) no metabolic abnormality without abdominal obesity; 2) mild metabolic abnormality without abdominal obesity; 3) moderate-to-severe metabolic abnormality without abdominal obesity; 4) no metabolic abnormality with abdominal obesity; 5) mild metabolic abnormality with abdominal obesity; and 6) moderate-to-severe metabolic abnormality with abdominal obesity. Hazard ratios, compared to the no metabolic abnormality without abdominal obesity group, were calculated for the five other groups. A Cox proportional hazard model was used to calculate the hazard ratios and their corresponding 95% confidence intervals for the outcomes in each group. This model incorporated the following variables as covariates: age (35-39, 40-44, 45-49, 50-54, 55-59 years), smoking habits (current, former, never smoked), drinking habits (heavy, light, occasional, no drinking), leisure-time physical activity (hard, moderate, light, no activity) and non-HDL cholesterol level ($< 170, \geq 170$ mg/dl). Non-HDL cholesterol was calculated as total cholesterol − HDL cholesterol and was used as a covariate instead of low-density lipoprotein cholesterol, the level of which could not be calculated for participants with extremely high triglyceride levels [22].

The population attributable fraction, which represents the contribution of mild and moderate-to-severe metabolic abnormalities to cardiovascular disease in the study population, was then estimated as proportion × (hazard ratio − 1)/hazard ratio [23], using the proportion of incident cases in the metabolic abnormality group and the multivariate-adjusted hazard ratio derived from this analysis.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 12.0J for Windows (SPSS Japan Inc., Tokyo, Japan). All probability values were two-tailed and the significance level was set at $p < 0.05$.

[Results]

Characteristics of the study population

The baseline characteristics of the 2,685 study participants in total and grouped according to the severity of metabolic abnormality and abdominal obesity status are summarized in Table 3. The mean age of the study population was 45.2 years. Of the total participants, 39.1% had neither metabolic abnormality nor abdominal obesity, 21.8% had a mild metabolic abnormality without abdominal obesity, 12.7% had a moderate-to-severe metabolic abnormality without abdominal obesity, 7.5% had isolated abdominal obesity without any metabolic abnormality, 9.8% had a mild metabolic abnormality with abdominal obesity and 9.0% had a moderate-to-severe metabolic abnormality with abdominal obesity. The mean age increased with worsening metabolic abnormalities for participants with and without abdominal obesity. With a few exceptions, mean blood pressure, triglyceride and fasting glucose levels increased with worsening metabolic abnormalities, whereas mean HDL cholesterol decreased with worsening metabolic status. Mean non-HDL cholesterol also increased with worsening metabolic abnormalities.

Individual risk of cardiovascular diseases due to each metabolic disorder and abdominal obesity
The study involved 26,882 person-years of follow-up in the 2,685 study participants. The mean overall follow-up period was 10.0 years. During follow-up, 58 first-ever incident events of cardiovascular diseases were recorded, including 20 myocardial infarctions, 4 sudden cardiac deaths, 5 cases of angina pectoris with coronary intervention, 17 cerebral infarctions, 8 cerebral hemorrhages, and 4 subarachnoid hemorrhages. The crude incidence rate of cardiovascular diseases in the study population was 2.16 / 1000 person-years.

Table 4 shows that increased severity of elevations in blood pressure, dyslipidemia or disordered glucose metabolism were likely to independently increase the risk of cardiovascular disease. Abdominal obesity was also an independent risk factor for cardiovascular diseases.

Individual risk of cardiovascular diseases due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity
Table 5 shows the hazard ratios for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity. Compared to the absence of any metabolic abnormality and abdominal obesity, a moderate-to-severe metabolic abnormality without abdominal obesity, a mild metabolic abnormality with abdominal obesity and a moderate-to-severe metabolic abnormality with abdominal obesity increased the risk of cardiovascular disease by 2.52-fold, 2.68-fold, and 4.12-fold, respectively. All three of these hazard ratios were statistically significant. A mild metabolic abnormality without abdominal obesity and isolated abdominal obesity without any metabolic abnormality also tended to increase the risk of cardiovascular disease by 1.49-fold and 2.36-fold, respectively.

Population risk of cardiovascular diseases due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity

Figure 1 shows the estimations of population attributable fractions for cardiovascular disease. These calculations showed 19.3% of cardiovascular diseases that occurred in the study population were attributable to either a mild metabolic abnormality or abdominal obesity alone without any metabolic abnormality, 5.7% to a mild metabolic abnormality without abdominal obesity, 5.0% to isolated abdominal obesity, and 8.6% to a mild metabolic abnormality with abdominal obesity. Furthermore, 28.4% of the cardiovascular diseases were attributable to a moderate-to-severe metabolic abnormality.

[Discussion]

This cohort study in middle-aged Japanese men demonstrated that the risk of cardiovascular disease was likely to be higher in participants who had a mild metabolic abnormality either with or without abdominal obesity and in participants who had isolated abdominal obesity without any metabolic abnormality for whom non-pharmacological therapy is required initially, compared to participants who had neither a metabolic abnormality nor abdominal obesity. A mild metabolic abnormality or isolated abdominal obesity contributed up to 20% of the cardiovascular diseases that occurred in the study population. The unique feature of this report is that the risk of cardiovascular disease due to components of the metabolic syndrome was evaluated from the viewpoint where intervention is a priority in health checkups and healthcare advice.

A mild metabolic abnormality based on our definitions is usually considered to require non-pharmacological therapy initially to improve the abnormality, regardless of the presence or absence of abdominal obesity. In contrast, a moderate-to-severe metabolic abnormality based on our definitions is usually considered to require consultation with a physician [6-8]. Our results are reasonable to this principle of health checkups and healthcare advice, when we viewed our results separately in obese participants and non-obese participants. The risk of cardiovascular disease tended to be the first and the second highest in participants with a moderate-to-severe metabolic abnormality and in participants with a mild metabolic abnormality, respectively, regardless of abdominal obesity status, despite the corresponding risk originally being higher in participants with abdominal obesity than in those without. Surprisingly, our results indicate that some obese individuals with a mild metabolic abnormality have a cardiovascular risk that is as high as that in non-obese individuals with a moderate-to-severe metabolic abnormality. This suggests that it may be better to advise some obese individuals with a mild metabolic abnormality to consult a physician prior to recommending non-pharmacological therapy, due to their possible high risk of cardiovascular disease. Obese participants with two or more mild metabolic disorders, who met the Japanese metabolic syndrome criteria (i.e., presence of abdominal obesity accompanied by two or more metabolic disorders) [9], may have a higher cardiovascular risk than obese participants with only a single metabolic disorder. This concern arises from the findings of a previous study in a Western population carried out by Vasan and colleagues [24]. They observed that coronary heart disease event rates rose with increasing number of borderline abnormalities in blood pressure (systolic 120-139 mmHg or diastolic 80-89 mmHg), serum low-density lipoprotein cholesterol (100-159 mg/dl), high-density lipoprotein cholesterol (40-59 mg/dl), glucose (fasting 110-125 mg/dl or 2-hour post-prandial 140-199 mg/dl) and smoking habits

(former smoking), although this previous study did not investigate abdominal obesity or serum triglycerides that are components of the metabolic syndrome, but did record serum low-density lipoprotein cholesterol levels and smoking habits [24]. In fact, the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on the metabolic syndrome) criteria [6-8] places importance on both the number and severity of metabolic abnormalities in health checkups and healthcare advice. Unfortunately, our study did not include a sufficiently large number of participants or events to conduct additional analyses using the number of mild metabolic abnormalities to further classify the participants. Further studies on a greater number of participants and cases are therefore warranted to clarify whether there is a further increase in cardiovascular disease risk in individuals with a cluster of mild metabolic disorders, compared to individuals with only a single metabolic disorder.

When non-obese and obese individuals were combined in our analyses, the burden of cardiovascular disease due to mild metabolic abnormalities and isolated abdominal obesity was equivalent to approximately two-thirds of the corresponding burden due to moderate-to-severe metabolic abnormalities. Approximately 15% of cardiovascular diseases in our study population were attributable to either abdominal obesity in association with a mild metabolic abnormality or isolated abdominal obesity. Ideally, rigorous lifestyle modification that decreases accumulation of abdominal fat without administration of medication is initially applicable. In other words, a value of 15% represents the ideal expected reduction in the burden of cardiovascular disease resulting from rigorous lifestyle modification to decrease abdominal fat accumulation without the need to take medication. On the other hand, other lifestyle modifications such as reducing dietary sodium intake are also of importance, especially in non-obese individuals with mild metabolic abnormalities, a group that contributed to approximately 5% of the cardiovascular diseases observed in our study population. This suggests that non-obese individuals with a mild metabolic abnormality should not be overlooked from the viewpoint of public health for the prevention of cardiovascular diseases in the Japanese population, who are relatively lean. The burden of cardiovascular disease due to combined mild and moderate-to-severe metabolic abnormalities was grater in obese participants than in non-obese participants: 30.6% (= 5.0% + 8.6% + 17.0%) vs. 17.1% (= 5.7% + 11.4%). This pattern is opposite to estimation in a previous Japanese study, which shows a grater population attributable fraction for ischemic cardiovascular disease among non-obese men with metabolic disorders (33%), compared to obese men with metabolic disorders and individuals with obesity alone (22%) [16]. This difference may be partially due to characteristics which differ between these two study populations, suggesting that our observed burden of cardiovascular disease due to mild and moderate-to-severe metabolic abnormalities without abdominal obesity is underestimated, whereas the corresponding burden due to mild and moderate-to-severe metabolic abnormalities with abdominal obesity is overestimated.

The present study had several limitations. First, as our study participants consisted solely of male workers in one factory, it is necessary to take care when generalizing our results. Furthermore, participants who had already started to take medication for metabolic disorders prior to study entry were excluded. Second, the

metabolic abnormalities in this report included high blood pressure, high triglycerides, low HDL cholesterol, and high glucose which are components of the metabolic syndrome, but did not include high total cholesterol which is another determinant of cardiovascular disease risk [2]. Dyslipidemia was evaluated using a combination of triglyceride and HDL cholesterol levels based on the Japanese metabolic syndrome criteria [9]. In addition, mildly abnormal glucose control was defined as a fasting glucose level between 110 and 125 mg/dl. However, broadly similar hazard ratios were observed for cardiovascular disease due to mild and moderate-to-severe metabolic abnormalities and/or abdominal obesity, when the lower cut-off value was set as 100 mg/d, based on the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on the metabolic syndrome) criteria [6-8] (data not shown). Third, we measured waist circumference, using the landmark above the iliac crest and below the lowest rib margin, which is different from the protocol in the Japanese metabolic syndrome criteria which uses the level of the umbilicus for the measurements [9]. However, one study suggests that the association between waist circumference and cardiovascular diseases is unlikely to depend on the measurement protocol [25]. Fourth, abdominal obesity was treated separately from blood pressure, lipids, and glucose, not only because it is an essential factor in the Japanese metabolic syndrome criteria [9], but also because of a lack of evidence on mild and moderate-to-severe increases in waist circumference. Fifth, the follow-up survey protocol differed between participants who stayed in the target factory and retired participants. Although information on cardiovascular disease could be easily and completely obtained for participants staying in the factory, there were difficulties and failures to obtain the corresponding information from retired participants. While this difference in data collection may have resulted in bias, the follow-up rate of the cohort was very high (99%) and therefore we consider it is acceptable to disregard this possibility. Finally, we used a composite outcome in which coronary heart disease and stroke events were combined due to the relatively small number of events. In addition, coronary heart disease included cases of angina pectoris that required intervention to the coronary arteries.

In conclusion, obese and non-obese individuals with mildly abnormal blood pressure, lipids and/or glucose and obese individuals without any metabolic disorders may have, on average, an approximately 2-fold increased risk of cardiovascular disease, compared to individuals with neither metabolic disorders nor abdominal obesity. The importance of lifestyle modification should be acknowledged especially in cases with a mild metabolic abnormality and/or abdominal obesity, who may contribute to approximately 20% of the population burden of cardiovascular diseases.

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Table 1. Definition of normal, mildly abnormal and moderate-to-severely abnormal levels of blood pressure, lipids and glucose.

	Normal	Abnormal	
		Mildly	Moderate-to-severely
Blood pressure	SBP <130 mmHg and DBP <85 mmHg	SBP 130-139 mmHg and/or DBP 85-89 mmHg	SBP ≥140 mmHg and/or DBP ≥90 mmHg
Lipids	TG <150 mg/dl and HDLC ≥40 mg/dl	TG 150-299 mg/dl and/or HDLC 35-39 mg/dl	TG ≥300 mg/dl and/or HDLC ≤34 mg/dl
Glucose	FPG <110 mg/dl	FPG 110-125 mg/dl	FPG ≥126 mg/dl

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.
The present definitions were based on the Japanese metabolic syndrome criteria [9] and the Japanese *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on the metabolic syndrome) criteria [6-8]; the lower cut-off value of mildly abnormal glucose was defined using the former criteria.

Table 2. Definition of no, mild or moderate-to-severe metabolic abnormality after comprehensively evaluating blood pressure, lipids and glucose.

No metabolic abnormality	Mild metabolic abnormality	Moderate-to-severe metabolic abnormality
Having all the following conditions; 1) Normal blood pressure (SBP <130 mmHg and DBP <85 mmHg) 2) Normal lipids (TG <150 mg/dl and HDLC ≥40 mg/dl) 3) Normal glucose (FPG <110 mg/dl)	Having at least one of the following conditions; 1) Mildly abnormal blood pressure (SBP 130-139 mmHg and/or DBP 85-89 mmHg) 2) Mildly abnormal lipids (TG 150-299 mg/dl and/or HDLC 35-39 mg/dl) 3) Mildly abnormal glucose (FPG 110-125 mg/dl) without any of the following conditions; 1) Moderate-to-severely abnormal blood pressure (SBP ≥140 mmHg and/or DBP ≥90 mmHg) 2) Moderate-to-severely abnormal lipids (TG ≥300 mg/dl and/or HDLC ≤34 mg/dl) 3) Moderate-to-severely abnormal glucose (FPG ≥126 mg/dl)	Having at least one of the following conditions; 1) Moderate-to-severely abnormal blood pressure (SBP ≥140 mmHg and/or DBP ≥90 mmHg) 2) Moderate-to-severely abnormal lipids (TG ≥300 mg/dl and/or HDLC ≤34 mg/dl) 3) Moderate-to-severely abnormal glucose (FPG ≥126 mg/dl)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

J Atheroscler Thromb (in press)

Table 3. Baseline risk characteristics of the 2,685 male study participants in a workplace, Toyama, Japan (1996). The data is presented for the total study population and also grouped according to metabolic abnormality and abdominal obesity status.

	Overall	Without abdominal obesity			With abdominal obesity			P values[†]
		No metabolic abnormality	Mild metabolic abnormality	Moder-to-sev metabolic abnormality	No metabolic abnormality	Mild metabolic abnormality	Moder-to-sev metabolic abnormality	
Participants	2,685	1,015	584	342	202	264	242	
Age (yrs)	45.2 (±6.5)	44.3 (±6.2)	45.3 (±6.3)	47.0 (±6.8)	44.9 (±6.2)	45.0 (±6.2)	47.0 (±6.9)	<0.01
Height (cm)	167.8 (±6.0)	167.4 (±6.0)	167.2 (±6.1)	167.0 (±6.1)	169.1 (±5.8)	169.2 (±6.0)	168.8 (±6.0)	<0.01
Weight (kg)	65.4 (±8.8)	61.4 (±6.7)	62.9 (±6.6)	62.7 (±7.2)	73.8 (±6.5)	75.0 (±7.0)	75.4 (±7.0)	<0.01
Body mass index (kg/m^2)	23.2 (±2.7)	21.8 (±2.0)	22.5 (±2.1)	22.4 (±2.1)	25.8 (±2.0)	26.1 (±2.2)	26.4 (±2.1)	<0.01
Waist circumference (cm)	79.8 (±7.6)	75.4 (±5.4)	77.6 (±4.9)	77.7 (±4.9)	88.7 (±3.7)	89.3 (±4.0)	89.8 (±4.3)	<0.01
Cigarette smoking habits (%)								0.34
Never	29.1%	29.8%	26.7%	31.9%	29.2%	29.5%	27.3%	
Former	11.3%	10.3%	10.8%	10.5%	15.3%	11.0%	14.9%	
Current	59.6%	59.9%	62.5%	57.6%	55.4%	59.5%	57.9%	
Alcohol drinking habits (%)								<0.01
No	22.7%	24.5%	20.5%	19.3%	18.3%	23.9%	27.3%	
Occasional	30.9%	31.0%	32.2%	28.9%	32.7%	29.2%	30.2%	
Light	27.6%	28.4%	26.0%	28.9%	29.7%	31.8%	19.4%	
Heavy	18.8%	16.1%	21.2%	22.8%	19.3%	15.2%	23.1%	
Leisure-time physical activity (%)								0.10
No	66.6%	66.7%	67.5%	61.7%	66.8%	68.2%	68.6%	
Light	19.4%	17.1%	19.9%	22.8%	21.3%	18.2%	23.6%	
Moderate	9.9%	11.4%	8.6%	10.8%	8.4%	10.6%	5.4%	
Hard	4.1%	4.8%	4.1%	4.7%	3.5%	3.0%	2.5%	
Systolic blood pressure (mmHg)	121.3 (±13.3)	113.4 (±8.6)	123.8 (±10.7)	135.3 (±14.4)	115.3 (±7.8)	123.6 (±10.0)	132.6 (±14.1)	<0.01
Diastolic blood pressure (mmHg)	76.3 (±10.0)	70.9 (±7.2)	77.1 (±8.2)	86.1 (±10.5)	72.9 (±7.0)	78.3 (±7.3)	84.4 (±10.8)	<0.01
Serum triglycerides (mg/dl)*	99 (70-146)	79 (61-102)	126 (81-173)	115 (72-177)	94 (72-116)	153 (100-190)	164 (110-260)	<0.01
Serum HDL cholesterol (mg/dl)	55.2 (±15.0)	59.9 (±14.1)	54.5 (±14.7)	54.7 (±18.2)	53.0 (±9.7)	48.5 (±11.8)	45.8 (±13.9)	<0.01
Serum non-HDL cholesterol (mg/dl)	148.5 (±34.0)	139.1 (±31.0)	149.6 (±34.9)	150.3 (±36.2)	150.6 (±28.4)	163.3 (±32.2)	166.9 (±32.6)	<0.01
Fasting plasma glucose (mg/dl)*	90 (85-97)	88 (83-93)	91 (85-97)	94 (87-105)	89 (85-95)	92 (86-98)	97 (89-109)	<0.01

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; Moder-to-sev, Moderate-to-severe.
Values are expressed as mean (±standard deviation), median (interquartile range) or the % of participants in that category; *median is presented due to the skewed distributions.
[†]One-way analysis of variance, Kruskal Wallis test or chi-square tests were used to compare each risk characteristic between the six groups.

J Atheroscler Thromb (in press)

Table 4. Hazard ratios for the incidence of cardiovascular disease due to mildly or moderate-to-severely abnormal levels of each metabolic disorder and abdominal obesity, in 2,685 male participants over 11 years of follow-up (1996-2007).

| | | Cardiovascular diseases | |
| | | | Multivariate-adjusted |
	Participants	Events	HR (95% CI)*
Blood pressure			
Normal	1,768	29	1.00 reference
Mildly abnormal	530	13	1.37 (0.70-2.65)
Moderate-to-severely abnormal	387	16	1.99 (1.04-3.79)
Lipids (triglycerides / high-density lipoprotein cholesterol)			
Normal	1,910	34	1.00 reference
Mildly abnormal	591	16	1.11 (0.60-2.07)
Moderate-to-severely abnormal	184	8	1.27 (0.55-2.93)
Glucose			
Normal	2,483	48	1.00 reference
Mildly abnormal	123	5	1.39 (0.54-3.57)
Moderate-to-severely abnormal	79	5	1.70 (0.65-4.45)
Abdominal obesity status			
Non-obese	1,977	32	1.00 reference
Obese	708	26	1.87 (1.07-3.26)

Abbreviations: HR, hazard ratio; CI, confidence interval.
Hazard ratios, with normal acting as the reference, were calculated using a Cox proportional hazards regression model adjusted for age, smoking habits, drinking habits, leisure-time physical activity, serum non-high-density lipoprotein cholesterol, the three residual factors (blood pressure, lipids, and glucose) and abdominal obesity status.