Table 2. Baseline characteristics of female study participants according to glycemic load quintiles

	Quintiles of dietary glycemic load					
Glycemic load (/1,000 kcal)	Q1 (lowest) $n=320$ ≤76.8	Q2 $n=320$ 76.9–84.8	Q3 $n=319$ 84.9–92.0	Q4 $n=320$ 92.1–101.3	Q5 (highest) $n=319$ ≥101.4	*p*
Age (years)	45.4±6.4	45.8±6.6	46.9±6.9	47.4±6.8	49.5±6.3	<0.001
Body height (cm)	156.8±5.4	156.4±5.5	156.0±5.2	156.0±5.7	154.4±5.7	<0.001
Body weight (kg)	55.1±8.7	54.6±8.8	54.5±8.3	54.8±8.8	53.5±8.9	0.044
Body mass index (kg/m^2)	22.4±3.4	22.3±3.4	22.3±3.3	22.5±3.4	22.4±3.5	0.668
Menopause (%)	31.3	31.3	39.5	41.9	53.0	<0.001
Current smoker (%)	4.7	4.7	3.1	1.6	3.1	0.160
Alcohol drinker (%)						<0.001
Nondrinkers	41.6	50.9	58.6	67.2	78.7	
Light drinkers (<20 g/day)	50.6	47.8	39.5	31.3	21.0	
Moderate/heavy drinkers (≥20 g/day)	7.8	1.3	1.9	1.6	0.3	
Habitual exercise (%)						0.007
No	73.4	75.9	80.6	81.9	85.6	
Light	13.4	12.2	11.6	8.8	6.6	
Moderate/Strong	12.5	11.9	7.2	9.1	7.5	
Energy intake (kcal/day)	2,112±614	1,977±452	1,846±407	1,744±471	1,568±461	<0.001
Carbohydrate intake (g/day)	265.6±78.4	274.9±65.2	271.2±60.9	273.1±75.5	268.0±80.0	0.830
Fat intake (g/day)	76.5±27.4	63.5±16.2	54.1±15.1	44.7±13.7	32.5±12.2	<0.001
Protein intake (g/day)	75.4±23.2	67.0±17.5	59.5±13.6	54.2±15.2	43.2±14.3	<0.001
Carbohydrate intake (%Energy)	50.3±4.2	55.5±2.5	58.8±2.5	62.6±2.8	68.4±4.2	<0.001
Fat intake (%Energy)	32.3±4.9	28.8±3.2	26.1±3.2	22.9±2.9	18.4±3.7	<0.001
SFA (g/day)	19.8±7.8	17.0±5.3	14.4±4.9	11.8±4.2	8.6±3.8	<0.001
MUFA (g/day)	27.6±10.9	22.2±6.0	18.8±5.6	15.1±4.9	10.9±4.2	<0.001
n3PUFA (g/day)	3.7±1.6	2.9±1.0	2.5±0.9	2.1±0.8	1.5±0.6	<0.001
n6PUFA (g/day)	14.7±5.5	12.1±3.3	10.4±2.9	8.6±2.6	6.5±2.2	<0.001
Dietary cholesterol (mg/day)	340.6±149.2	296.3±120.4	236.8±82.3	200.1±80.2	137.9±80.5	<0.001
Fiber intake (g/day)	14.1±5.4	13.1±4.3	12.0±3.7	11.0±3.7	9.0±3.4	<0.001
Dietary glycemic index	65.3±4.0	67.1±3.3	68.1±3.0	68.7±3.1	70.6±3.0	<0.001
Glycemic index-white rice (%)	41.3±21.1	48.7±18.1	54.0±18.6	58.2±17.8	65.5±17.4	<0.001
Glycemic index-bread (%)	9.7±7.9	9.9±8.0	9.0±8.1	8.7±9.0	6.7±7.7	<0.001
Glycemic index-noodles (%)	5.5±5.0	4.8±4.7	4.0±3.9	4.3±4.3	3.4±4.2	<0.001
Glycemic index-confectioneries (%)	11.9±7.9	11.1±6.3	9.8±6.1	8.4±6.0	7.5±6.0	<0.001
Glycemic index-sugar (%)	6.2±3.6	5.7±3.4	5.1±3.5	5.0±3.8	4.1±2.6	<0.001
White rice intake (g/day)	212.8±119.0	273.6±115.3	305.7±111.3	337.5±123.2	392.3±136.1	<0.001

Values are the mean ± standard deviation or %.

Women were analyzed separately in subgroups based on the menopausal status (pre- or postmenopause, data shown in **Supplement Table 5**). Although no difference in GI was observed between pre- and post-menopause, postmenopausal women were associated with a higher GL than premenopausal women, higher carbohydrate intake, and lower fat intake. Postmenopausal women showed higher mean serum lipids than premenopausal women. The associations between GL and serum lipid levels were similar between pre- and postmenopausal women.

Discussion

The present study investigated the association between serum lipids and dietary GI/GL in a large population of Japanese middle-aged men and women. The results indicated a significant inverse association

Table 3. Means lipid levels according to glycemic load quintiles for men

	Quintiles of dietary glycemic load					
Glycemic load (/1,000kcal)	Q1 (lowest) n=452 ≤73.0	Q2 n=451 73.1-83.4	Q3 n=452 83.5-91.9	Q4 n=451 92.0-103.3	Q5 (highest) n=451 ≥103.4	p for trend
Total cholesterol (mg/dL)						
Model 1 (no adjustment)	204.7±1.6	205.0±1.6	205.1±1.6	208.1±1.5	207.7±1.5	0.067
Model 2 (adjusted for age and BMI)	204.8±1.5	204.7±1.5	204.9±1.5	208.6±1.5	207.5±1.5	0.066
Model 3 (adjusted for multivariate)	207.4±1.8	205.9±1.6	205.2±1.5	207.4±1.6	204.6±2.0	0.515
Triglycerides (mg/dL)*						
Model 1 (no adjustment)	99.1 (94.1-104.4)	94.0 (89.4-99.0)	104.5 (99.6-109.6)	94.8 (90.3-99.5)	98.3 (93.7-103.2)	0.884
Model 2 (adjusted for age and BMI)	100.0 (95.5-104.7)	94.6 (90.4-99.1)	104.7 (100.0-109.7)	97.7 (93.3-102.3)	99.3 (94.8-104.0)	0.882
Model 3 (adjusted for multivariate)	99.8 (94.4-105.4)	94.6 (90.1-99.3)	104.0 (99.3-108.9)	97.1 (92.5-101.8)	95.3 (89.8-101.1)	0.508
HDL cholesterol (mg/dL)						
Model 1 (no adjustment)	62.2±0.7	59.7±0.7	57.4±0.7	57.9±0.6	55.8±0.6	<0.001
Model 2 (adjusted for age and BMI)	62.3±0.6	59.8±0.6	57.7±0.6	57.4±0.6	55.8±0.6	<0.001
Model 3 (adjusted for multivariate)	61.0±0.7	59.4±0.6	57.8±0.6	58.1±0.6	56.8±0.8	0.001
LDL cholesterol (mg/dL)						
Model 1 (no adjustment)	118.9±1.5	123.0±1.5	123.5±1.5	128.1±1.4	129.0±1.4	<0.001
Model 2 (adjusted for age and BMI)	119.0±1.4	122.7±1.4	123.2±1.4	128.7±1.4	128.8±1.4	<0.001
Model 3 (adjusted for multivariate)	122.7±1.7	124.1±1.5	123.2±1.4	126.8±1.5	125.7±1.8	0.194
Non-HDL cholesterol (mg/dL)						
Model 1 (no adjustment)	142.4±1.7	145.3±1.7	147.7±1.6	150.1±1.6	151.9±1.6	<0.001
Model 2 (adjusted for age and BMI)	142.5±1.5	144.9±1.5	147.2±1.5	151.1±1.5	151.7±1.5	<0.001
Model 3 (adjusted for multivariate)	146.5±1.8	146.5±1.6	147.4±1.5	149.3±1.6	147.8±2.0	0.471

Values are the mean±standard error.
*Values are geomerric means (95% confidence interval).
Model 1, no adjustment; Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index, smoking, alcohol drinking, habitual exercise, dietary total energy, SFA, MUFA, n-3 PUFA, n-6 PUFA, dietary cholesterol, and dietary fiber intake.

between GL and HDL-C in both men and women. Furthermore, GL was significantly and positively associated with non-HDL-C and LDL-C in women. Previous studies on the association between GI/GL and serum lipids have been reported, primarily in the U.S. and Europe[4-7, 11]; but relatively few are available from Asian countries where there is higher rice intake and lower fat intake.

Dietary GI/GL is inversely associated with HDL-C[4-10] and is positively associated with LDL-C[7]; however, some reports show no association between dietary GI/GL and HDL-C[11, 12] or LDL-C[4, 9, 19]; the results on the association between GI/GL and serum lipids are therefore inconsistent. In the present study, the multivariate-adjusted models indicated that GL was significantly associated with HDL-C, LDL-C, and non-HDL-C in women but was associated only with HDL-C in men. Differences in these results are probably due to different characteristics, such as age, gender and ethnicity, and the life styles of the participants.

The results from the Third National Health and Nutrition Examination Survey in the U.S. demonstrated an inverse association between GL and HDL-C in men, but not in women[12]. That study included relatively young and largely premenopausal women, and the authors postulated that the effect of sex hormones in women could explain such gender differences; however, no previous study has evaluated the effects of sex hormones on GI/GL-serum lipid associations. Thus, we analyzed using the menopausal status in women. Although the mean LDL-C and non-HDL-C values were significantly higher in postmenopausal women than in premenopausal women, the associations between GL and serum lipid levels were similar. These results indicated that differences in sex hormones cannot fully explain the gender difference.

Differences in lifestyle and dietary factors may also have influenced the gender results. For example, alcohol intake can affect not only serum lipid levels but also food intake patterns, and alcohol consumption was more common in men than in women. In

Table 4. Means lipid levels according to glycemic load quintiles for women

	Quintiles of dietary glycemic load					
Glycemic load (/1,000kcal)	Q1 (lowest) n=320 ≤76.8	Q2 n=320 76.9-84.8	Q3 n=319 84.9-92.0	Q4 n=320 92.1-101.3	Q5 (highest) n=319 ≥101.4	p for trend
Total cholesterol (mg/dL)						
Model 1 (no adjustment)	204.8±1.9	207.3±1.8	208.6±1.9	213.1±1.9	214.0±1.9	<0.001
Model 2 (adjusted for age and BMI)	207.5±1.7	209.4±1.7	208.7±1.7	212.2±1.7	209.8±1.8	0.214
Model 3 (adjusted for multivariate)	207.1±2.2	209.9±1.9	208.6±1.8	212.4±1.9	209.6±2.5	0.398
Triglycerides (mg/dL)*						
Model 1 (no adjustment)	62.0 (58.9-65.3)	63.3 (60.2-66.5)	66.6 (63.3-70.0)	67.8 (64.3-71.4)	72.8 (69.1-76.7)	<0.001
Model 2 (adjusted for age and BMI)	64.0 (61.0-67.1)	65.3 (62.3-68.5)	67.6 (64.5-70.9)	67.8 (64.6-71.0)	71.3 (67.9-74.8)	0.003
Model 3 (adjusted for multivariate)	62.5 (58.9-66.4)	63.8 (60.5-67.3)	66.5 (63.3-69.9)	68.2 (64.8-71.9)	71.3 (66.6-76.2)	0.011
HDL cholesterol (mg/dL)						
Model 1 (no adjustment)	69.9±0.9	70.1±0.8	66.8±0.8	68.1±0.8	65.4±0.8	<0.001
Model 2 (adjusted for age and BMI)	69.8±0.8	69.9±0.8	66.7±0.8	68.3±0.8	65.6±0.8	<0.001
Model 3 (adjusted for multivariate)	70.7±1.0	70.6±0.9	67.0±0.8	67.7±0.8	64.3±1.1	<0.001
LDL cholesterol (mg/dL)						
Model 1 (no adjustment)	120.8±1.8	122.9±1.6	126.7±1.7	129.5±1.8	131.9±1.8	<0.001
Model 2 (adjusted for age and BMI)	123.4±1.6	124.9±1.6	126.9±1.6	128.7±1.6	128.0±1.6	0.013
Model 3 (adjusted for multivariate)	122.3±2.0	125.0±1.8	126.6±1.6	129.1±1.7	129.0±2.2	0.035
Non-HDL cholesterol (mg/dL)						
Model 1 (no adjustment)	135.0±1.9	137.2±1.8	141.8±1.9	144.9±2.0	148.5±1.9	<0.001
Model 2 (adjusted for age and BMI)	137.8±1.7	139.5±1.7	142.0±1.7	143.9±1.7	144.2±1.7	0.002
Model 3 (adjusted for multivariate)	136.4±2.1	139.3±1.9	141.6±1.8	144.7±1.9	145.4±2.4	0.010

Values are the mean ± standard error.
*Values are geometric means (95% confidence interval).
Model 1, no adjustment; Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index, menopause status, smoking, alcohol drinking, habitual exercise, dietary total energy, SFA, MUFA, n-3 PUFA, n-6 PUFA, dietary cholesterol, and dietary fiber intake.

the model adjusted for alcohol consumption, significant associations between GL and both LDL-C and non-HDL-C were observed for women but not for men. GL was associated with non-HDL-C in female nondrinkers, suggesting that the association between GL and non-HDL-C might be independent of alcohol consumption. Although there were no significant associations in male nondrinkers, the sample size may have been too small for an association to be apparent. On the other hand, a gender difference was observed in the influence of alcohol drinking on food intake patterns. A lower carbohydrate intake was observed in drinkers than in nondrinkers, a tendency that was more pronounced in men, and fat intake was higher in male nondrinkers, whereas in women it was higher in drinkers. We should consider these differences in lifestyle and food intake patterns when evaluating the association between GI/GL and diseases and gender differences.

Non-HDL-C represents a measure of serum lipids, which is a better predictor of the development of cardiovascular disease[20-23]. A previous study showed that GI was significantly associated with the total cholesterol/HDL-C ratio[19] or LDL-C/HDL-C ratio[7]; however, no studies have evaluated the association between GI/GL and non-HDL-C. In our study, a gender difference was observed in the association between GL and non-HDL-C; GL was positively associated with non-HDL-C only in women. A high GL diet in women may lead to the development of atherosclerosis, because it is associated with low HDL-C and high non-HDL-C, which are closely related to atherogenesis.

A potential mechanism for the association between a high GL diet and serum lipids is abnormal lipid metabolism due to postprandial hyperglycemia and insulin resistance. Reducing postprandial hyperglycemia with an alpha-glucosidase inhibitor may increase lipoprotein lipase mass and prevent carotid atherosclerosis in patients with type 2 diabetes[24]; however, the present study did not determine measures related to insulin resistance, or postprandial

Table 5. Multivariate-adjusted mean lipid levels according to glycemic load quintiles for male nondrinkers (n=377) and drinkers (n=1,880)

	Quintiles of dietary glycemic load					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Nondrinkers	n=76 ≤87.4	n=76 87.5-97.0	n=76 97.1-105.0	n=74 105.1-115.0	n=75 ≥115.1	p for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	203.7±3.4	204.6±3.4	217.6±3.4	207.7±3.5	210.9±3.4	0.125
Model 3 (adjusted for multivariate)	208.0±4.7	206.0±4.0	218.3±3.6	205.4±3.9	206.8±5.1	0.976
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	94.0 (84.0-105.2)	97.3 (87.0-108.8)	102.1 (91.2-114.2)	110.1 (98.2-123.3)	101.3 (90.4-113.4)	0.155
Model 3 (adjusted for multivariate)	99.9 (85.3-116.9)	101.2 (88.6-115.6)	99.8 (88.6-112.4)	107.1 (94.0-122.0)	96.2 (81.1-114.0)	0.909
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	53.4±1.3	54.3±1.3	53.9±1.3	51.6±1.3	53.2±1.3	0.504
Model 3 (adjusted for multivariate)	52.1±1.7	52.2±1.5	53.2±1.3	52.5±1.4	56.5±1.9	0.211
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	128.4±3.2	127.5±3.2	139.8±3.2	130.1±3.2	133.8±3.2	0.204
Model 3 (adjusted for multivariate)	132.3±4.5	130.6±3.8	141.9±3.4	127.3±3.7	127.2±4.8	0.595
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	150.4±3.4	150.4±3.4	163.7±3.4	156.1±3.5	157.7±3.5	0.076
Model 3 (adjusted for multivariate)	155.9±4.7	153.8±4.0	165.2±3.6	152.9±3.9	150.3±5.1	0.628
Drinkers	n=380 ≤70.8	n=377 70.9-80.8	n=371 80.9-89.0	n=377 89.1-99.3	n=375 ≥99.4	p for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	204.7±1.7	204.9±1.7	205.0±1.7	206.8±1.7	206.2±1.7	0.379
Model 3 (adjusted for multivariate)	206.5±1.9	205.4±1.8	205.2±1.7	206.3±1.7	204.2±2.1	0.572
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	101.3 (96.3-106.5)	91.7 (87.2-96.4)	102.3 (97.3-107.7)	99.3 (94.4-104.4)	93.7 (89.1-98.6)	0.239
Model 3 (adjusted for multivariate)	100.9 (95.3-106.9)	91.8 (87.1-96.8)	102.6 (97.5-108.0)	100.3 (95.3-105.7)	92.7 (87.1-98.6)	0.333
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	62.1±0.7	61.3±0.7	58.3±0.7	59.1±0.7	57.5±0.7	<0.001
Model 3 (adjusted for multivariate)	61.5±0.8	61.3±0.7	58.5±0.7	59.1±0.7	57.9±0.8	0.002
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	118.6±1.6	121.8±1.6	122.8±1.6	124.7±1.6	127.1±1.6	<0.001
Model 3 (adjusted for multivariate)	121.0±1.8	122.4±1.6	122.7±1.6	124.0±1.6	124.9±1.9	0.170
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	142.7±1.7	143.6±1.7	146.7±1.7	147.7±1.7	148.7±1.7	0.003
Model 3 (adjusted for multivariate)	145.0±1.9	144.1±1.8	146.7±1.7	147.2±1.7	146.2±2.1	0.503

Values are the mean±standard error.
*Values are geometric means (95% confidence interval).
Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index, smoking, habitual exercise, dietary total energy, SFA, MUFA, n-3 PUFA, n-6 PUFA, dietary cholesterol, and dietary fiber intake.

hyperglycemia. Further investigation into the potential mechanism is warranted.

The strengths of this study include a large Japanese population, which is significantly different in terms of the foods contributing to dietary GI from a U.S. or European population, and this is the first such study to include Japanese men. Additionally, all serum lipid data were measured in a standardized way using fasting blood samples, and GI and GL were calculated using responses to a validated questionnaire. The limitations of this study include the factors that the study population was exclusive, because the participants were employed by a company in a rural city, and that the study was cross-sectional. Given that there are

Table 6. Multivariate-adjusted mean lipid levels according to glycemic load quintiles for female nondrinkers ($n=949$) and drinkers ($n=649$)

	Quintiles of dietary glycemic load					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Nondrinkers	$n=192$ ≤80.1	$n=188$ 80.2-87.6	$n=192$ 87.7-95.5	$n=189$ 95.6-104.1	$n=188$ ≥104.2	p for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	206.9±2.2	213.7±2.3	208.5±2.2	214.2±2.2	209.8±2.3	0.379
Model 3 (adjusted for multivariate)	206.4±2.9	214.0±2.6	208.5±2.4	215.1±2.5	209.0±3.3	0.460
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	62.6 (58.8-66.6)	68.8 (64.6-73.2)	65.0 (61.2-69.2)	68.7 (64.5-73.1)	72.7 (68.3-77.5)	0.003
Model 3 (adjusted for multivariate)	59.5 (54.8-64.6)	66.3 (61.7-71.3)	64.6 (60.5-69.0)	71.7 (66.9-76.9)	76.6 (69.7-84.1)	0.001
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	68.2±1.0	68.1±1.0	66.2±1.0	66.8±1.0	64.2±1.0	0.003
Model 3 (adjusted for multivariate)	69.8±1.3	69.1±1.1	66.3±1.0	65.6±1.1	62.6±1.5	0.002
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	124.3±2.0	129.9±2.1	127.5±2.0	132.1±2.1	128.8±2.1	0.095
Model 3 (adjusted for multivariate)	123.1±2.7	129.8±2.4	127.4±2.2	133.4±2.3	128.8±3.1	0.137
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	138.7±2.2	145.6±2.2	142.3±2.2	147.4±2.2	145.6±2.2	0.025
Model 3 (adjusted for multivariate)	136.6±2.8	144.9±2.5	142.1±2.3	149.5±2.4	146.5±3.2	0.029
Drinkers	$n=132$ ≤73.2	$n=129$ 73.3-80.7	$n=132$ 80.8-87.0	$n=130$ 87.1-95.2	$n=126$ ≥95.3	p for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	205.3±2.7	207.8±2.8	206.4±2.7	208.2±2.8	212.7±2.8	0.072
Model 3 (adjusted for multivariate)	203.3±3.2	208.0±3.0	205.0±2.9	210.6±3.0	213.5±3.7	0.077
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	63.1 (58.7-67.9)	63.4 (58.9-68.3)	64.9 (60.4-69.9)	64.5 (59.9-69.4)	68.7 (63.7-74.0)	0.107
Model 3 (adjusted for multivariate)	63.5 (58.2-69.1)	63.2 (58.3-68.5)	64.8 (60.0-69.9)	65.2 (60.2-70.6)	68.0 (61.7-75.0)	0.343
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	72.3±1.2	69.8±1.2	69.0±1.2	70.6±1.2	68.6±1.3	0.077
Model 3 (adjusted for multivariate)	73.8±1.4	70.7±1.4	68.7±1.3	70.6±1.3	66.6±1.6	0.006
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	118.7±2.5	123.6±2.5	123.1±2.5	123.0±2.5	128.1±2.5	0.017
Model 3 (adjusted for multivariate)	115.2±2.9	123.0±2.7	122.1±2.6	125.2±2.7	131.1±3.3	0.002
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	132.9±2.7	138.0±2.7	137.4±2.7	137.6±2.7	144.1±2.7	0.008
Model 3 (adjusted for multivariate)	129.5±3.2	137.3±3.0	136.3±2.8	140.0±3.0	146.9±3.6	0.002

Values are the mean ± standard error.
*Values are geometric means (95% confidence interval).
Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index, menopause status, smoking, habitual exercise, dietary total energy, SFA, MUFA, n-3 PUFA, n-6 PUFA, dietary cholesterol, and dietary fiber intake.

many confounding factors between nutrition and clinical measures, and that dietary habits over a relatively long period need to be considered when examining the relationship between regular dietary habits and the development of metabolic abnormalities, an observational study of long duration using repeated nutrition surveys may be essential in the future.

The present study suggests that GL is inversely associated with HDL-cholesterol and positively associated with non-HDL-cholesterol in Japanese women. Although GL was also inversely associated with HDL-C in Japanese men, this association might have been affected by alcohol consumption. A diet low in GL might be beneficial in preventing lipid abnormali-

ties and cardiovascular diseases, especially in women.

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Supplemental Table 1. Characteristics of study participants

	Men (n=2,257)	Women (n=1,598)
Age (years)	47.4±6.9	47.0±6.8
Body height (cm)	169.1±6.1	155.9±5.6
Body weight (kg)	66.9±9.4	54.5±8.7
Body mass index (kg/m^2)	23.3±2.9	22.4±3.4
Total cholesterol (mg/dL)	206.1±32.7	209.5±33.4
Triglycerides (mg/dL)*	99.2 (67.0–143.0)	67.1 (48.0–89.0)
HDL cholesterol (mg/dL)	58.6±14.3	68.1±14.6
LDL cholesterol (mg/dL)	124.5±31.0	126.4±31.1
Non-HDL cholesterol (mg/dL)	147.5±34.7	141.5±34.2
Menopause (%)		39.4
Current smoker (%)	53.5	3.4
Alcohol consumption (%)		
Nondrinkers	16.9	59.4
Light drinkers (<20 g/day)	40.7	38.0
Moderate/heavy drinkers (≥20 g/day)	42.4	2.6
Habitual exercise (%)		
No	68.3	79.0
Light	18.7	11.0
Moderate/Strong	12.5	10.0
Energy intake (kcal/day)	2,201±607	1,849±520
Carbohydrate intake (g/day)	315.0±91.6	270.5±72.4
Protein intake (g/day)	65.5±23.4	59.9±20.3
Fat intake (g/day)	53.1±24.5	54.2±23.3
SFA (g/day)	13.5±6.6	14.3±6.7
MUFA (g/day)	19.1±9.5	18.9±8.8
n3PUFA (g/day)	2.6±1.4	2.5±1.3
n6PUFA (g/day)	10.5±4.7	10.5±4.5
Dietary cholesterol (mg/day)	259.8±146.0	242.4±127.8
Fiber intake (g/day)	11.1±4.4	11.8±4.5
Carbohydrate intake (%Energy)	57.8±8.7	59.2±7.0
Fat intake (%Energy)	21.4±6.5	25.8±6.0
Dietary glycemic index	69.3±3.9	68.0±3.7
Dietary glycemic load (/1,000kcal)	88.2±18.3	89.2±14.9

Values are the mean±standard deviation or %.
*Values are geometric means (interquartile range).

Supplemental Table 2. Contribution (%) of main food groups to dietary glycemic index in Japanese men and women

	Men			Women		
	Mean		SD	Mean		SD
White rice	61.6	±	21.7	53.6	±	20.4
Bread	6.9	±	8.2	8.9	±	8.2
Noodles	5.5	±	5.6	4.5	±	4.5
Confectioneries	5.1	±	4.8	10.1	±	6.9
Sugar	4.9	±	3.5	5.3	±	3.5
Brown rice and other grains	4.4	±	15.7	4.1	±	14.5
Soft drinks	3.6	±	5.6	2.8	±	4.4
Fruits	1.9	±	2.3	3.1	±	2.7
Potatoes	1.4	±	1.3	1.8	±	1.4
Pizza and other grain products	1.2	±	2.5	1.5	±	2.6
Fruit and vegetable juice	1.2	±	2.5	1.2	±	2.3

Values are the mean ± standard deviation.

Supplemental Table 3. Mean lipid levels according to glycemic index quintiles for men and women

	Quintiles of dietary glycemic index					*p* for trend
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Men	*n*=456	*n*=478	*n*=423	*n*=453	*n*=447	
Glycemic index	≤66.10	66.11-68.70	68.71-70.40	70.41-72.60	≥72.61	
Total cholesterol (mg/dL)	206.2±1.5	207.6±1.5	206.2±1.6	208.6±1.6	201.8±1.5	0.122
Triglycerides (mg/dL)†	99.0 (34.8-281.5)	99.9 (34.9-285.9)	105.8 (37.2-300.9)	97.4 (33.2-285.7)	94.6 (33.1-270.4)	0.200
HDL cholesterol (mg/dL)	58.7±0.7	58.0±0.6	58.5±0.7	58.8±0.7	59.1±0.7	0.484
LDL cholesterol (mg/dL)	124.6±1.4	126.5±1.4	123.2±1.6	127.1±1.5	120.8±1.4	0.131
Non-HDL cholesterol (mg/dL)	147.5±1.6	149.7±1.6	147.6±1.7	149.8±1.7	142.6±1.6	0.080
Women	*n*=323	*n*=318	*n*=332	*n*=313	*n*=312	
Glycemic index	≤65.10	65.11-67.10	67.11-69.00	69.01-71.00	≥71.01	
Total cholesterol (mg/dL)	209.5±1.8	208.5±1.8	208.1±1.8	207.4±1.9	214.3±1.9	0.145
Triglycerides (mg/dL)*	63.8 (24.9-163.4)	68.4 (26.5-176.7)	65.0 (26.9-156.7)	69.9 (28.1-174.1)	68.9 (27.4-173.2)	0.030
HDL cholesterol (mg/dL)	69.9±0.8	67.0±0.8	68.3±0.8	67.2±0.8	67.9±0.8	0.098
LDL cholesterol (mg/dL)	125.1±1.7	126.0±1.7	125.4±1.7	124.5±1.8	130.9±1.8	0.055
Non-HDL cholesterol (mg/dL)	139.5±1.8	141.6±1.9	139.9±1.8	140.2±2.0	146.4±2.0	0.030

Values are the mean ± standard error.
*Values are geometric means (95% confidence interval).

Supplemental Table 4. Differences in baseline characteristics between nondrinkers and drinkers

	Men						Women					
	Nondrinkers (n=377)			Drinkers (n=1,880)			Nondrinkers (n=949)			Drinkers (n=649)		
	Mean	±	SD	Mean	±	SD	p*	Mean	±	SD	Mean	±	SD	p*
Age (years)	47.5	±	6.7	47.4	±	6.9	0.785	47.7	±	6.8	46.0	±	6.6	<0.001
Body mass index (kg/m^2)	23.2	±	3.1	23.3	±	2.8	0.454	22.4	±	3.4	22.4	±	3.4	0.947
Total cholesterol (mg/dL)	208.9	±	30.4	205.5	±	33.1	0.053	210.6	±	32.8	208.0	±	34.3	0.134
Triglycerides (mg/dL)†	100.8 (34.2-296.6)			97.6 (34.1-278.9)			0.289	67.4 (26.5-171.4)			64.9 (26.3-159.8)			0.104
HDL cholesterol (mg/dL)	53.3	±	12.4	59.7	±	14.4	<0.001	66.7	±	14.3	70.1	±	14.7	<0.001
LDL cholesterol (mg/dL)	131.9	±	28.6	123.0	±	31.3	<0.001	128.5	±	30.5	123.3	±	31.8	<0.001
Non-HDL cholesterol (mg/dL)	155.6	±	32.1	145.9	±	35.0	<0.001	143.9	±	33.3	137.9	±	35.1	<0.001
Dietary glycemic index	69.2	±	3.6	69.3	±	3.9	0.831	68.2	±	3.7	67.6	±	3.7	0.003
Dietary glycemic load (/1,000kcal)	101.5	±	16.4	85.4	±	17.4	<0.001	92.2	±	14.7	84.6	±	14.1	<0.001
Energy intake (kcal/day)	2,119	±	635	2,217	±	600	0.004	1,818	±	510	1,895	±	532	0.004
Fat intake (%Energy)	22.2	±	6.6	21.1	±	6.5	0.004	25.4	±	5.9	26.2	±	6.1	0.010
Carbohydrate intake (%Energy)	63.8	±	7.7	56.5	±	8.4	<0.001	60.5	±	6.9	57.2	±	6.7	<0.001
Fiber intake (g/day)	11.4	±	4.6	11.0	±	4.4	0.164	11.8	±	4.5	11.8	±	4.6	0.930
SFA (g/day)	13.8	±	6.6	13.5	±	6.5	0.398	13.9	±	6.3	14.9	±	7.1	0.004
MUFA (g/day)	18.8	±	9.5	19.1	±	9.5	0.510	18.2	±	8.3	20.0	±	9.5	<0.001
n3PUFA (g/day)	2.5	±	1.4	2.6	±	1.4	0.067	2.5	±	1.2	2.7	±	1.3	0.005
n6PUFA (g/day)	10.4	±	4.7	10.6	±	4.7	0.648	10.1	±	4.2	11.0	±	4.8	<0.001
Dietary cholesterol (mg/day)	249.4	±	146.2	261.9	±	145.9	0.129	236.4	±	126.1	251.3	±	129.7	0.022

* t-test was used to compare the difference between nondrinkers and drinkers.
† Values are geometric means (95% confidence interval).

Supplemental Table 5. Multivariate-adjusted mean lipid levels according to glycemic load quintiles for premenopausal and postmenopausal women

	Quintiles of dietary glycemic load					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Premenopausal women	*n* = 220 ≥76.89	*n* = 220 76.90-84.81	*n* = 193 84.82-92.03	*n* = 186 92.04-103.33	*n* = 150 ≥103.34	*p* for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	198.3 ± 2.0	201.0 ± 2.0	202.1 ± 2.1	202.9 ± 2.2	199.7 ± 2.4	0.431
Model 3 (adjusted for multivariables)	198.2 ± 2.5	201.3 ± 2.2	201.8 ± 2.2	203.1 ± 2.5	199.7 ± 3.4	0.522
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	59.6 (56.2-63.1)	61.2 (57.8-64.9)	63.4 (59.6-67.4)	62.2 (58.4-66.3)	64.9 (60.4-69.6)	0.068
Model 3 (adjusted for multivariables)	58.1 (54.1-62.3)	60.3 (56.5-64.2)	62.8 (59.0-66.9)	62.8 (58.6-67.3)	64.3 (58.4-70.7)	0.224
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	70.0 ± 0.9	70.2 ± 0.9	68.0 ± 1.0	69.2 ± 1.0	66.7 ± 1.1	0.019
Model 3 (adjusted for multivariables)	70.9 ± 1.1	70.8 ± 1.0	68.1 ± 1.0	68.7 ± 1.1	65.0 ± 1.5	0.009
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	114.9 ± 1.8	117.0 ± 1.8	119.9 ± 1.9	119.8 ± 2.0	117.9 ± 2.2	0.130
Model 3 (adjusted for multivariables)	114.0 ± 2.3	116.8 ± 2.0	119.4 ± 2.0	120.2 ± 2.2	119.9 ± 3.1	0.100
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	128.4 ± 1.9	130.8 ± 1.9	134.1 ± 2.1	133.7 ± 2.1	133.0 ± 2.4	0.057
Model 3 (adjusted for multivariables)	127.3 ± 2.4	130.6 ± 2.1	133.6 ± 2.2	134.4 ± 2.4	134.8 ± 3.3	0.063
Postmenopausal women	*n* = 100 ≤76.89	*n* = 100 76.90-84.81	*n* = 126 84.82-92.03	*n* = 134 92.04-103.33	*n* = 169 ≥103.34	*p* for trend
Total cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	221.5 ± 3.3	222.8 ± 3.3	219.1 ± 2.9	226.5 ± 2.8	224.2 ± 2.5	0.323
Model 3 (adjusted for multivariables)	220.6 ± 4.4	223.6 ± 3.8	218.7 ± 3.2	227.5 ± 3.2	223.7 ± 3.6	0.595
Triglycerides (mg/dL)*						
Model 2 (adjusted for age and BMI)	71.1 (65.4-77.3)	71.8 (66.1-78.0)	74.6 (69.3-80.4)	77.3 (71.9-83.0)	81.1 (76.1-86.4)	0.004
Model 3 (adjusted for multivariables)	68.4 (61.3-76.4)	69.2 (62.8-76.2)	72.4 (66.9-78.5)	77.8 (71.8-84.3)	82.8 (75.6-90.7)	0.016
HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	69.5 ± 1.4	69.8 ± 1.4	65.0 ± 1.3	66.9 ± 1.2	64.1 ± 1.1	0.001
Model 3 (adjusted for multivariables)	70.6 ± 1.9	70.9 ± 1.6	65.2 ± 1.4	66.4 ± 1.4	63.1 ± 1.6	0.006
LDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	136.1 ± 3.0	137.4 ± 3.0	137.6 ± 2.7	142.1 ± 2.6	142.3 ± 2.3	0.049
Model 3 (adjusted for multivariables)	134.7 ± 4.0	137.6 ± 3.5	137.2 ± 2.9	143.3 ± 2.9	142.3 ± 3.3	0.180
Non-HDL cholesterol (mg/dL)						
Model 2 (adjusted for age and BMI)	152.0 ± 3.3	153.0 ± 3.2	154.1 ± 2.9	159.5 ± 2.8	160.1 ± 2.5	0.014
Model 3 (adjusted for multivariables)	150.0 ± 4.3	152.7 ± 3.7	153.5 ± 3.1	161.1 ± 3.1	160.6 ± 3.5	0.079

Values are the mean ± standard error.
*Values are geometric means (95% confidence interval).
Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index, smoking, alcohol drinking, habitual exercise, dietary total energy, SFA, MUFA, n-3 PUFA, n-6 PUFA, dietary cholesterol, and dietary fiber intake.

Original Article

Mild Metabolic Abnormalities, Abdominal Obesity and the Risk of Cardiovascular Diseases in Middle-Aged Japanese Men

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Aim: We investigated the individual and population impacts of mild abnormalities associated with metabolic syndrome (blood pressure, lipids and glucose) and abdominal obesity, for 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 the 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 of mild metabolic abnormality and/or abdominal obesity, which may contribute to approximately 20% of the population burden for cardiovascular diseases.

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Key words; Abdominal obesity, Blood pressure, Cardiovascular diseases, Glucose, Lipids

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 for worse conditions. 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, at health checkups and with healthcare advice,

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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 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 the accumulation of abdominal fat, which in turn may lead to the 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 mild metabolic abnormality with and without abdominal obesity, for which appropriate non-pharmacological therapy should be applied, depending on the presence or absence of abdominal obesity. To the best of our knowledge, little is known about the risk of developing cardiovascular diseases due to mild metabolic abnormalities associated with 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 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, and 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 (triglycer-

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 metabolic syndrome) criteria[6-8]; the lower cut-off value of mildly abnormal glucose was defined using the former criteria.

ides 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 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 for which individuals need support to modify their undesirable lifestyle in order to improve metabolic disorders according to the criteria of the *Tokutei Kenshin Tokutei Hoken Shidou* (health checkups and healthcare advice specifically focusing on metabolic syndrome). Moderately-to-severely abnormal blood pressure, lipids and glucose were defined as meeting the criteria for which 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 metabolic syndrome)[6-8].

The study participants were diagnosed as having no, 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 of 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 Japanese metabolic syndrome regards it as a mandatory element[9].

Follow-Up Survey

Vital status and the incidence of cardiovascular diseases were ascertained in March 2007, representing a follow-up period of over 11 years. For participants who stayed at the target factory, questionnaires on medical history at annual health checkups and medical certifications of sickness absence were used to obtain information on the cardiovascular disease history during the follow-up period. For retired participants, questionnaires on cardiovascular disease history were sent annually by mail. For 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 had died or a retired participant did not reply to the questionnaire on cardiovascular disease history, follow-up was stopped at that point.

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.

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 individuals 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.

The 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 for the coronary arteries, while the latter included cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and unspecified stroke.

Statistical Analysis

The three metabolic abnormality groups (i.e., 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, ≥ 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

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

		Without abdominal obesity			With abdominal obesity			
	Overall	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moder-to-sev metabolic abnormalitiy	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moder-to-sev metabolic abnormalitiy	*p* values[†]
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 (%)								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 (%)								<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 the 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 among the six groups.

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 abnormal-

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)

	Participants	Cardiovascular diseases	
		Events	Multivariate-adjusted 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.

ity 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 the increased severity of elevations in blood pressure, dyslipidemia or disordered glucose metabolism was 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

Table 5. Hazard ratios for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in 2,685 male participants over 11 years of follow-up (1996–2007)

	No metabolic abnormalitiy	Mild metabolic abnormalitiy	Moderate-to-severe metabolic abnormalitiy
Without abdominal obesity			
Participants	1,051	584	342
Total person-years of follow-up	10,739	5,821	3,399
Cardiovascular events	11	10	11
Crude rate per 1000 person-years	1.02	1.72	3.24
Age- adjusted HR (95% CI)*	1.00 reference	1.54 (0.65–3.63)	2.51 (1.08–5.82)
Multivariate-adjusted HR (95% CI)**	1.00 reference	1.49 (0.63–3.52)	2.52 (1.08–5.87)
With abdominal obesity			
Participants	202	264	242
Total person-years of follow-up	1,982	2,611	2,329
Cardiovascular events	5	8	13
Crude rate per 1000 person-years	2.52	3.06	5.58
Age-adjusted HR (95% CI)*	2.34 (0.81–6.74)	2.81 (1.13–7.00)	4.36 (1.94–9.82)
Multivariate-adjusted HR (95% CI)**	2.36 (0.81–6.82)	2.68 (1.07–6.73)	4.12 (1.80–9.43)

Abbreviations: HR, hazard ratio; CI, confidence interval.
Hazard ratios were calculated by a Cox proportional hazards regression model, with no metabolic abnormality without abdominal obesity acting as the reference; *adjusted for age; **adjusted for age, smoking habits, drinking habits, leisure-time physical activity and serum non-high-density lipoprotein cholesterol.

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. 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

Fig. 1 shows the estimations of population attributable fractions for cardiovascular disease. These calculations showed that 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 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 was required initially, compared to participants who had neither a metabolic abnormality nor abdominal obesity. 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 the components of metabolic syndrome was evaluated from the viewpoint of intervention as a priority in health checkups and healthcare advice.

The 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, moderate-to-severe metabolic abnormality based on our definitions is usually considered to require consultation with a physician[6-8]. Our results are reasonable according to this principle of health checkups and healthcare advice, when we viewed our results separately in obese and non-obese participants. The risk of cardiovascular disease tended to be the first and second highest in participants with a moderate-to-severe metabolic abnormality and in

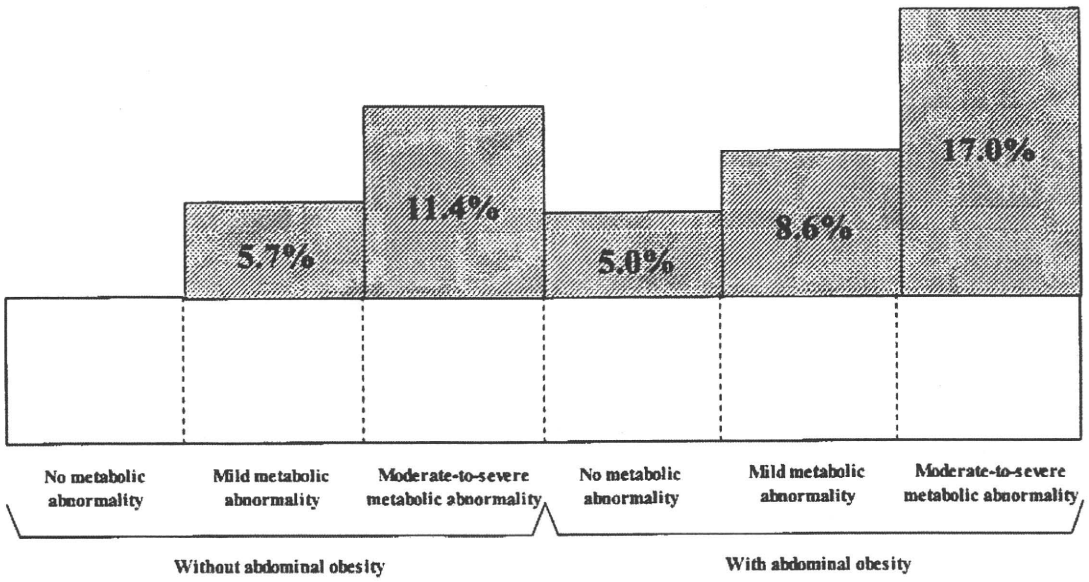

Fig. 1. Population attributable fraction for the incidence of cardiovascular disease due to mild or moderate-to-severe metabolic abnormalities and/or abdominal obesity, in the study population over 11 years of follow-up (1996-2007).

participants with a mild metabolic abnormality, respectively, regardless of the 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, which 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 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 the accumulation of abdominal fat without the administration of medica-

tion 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 greater 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 contradicts the finding in a previous Japanese study, which showed a greater population attributable fraction for ischemic cardiovascular disease among non-obese men with metabolic disorders (33%) than obese men with metabolic disorders and individuals with obesity alone (22%)[16]. This difference may be partially due to the different characteristics 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 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 check-ups and healthcare advice specifically focusing on 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 Japanese metabolic syndrome criteria, which uses the level of the umbilicus for the measurements[9]; however, one study suggested 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 Japanese metabolic syndrome criteria[9], but also because of a lack of evidence of mild and moderate-to-severe increases in waist circumference. Fifth, the follow-up survey protocol differed between participants who stayed at the target factory and retired participants. Although information on cardiovascular disease could be easily and completely obtained for participants staying at the factory, there were difficulties and failures in obtaining 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 that 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 for 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 of a mild metabolic abnormality and/or abdominal obesity, which may contribute to approximately 20% of the population burden of cardiovascular diseases.

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