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 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, 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/m²)	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.

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ARTICLE

Homeostasis model assessment of insulin resistance and the risk of cardiovascular events in middle-aged non-diabetic Japanese men

K. Nakamura · M. Sakurai · K. Miura · Y. Morikawa · M. Ishizaki · K. Yoshita · T. Kido · Y. Naruse · H. Nakagawa

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Abstract
Aims/hypothesis Little is known about the relationship between the HOMA of insulin resistance (HOMA-IR) and the risk of cardiovascular events in Asian populations, which have lower levels of HOMA-IR than Western populations. Accordingly, we determined the predictive value of HOMA-IR for cardiovascular risk in a Japanese population that was apparently free of diabetes, addressing whether insulin resistance itself increases cardiovascular risk independently of other relevant metabolic disorders.
Methods We followed 2,548 non-diabetic men aged 35 to 59 years for 11 years. The hazard ratios for the incidence of cardiovascular events due to increased HOMA-IR were estimated using a Cox proportional hazards model that was adjusted for potential confounding factors.
Results The multivariate-adjusted hazard ratio for cardiovascular events compared with the first quartile of HOMA-IR (≤0.66) was 1.07 (95% CI 0.44–2.64) for the second (HOMA-IR 0.67–1.01), 1.36 (0.56–3.28) for the third (HOMA-IR 1.02–1.51) and 2.50 (1.02–6.10) for the fourth quartile (HOMA-IR ≥1.52). The hazard ratio associated with a one SD (0.61) increment in log-transformed HOMA-IR was 1.51 (1.13–2.02). A similar positive relationship was observed for coronary events and stroke. In addition, the relationship between HOMA-IR and cardiovascular risk was broadly similar in participants with and without hypertension, dyslipidaemia (elevated triacylglycerol and/or reduced HDL-cholesterol), abdominal obesity and current smoking.
Conclusions/interpretation Increased HOMA-IR predicted subsequent cardiovascular events in non-diabetic Japanese men. The association was independent of traditional cardiovascular risk factors and other relevant metabolic disorders.

Keywords Cardiovascular diseases · Coronary heart disease · Epidemiology · Homeostasis model assessment · Insulin resistance · Stroke

Abbreviation
HOMA-IR HOMA of insulin resistance

K. Nakamura (✉) · M. Sakurai · Y. Morikawa · H. Nakagawa
Department of Epidemiology and Public Health,
Kanazawa Medical University,
1-1 Daigaku, Uchinada,
Ishikawa 920-0293, Japan
e-mail: knaka@kanazawa-med.ac.jp

K. Miura
Department of Health Science,
Shiga University of Medical Science,
Otsu, Japan

M. Ishizaki
Department of Social and Environmental Medicine,
Kanazawa Medical University,
Uchinada, Japan

K. Yoshita
Department of Food and Human Health Sciences,
Osaka City University Graduate School of Human Life Science,
Osaka, Japan

T. Kido
School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University,
Kanazawa, Japan

Y. Naruse
Department of Human Science and Fundamental Nursing,
Toyama University School of Nursing,
Toyama, Japan

Introduction

Insulin resistance characterised by decreased sensitivity of tissue to insulin and compensatory elevation in fasting plasma insulin leads not only to abnormal glucose metabolism [1, 2], but also to elevated blood pressure and abnormal lipid profiles such as elevated triacylglycerol and reduced HDL-cholesterol [3–6]. Some investigators have suggested that insulin resistance with compensatory hyperinsulinaemia plays a key role in the clustering of relevant metabolic disorders in the same individual (the metabolic syndrome) [7–10] and that this clustering is a high-risk state for the development of cardiovascular disease [11–14]. However, the contribution of insulin resistance with compensatory hyperinsulinaemia to the development of cardiovascular disease is likely to be independent of abnormal glucose metabolism and other relevant metabolic disorders [1, 6, 15–22]. Since insulin resistance is highly prevalent in the general population [3, 18, 23, 24], it is important to know whether the presence of insulin resistance is an early indicator of increased cardiovascular risk and whether physicians should evaluate insulin resistance to improve overall cardiovascular risk prediction.

The HOMA of insulin resistance (HOMA-IR) is easily available for estimating insulin resistance and is well correlated with estimates of insulin resistance obtained from the euglycaemic–hyperinsulinaemic clamp technique (gold standard) [25, 26]. A number of cohort studies, mainly in Western populations, have examined the relationship between HOMA-IR and the risk of cardiovascular events (including coronary events and stroke) in a general or non-diabetic population [11, 12, 19–21, 27–36]. However, only a few of these studies showed that increased HOMA-IR predicts subsequent cardiovascular events separately from other relevant metabolic disorders [19–21]. In addition, little is known about the relationship between HOMA-IR and the risk of cardiovascular events in Asian populations [35, 36], which have a relatively lower prevalence of obesity and lower levels of HOMA-IR than Western populations [12, 19, 21, 24]. We therefore attempted to determine the predictive value of HOMA-IR for the occurrence of a first-ever cardiovascular event in middle-aged Japanese men who were apparently free of diabetes.

Methods

Study design and participants The study population consisted of Japanese men who worked for a metal products factory in Toyama prefecture, Japan; this factory employed approximately 4,400 men and 2,600 women. The Industrial Safety and Health Law in Japan requires employers to conduct annual health examinations on all employees. Examinations include screening tests for traditional cardiovascular risk factors and questionnaires on medical history and lifestyle. Details of this study population have been reported previously [37, 38]. In 1996, 2,952 male employees aged 35 to 59 years, who accounted for approximately 90% of all male workers of target age, participated in a baseline survey that included a usual health examination and measurement of fasting plasma insulin. The participants were followed-up for 11 years until March 2007. Written informed consent was obtained. The present cohort study was approved by the Institutional Review Committee of Kanazawa Medical University for Ethical Issues.

Of the 2,952 participants, 59 were excluded due to a history of previous cardiovascular events (n=11), missing information at the time of the baseline survey (n=15) or failure to obtain information in the follow-up survey (n=33). To evaluate the true effect of insulin resistance on the occurrence of cardiovascular events independently of abnormal glucose metabolism and to diminish the possibility of inaccurate estimates of insulin resistance from HOMA-IR [39, 40], participation in the study was restricted to individuals who were apparently free of diabetes at baseline in order. Thus, 345 additional participants were excluded due to abnormal glucose metabolism defined as fasting glucose ≥6.11 mmol/l, HbA_{1c} ≥5.8% and/or taking medication for diabetes [41]. The remaining 2,548 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, triacylglycerol, fasting plasma glucose, insulin and HbA_{1c}. Fasting blood samples were obtained by cubital venipuncture and then shipped to a single laboratory (BML, Toyama, Japan) for analysis. Plasma fasting glucose levels were measured enzymatically using an automatic analyser (GA1140; Kyoto Daiichi Kagaku, Kyoto, Japan). Fasting plasma insulin was measured by radioimmunoassay (Gamma Counter ARC-950; Aloka, Tokyo, Japan). HOMA-IR was calculated using a previously published formula [25]. Other blood chemical markers were also measured using widely accepted methods. Measurements of anthropometric indices and blood pressure were carried out by trained staff. Information on medical history and lifestyle was obtained using a self-administered questionnaire.

Follow-up survey Vital status and the incidence of cardiovascular events were ascertained in March 2007, representing a follow-up period of over 11 years. Questionnaires on medical history in the annual health check-ups and medical certifications for absence due to illness were used to obtain

information on cardiovascular event history for participants who remained employed at the target factory. Similar questionnaires were sent by mail once a year to retired participants. The medical records of all participants who were thought to have a cardiovascular event were reviewed to confirm the diagnosis.

The diagnostic criteria for myocardial infarction were modified on the basis of those of the Monitoring trends and determinants of cardiovascular disease (MONICA) project conducted by the World Health Organization [42]. Myocardial infarction was defined as typical chest pain with abnormal and persistent Q or QS waves in the electrocardiogram and/or changes in cardiac enzyme activity. Sudden cardiac death was defined as death within 1 h of onset, a witnessed cardiac arrest or abrupt collapse. Angina pectoris was also included as a coronary event when patients underwent coronary artery angioplasty or bypass surgery. Stroke was defined as a focal neurological disorder with rapid onset, which persisted for at least 24 h or until death, with supporting evidence from examinations such as computed tomography or magnetic resonance imaging.

The primary outcome in the present study was the incidence of a first-ever cardiovascular event. All such events were classified into two categories: coronary events and stroke. The former included myocardial infarction, sudden cardiac death and angina pectoris requiring an intervention, whereas the latter included cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage and unspecified stroke.

Statistical analysis Initially, hazard ratios and their corresponding 95% CIs for the outcomes of interest were calculated for each quartile of HOMA-IR at baseline, with the first quartile serving as the reference. A Cox proportional hazards regression model was used that incorporated the following variables as covariates: age (years), waist circumference (cm), smoking habits (current, former or never smoking), drinking habits (heavy, light, occasional or no drinking), leisure-time physical activity (hard, moderate, light or no activity), systolic blood pressure (mmHg), medication for hypertension (yes or no), log-transformed triacylglycerol (mmol/l), HDL-cholesterol (mmol/l), non-HDL-cholesterol (mmol/l), medication for hypercholesterolaemia (yes or no) and HbA_{1c} (%). Non-HDL-cholesterol was calculated as total cholesterol minus HDL-cholesterol and used as a covariate instead of LDL-cholesterol [43]. Values for triacylglycerol were logarithmically transformed due to their skewed distribution. In addition, the trend between HOMA-IR and the risk of cardiovascular events was explored in a multivariate Cox model with a continuous term for log-transformed HOMA-IR (due to their skewed distribution) instead of HOMA-IR category. We also conducted a similar analysis, in which the reference was the combination of the first and second quartiles of HOMA-IR. Hazard ratios associated with a one SD increment in log-transformed HOMA-IR were also estimated in the Cox model. This approach was applied to fasting insulin, as well as to HOMA-IR, to see whether the association with cardiovascular risk was similar for these two indices.

An analysis was also performed based on previous evidence of the association between HOMA-IR and insulin resistance in a Japanese population. Oimatsu et al. [44] reported that when setting the cut-off value for HOMA-IR at 1.73 in a Japanese population, the sensitivity and specificity for the presence of insulin resistance evaluated by the euglycaemic–hyperinsulinaemic clamp technique were 64.3% and 78.9%, respectively. Using this evidence as a landmark for grouping HOMA-IR, we divided the participants in our study into the following five groups: (1) HOMA-IR<1.00; (2) 1.00≤HOMA-IR<1.50; (3) 1.50≤HOMA-IR<2.00; (4) 2.00≤HOMA-IR<2.50; and (5) 2.50≤HOMA-IR. Hazard ratios in each HOMA-IR group were calculated in a multivariate Cox model, with the HOMA-IR<1.00 group serving as reference.

Finally, analyses were repeated after study participants had been stratified by the presence or absence of: (1) hypertension (defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg and/or taking medication for hypertension); (2) dyslipidaemia (defined as triacylglycerol ≥1.69 mmol/l and/or HDL-cholesterol <1.03 mmol/l); and (3) abdominal obesity (defined as waist circumference ≥85 cm). The above are based on the Japanese criteria for metabolic syndrome [45] and are all closely linked with insulin resistance with compensatory hyperinsulinaemia [3–6, 24, 46]. This stratification was done to avoid the potential confounding effect of other relevant disorders on cardiovascular risk prediction and to determine whether there was an interaction between each disorder and insulin resistance with regard to risk of cardiovascular events. Similar stratified analyses were also conducted on the basis of smoking status (current smoking or not), because smoking remains a major cardiovascular risk factor in Japanese men [47] and is known to influence plasma insulin levels [48]. The significance of the interaction between increased HOMA-IR and each of the four factors (hypertension, dyslipidaemia, abdominal obesity and smoking) for the risk of cardiovascular events was tested using an interaction term for the categorical variables in the multivariate Cox model.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 12.0J for Windows (SPSS Japan, 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 2,548 study participants (mean age 45.0 years) grouped by quartile of HOMA-IR are summarised in Table 1. The mean age decreased slightly with increasing HOMA-IR. The mean values for body mass index, waist circumference, systolic and diastolic blood pressure, and serum total and non-HDL-cholesterol, as well as the median values for triacylglycerol, fasting plasma glucose and fasting plasma insulin increased with increasing HOMA-IR, whereas the mean value for HDL-cholesterol and the rates of current smoking, light-to-heavy alcohol drinking and moderate-to-hard activity decreased with increasing HOMA-IR.

HOMA-IR and the risk of cardiovascular events The study involved 25,506 person-years of follow-up in 2,548 study participants. The mean overall follow-up period was 10.0 years. During follow-up, 58 first-ever cardiovascular events were recorded, including 25 myocardial infarctions, three sudden cardiac deaths, five cases of angina pectoris with coronary intervention, 13 cerebral infarctions, eight cerebral haemorrhages and four subarachnoid haemorrhages. The crude incidence rate of a first cardiovascular event in the study population was 2.27 per 1,000 person-years.

Compared with the first quartile of HOMA-IR, the second quartile showed little increase in the risk of cardiovascular events, but the third and fourth quartiles showed a gradual trend towards increased risk. The age-adjusted hazard ratio (95% CI) was 1.09 (0.45–2.62) for the second, 1.50 (0.66–3.43) for the third and 2.95 (1.41–6.14) for the fourth quartile. After further adjustment for traditional cardiovascular risk factors and other metabolic disorders relevant to insulin resistance, the hazard ratio was 1.07 (0.44–2.64), 1.36 (0.56–3.28) and 2.50 (1.02–6.10), respectively (Fig. 1a). When cardiovascular events were divided into coronary events and stroke, a similar pattern was observed for both event subtypes; the multivariate-adjusted hazard ratio comparing the fourth with the first quartile of HOMA-IR was 2.03 (0.61–6.75) for coronary events and 3.23 (0.82–12.79) for stroke (Fig. 1b, c). When the first and second quartiles were combined as reference, the multivariate-adjusted hazard ratio comparing the fourth with the first and second quartiles combined was 2.40 (1.16–4.94) for cardiovascular events (Table 2), 2.27 (0.86–6.00) for coronary events and 2.64 (0.89–7.85) for stroke.

The trend was significant for all the outcomes, with $p<0.01$ for trend for cardiovascular events, $p=0.04$ for coronary events and $p=0.05$ for stroke. The hazard ratio associated with a one SD (0.61) increment in log-transformed HOMA-IR was 1.51 (1.13–2.02) for cardiovascular events (Table 2), 1.48 (1.02–2.14) for coronary events and 1.59 (1.00–2.54) for stroke.

The observed patterns were quite similar between HOMA-IR and fasting insulin (pmol/l) for all the outcomes. The multivariate-adjusted hazard ratio for cardiovascular events was 0.91 (0.40–2.05) for the second (20.85–34.73 pmo/l), 1.43 (0.62–3.34) for the third (34.74–48.62 pmol/l) and 2.60 (1.10–6.15) for the fourth (48.63–506.99 pmol/l) quartile, with the first quartile of fasting insulin (6.95–20.84 pmo/l) serving as the reference. The multivariate-adjusted hazard ratio comparing the fourth with the first quartile of fasting insulin was 1.85 (0.57–5.93) for coronary events and 4.01 (1.10–14.67) for stroke. The trend was of definite significance or borderline significance for each outcome, with $p<0.01$ for trend for cardiovascular events, $p=0.09$ for coronary events and $p=0.04$ for stroke. The hazard ratio associated with a one SD (0.58 pmol/l) increment in log-transformed fasting insulin was 1.47 (1.10–1.96) for cardiovascular events, 1.39 (0.95–2.02) for coronary events and 1.62 (1.03–2.57) for stroke.

In the second approach, the crude incidence rate per 1,000 person-years was 1.56 for HOMA-IR<1.00 ($n=1,265$), 1.62 for 1.00≤HOMA-IR<1.50 ($n=620$), 2.92 for 1.50≤HOMA-IR<2.00 ($n=349$), 3.37 for 2.00≤HOMA-IR<2.50 ($n=151$) and 8.15 for 2.50≤HOMA-IR ($n=163$), with each group having 20, 10, 10, 5 and 13 cardiovascular events, respectively. The age-adjusted hazard ratio for cardiovascular events compared with HOMA-IR<1.00 was 1.10 (0.52–2.36) for 1.00≤HOMA-IR<1.50, 2.07 (0.97–4.43) for 1.50≤HOMA-IR<2.00, 2.37 (0.89–6.32) for 2.00≤HOMA-IR<2.50 and 5.83 (2.90–11.74) for 2.50≤HOMA-IR; the multivariate-adjusted hazard ratio was 1.07 (0.48–2.36), 1.95 (0.84–4.53), 2.51 (0.85–7.48) and 5.54 (2.33–13.15), respectively.

HOMA-IR and the risk of cardiovascular events in patients grouped according to blood pressure, lipids, abdominal obesity or smoking status The associations observed in the overall population were broadly similar in participants with and without hypertension, dyslipidaemia, abdominal obesity or current smoking (Table 2). There was no significant interaction between increased HOMA-IR and any of these four factors with regard to the risk of cardiovascular events (p values for interaction, see Table 2).

Discussion

The present cohort study demonstrated a positive relationship between HOMA-IR and the risk of a first-ever cardiovascular event in middle-aged Japanese men who were apparently free of diabetes, adjusting for major cardiovascular risk factors.

Table 1 Baseline risk characteristics of the 2,548 non-diabetic men participants in Toyama, Japan (1996) grouped by quartile of HOMA-IR

Characteristic	HOMA-IR				*p* value for difference[b]
	1st quartile (0.18–0.66)	2nd quartile (0.67–1.01)	3rd quartile (1.02–1.51)	4th quartile (1.52–18.73)	
Participants (*n*)	649	629	624	646	
Age (years)	45.7±6.5	45.3±6.2	44.9±6.5	44.3±6.5	<0.01
HOMA-IR[a]	0.48 (0.42–0.62)	0.84 (0.76–0.91)	1.24 (1.12–1.38)	1.98 (1.71–2.52)	
Height (cm)	166.9±6.3	167.7±6.2	168.2±5.7	168.4±5.7	<0.01
Weight (kg)	60.3±7.3	63.9±7.4	67.1±7.7	71.0±8.5	<0.01
BMI (kg/m^2)	21.6±2.2	22.7±2.3	23.7±2.4	25.0±2.6	<0.01
Waist circumference (cm)	75.3±6.3	78.5±6.6	81.4±6.6	84.7±7.0	<0.01
Cigarette smoking habits (%)					
Never	22.5	30.2	33.2	32.8	<0.01
Former	7.9	12.1	11.5	14.2	
Current	69.6	57.7	55.3	52.9	
Alcohol drinking habits (%)					
None	20.3	20.7	22.1	27.2	0.01
Occasional	28.0	32.6	31.9	31.1	
Light	28.8	28.5	28.5	25.5	
Heavy	22.8	18.3	17.5	16.1	
Leisure-time physical activity (%)					
None	65.5	64.1	65.7	69.7	0.02
Light	16.5	21.1	21.3	19.2	
Moderate	12.0	10.7	9.6	7.6	
Hard	6.0	4.1	3.4	3.6	
Systolic BP (mmHg)	118.8±13.1	120.6±13.4	122.5±14.0	124.9±14.3	<0.01
Diastolic BP (mmHg)	74.6±9.9	76.2±10.2	77.0±10.6	78.8±10.4	<0.01
Medication for hypertension (%)	2.9	4.3	4.5	7.9	<0.01
Serum total cholesterol (mmol/l)	5.07±0.79	5.32±0.84	5.33±0.89	5.43±0.85	<0.01
Serum non-HDL-cholesterol (mmol/l)	3.51±0.82	3.81±0.85	3.96±0.91	4.16±0.86	<0.01
Hypercholesterolaemia medication (%)	0.5	0.8	2.1	1.4	0.04
Serum triacylglycerol (mmol/l)[a]	0.90 (0.68–1.24)	1.02 (0.77–1.42)	1.22 (0.89–1.70)	1.53 (1.07–2.15)	<0.01
Serum HDL-cholesterol (mmol/l)	1.56±0.42	1.51±0.40	1.38±0.35	1.27±0.33	<0.01
Fasting plasma glucose (mmol/l)[a]	4.77 (4.50–4.94)	5.00 (4.61–5.27)	5.00 (4.77–5.27)	5.16 (4.88–5.55)	<0.01
Fasting plasma insulin (pmol/l)[a]	13.89 (13.89–20.84)	27.78 (20.84–27.78)	41.67 (34.73–41.67)	62.51 (48.62–76.40)	<0.01
HbA_{1c} (%)	4.99±0.33	5.01±0.32	5.00±0.34	5.03±0.33	0.12

Values are expressed as mean ± SD, median (interquartile range) or per cent of participants in the respective category

[a] Median is presented due to a skewed distribution

[b] One-way analysis of variance, Kruskal–Wallis test or χ^2 test to compare each risk characteristic among the quartiles of HOMA-IR

Similar positive relationships were observed for coronary events and stroke. This pattern was broadly similar regardless of the presence or absence of other relevant metabolic disorders (hypertension and dyslipidaemia), abdominal obesity and smoking, with no evidence of an interaction effect between increased HOMA-IR and each of these four factors on the risk of cardiovascular events. To the best of our knowledge, this is the first prospective survey that shows a

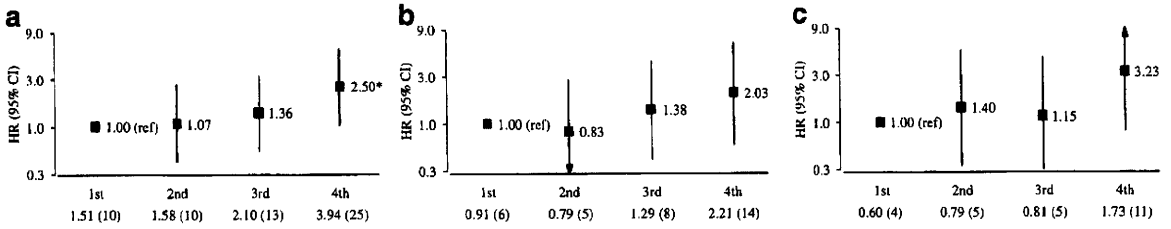

Fig. 1 Hazard ratios for the incidence of (**a**) cardiovascular events, (**b**) coronary events and (**c**) stroke in each quartile of HOMA-IR in 2,548 men over 11 years of follow-up (1996–2007). A Cox proportional hazards regression model was used with adjustment for age, waist circumference, smoking habits, drinking habits, leisure-time physical activity, systolic blood pressure, medication for hypertension, serum non-HDL-cholesterol, medication for hypercholesterolaemia, log-serum triacylglycerol, serum HDL-cholesterol and HbA_{1c}. The ranges of the first (n=649), second (n=629), third (n=624) and fourth (n=646) quartiles of HOMA-IR were 0.18–0.66, 0.67–1.01, 1.02–1.51 and 1.52–18.73, respectively. Values, x-axes are crude incidence rates per 1,000 person-years (n events). y-Axes are $\log_3$ scale. *p<0.05. ref, reference

significantly positive relationship between HOMA-IR and the risk of coronary events and stroke in an Asian population, avoiding the potential confounding effect of other relevant metabolic disorders on the risk of cardiovascular events. Although a previous Chinese study examined the relationship between HOMA-IR and the risk of cardiovascular events, that study reported a positive trend, which did not reach statistical significance [36].

Hedblad et al. [19] reported that non-diabetic individuals with the 75th percentile value of the distribution of HOMA-IR (≥2.12 for men, ≥1.80 for women) of their study population had a significantly higher risk of myocardial infarction than those without these HOMA-IR values, after adjustment for traditional risk factors including fasting glucose. In addition, the Bruneck study [20] reported a similar relationship between HOMA-IR and the risk of cardiovascular events. Furthermore, the San Antonio Heart Study [21] reported that non-diabetic individuals with HOMA-IR ≥2 (which was close to the median value) were at increased risk of coronary artery disease and stroke compared with those with HOMA-IR <2. Our results are consistent with the findings of these previous Western studies. An important finding of our study was that increased HOMA-IR can predict subsequent coronary events and stroke in Asians, in whom stroke is the predominant subtype of cardiovascular event and the ratio of ischaemic stroke:haemorrhagic stroke differs from that in Whites [49]. In addition, our data suggest an apparent increase in the risk of cardiovascular events with an HOMA-IR of about 1.5, although the cardiovascular risk remains unchanged below 1.5. Interestingly, our findings support a previous Japanese study, which suggested that a HOMA-IR value of 1.73 was the appropriate cut-off level for insulin resistance [44]. However, further studies are required to provide more detailed information on this issue.

Our stratified analyses further emphasise that insulin resistance with compensatory hyperinsulinaemia has an effect on development of the diseases studied that is distinct from that of other relevant metabolic disorders. In theory, even isolated insulin resistance without any other relevant metabolic disorders may predict subsequent coronary events and stroke. Consequently, measures to reverse insulin resistance in addition to the management of traditional cardiovascular risk factors may improve the overall cardiovascular risk profile, particularly in non-diabetic individuals. In addition, insulin resistance and abdominal obesity may play independent roles, at least in part, in the development of cardiovascular disease, although obesity is closely associated with insulin resistance [24, 46]. Our observations are consistent with the findings of the San Antonio Heart Study [21]. However, the present study did not elucidate the underlying mechanism for the possible causal relationship between insulin resistance with compensatory hyperinsulinaemia and cardiovascular events. It is also unlikely that smoking and insulin resistance have a synergistic effect on the development of cardiovascular disease.

Our study has several limitations. First, as our study participants consisted solely of male workers in one factory, caution should be exercised when generalising our results. Second, only participants who were apparently free of diabetes at baseline were included in the analyses. This inclusion was based on fasting glucose <6.11 mmol/l and HbA_{1c} <5.8% [41], because we had no data on plasma glucose and insulin after glucose loading. Third, no information was available on other factors that affect fasting insulin, e.g. the presence of an insulin-producing tumour. Finally, coronary events included only cases of angina pectoris requiring coronary intervention; medication-managed cases of angina pectoris were excluded. Furthermore, we were not able to divide stroke into ischaemic and haemorrhagic types in our study due to the relatively small numbers of each event.

In conclusion, our data suggest that HOMA-IR is a useful index for prediction of subsequent coronary events and stroke in a non-diabetic Japanese male population. In addition, insulin resistance with compensatory hyperinsulinaemia is

Table 2 Hazard ratios for the incidence of cardiovascular events in the third and fourth quartiles of HOMA-IR compared with the combination of the first and second quartiles in 2,548 non-diabetic men over 11 years of follow-up (1996–2007)

Variable	HOMA-IR by quartile			Log-HOMA-IR	*p* value for interaction[c]
	1st+2nd (0.18–1.01)	3rd (1.02–1.51)	4th (1.52–18.73)	1 SD (0.61) increment	
Overall					
Events/participants (*n*/*n*)	20/1,278	13/624	25/646		
Crude rate per 1,000 person-years	1.54	2.10	3.94		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.31 (0.63–2.73)	2.40 (1.16–4.94)	1.51 (1.13–2.02)	
Absence of hypertension					
Events/participants (*n*/*n*)	9/886	3/393	14/362		
Crude rate per 1,000 person-years	1.00	0.77	3.91		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	0.68 (0.18–2.61)	3.09 (1.11–8.62)	1.34 (0.90–1.99)	
Presence of hypertension[b]					0.42
Events/participants (*n*/*n*)	11/392	10/231	11/284		
Crude rate per 1,000 person-years	2.80	4.37	3.98		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.84 (0.73–4.64)	1.80 (0.64–5.08)	1.69 (1.08–2.64)	
Absence of dyslipidaemia					
Events/participants (*n*/*n*)	15/1,061	6/426	14/322		
Crude rate per 1,000 person-years	1.39	1.40	4.43		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	0.81 (0.29–2.23)	3.02 (1.22–7.44)	1.69 (1.16–2.47)	
Presence of dyslipidaemia[b]					0.26
Events/participants (*n*/*n*)	5/217	7/198	11/324		
Crude rate per 1,000 person-years	2.33	3.66	3.45		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.89 (0.58–6.20)	1.65 (0.51–5.35)	1.19 (0.76–1.87)	
Absence of abdominal obesity					
Events/participants (*n*/*n*)	17/1,114	9/433	11/331		
Crude rate per 1,000 person-years	1.50	2.08	3.38		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.26 (0.54–2.97)	1.96 (0.82–4.66)	1.47 (1.01–2.13)	
Presence of abdominal obesity[b]					0.91
Events/participants (*n*/*n*)	3/164	4/191	14/315		
Crude rate per 1,000 person-years	1.88	2.14	4.54		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.21 (0.26–5.58)	3.85 (0.93–15.93)	1.72 (1.04–2.84)	
Absence of current smoking					
Events/participants (*n*/*n*)	4/463	1/279	10/304		
Crude rate per 1,000 person-years	0.85	0.36	3.22		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	0.48 (0.05–4.58)	4.60 (1.11–19.17)	2.06 (1.20–3.54)	
Presence of current smoking					0.76
Events/participants (*n*/*n*)	16/815	12/345	15/342		
Crude rate per 1,000 person-years	1.94	3.52	4.51		
Multivariate-adjusted HR (95% CI)[a]	1.00 (reference)	1.56 (0.70–3.46)	1.79 (0.76–4.22)	1.38 (0.97–1.94)	

Data are presented for the total study population (overall) and also grouped according to characteristics as indicated

[a] Cox proportional hazards regression model with multivariate adjustment for age, waist circumference, smoking habits, drinking habits, leisure-time physical activity, systolic blood pressure, medication for hypertension, serum non-HDL-cholesterol, medication for hypercholesterolaemia, log-serum triacylglycerol, serum HDL-cholesterol and HbA_{1c}

[b] Definitions based on the Japanese criteria for metabolic syndrome; hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg and/or taking medication for hypertension; dyslipidaemia was defined as triacylglycerol ≥1.69 mmol/l and/or HDL-cholesterol <1.03 mmol/l; abdominal obesity was defined as waist circumference ≥85 cm [45]

[c] The significance of the interaction effect between increased HOMA-IR and each of the four factors on the risk of cardiovascular events was tested using an interaction term for the categorical variables in the Cox model

likely to have an effect on the development of cardiovascular disease separately from other relevant metabolic disorders. Given that HOMA-IR is calculated after the assessment of traditional cardiovascular risk factors and the measurement of fasting insulin, HOMA-IR could provide additional information that could improve overall prediction of cardiovascular risk.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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厚生労働省科学研究費補助金循環器疾患等生活習慣病対策総合研究事業
愛媛県大洲地区コホート研究

分担研究者　斉藤　功　愛媛大学大学院医学系研究科公衆衛生・健康医学　准教授

研究要旨
平成21～22年度の愛媛県大洲市の特定健診受診者のうち、本研究への同意が得られた2998人を対象に5分間の自律神経系機能測定を実施した。既知の循環器疾患危険因子（BMI、腹囲、収縮期・拡張期血圧値、HDL・LDLコレステロール、HbA1c）との関連を検討したところ、男女とも心拍変動と血圧との有意な関連を認めた。さらに、年齢、BMI、降圧薬服用の有無、飲酒、喫煙、生活活動強度で調整した場合、男性での関連は弱まったが、女性では依然として収縮期血圧、拡張期血圧との強い関連が認められた。なお、男性では飲酒習慣との交互作用を認めたため、飲酒習慣別に検討したところ、非飲酒者において心拍変動と高血圧との有意な関連を認めた。

A．研究目的

自律神経系機能の低下は、循環器疾患や糖尿病の危険因子であることが欧米のコホート研究により報告されている。しかしながら、日本において地域住民を対象に自律神経系機能と循環器疾患の危険因子との関連を検討した研究はほとんど見当たらない。

そこで、本研究は、愛媛県大洲市の特定健診受診者を対象に、加速度脈波測定器による5分間の心拍変動の計測を実施し、循環器疾患の危険因子であるBMI、腹囲、収縮期血圧値、拡張期血圧値、HDLコレステロール、LDLコレステロール、HbA1cとの関連について検討した。

B．研究方法

1）対象地域

対象地域は、愛媛県大洲市（2010年10月31日現在48,523人）である。2005年に旧大洲市、喜多郡長浜町・肱川町・河辺村と合併し、大洲市となった。大洲市の地理的環境を見ると、山間部の肱川地区、河辺地区、市街地にあたる平野部の旧大洲地区、海岸部の長浜地区がある。現在大洲市保健センターの他に、各旧長浜地区、肱川地区、河辺地区にも保健師が配置され地域の保健活動を行っている。

2）研究方法

平成21～22年度の愛媛県大洲市の特定健診受診者（40～74歳）であり、本研究の同意の得られた2998人に対して、5分間の心拍変動測定を実施した。さらに通常の特定健診項目に追加して心電図検査、貧血検査、眼底検査を実施した。心電図検査において期外収縮と心房細動が認められた受診者(男性46人、女性44人)を除いた男性1164人、女性1744人を分析対象とした。

心拍変動測定には、Pulse Analyzer Plus TAS9(YKC Co.)を用いた。心拍変動の測定は、午前9時から12時の間に、安静の後、座位で行った。分析に用いた自律神経系機能指標は、時間領域パラメータであるSDNN(心拍のRR間隔の標準偏差)、RMSSD(隣接するRR間隔の差を2乗したものの平方根)、および周波数領域パラメータであるLnLF(低周波のパワースペクトルを示し、交感神経と副交感神経の両方を反映する）、LnHF(高周波のパワースペクトルを示し、副交感神経の活動を反映する)、LnLFHF（LnLFとLnHFのパワーの比率であり、交感神経と副交感神経の全体のバランスを反映する。数値が高いと交感神経の有意を示す）とした。

C．研究結果

1)対象者の特徴

表1に対象者の特性を示した。平均年齢は男性63.6歳、女性64.5歳であった。

2)自律神経系機能指標の4分位別年齢調整済み平均値

性別に自律神経系機能指標を4分位に分け、それぞれの群を低群、中群、中高群、高群とし、各指標の年齢調整済み平均値を共分散分析を用いて求めた（表2）。男性ではSDNN、RMSSD、LnLF、LnHFそれぞれについて低群の方が高群より拡張期血圧平均値が有意に高い傾向を認め、女性ではSDNN、RMSSD、LnLF、LnHF、の低群が高群より収縮期・拡張期血圧平均値が有意に高く、LnLFHFは低群が高群よりも有意に低かった。また、男性のSDNN、LnLF、LnHF低群は、高群よりBMI平均値、腹囲平均値が有意に高く、LnLFが低群では高群よりHDLコレステロール平均値が有意に低かった。

さらに、降圧薬服用の有無、飲酒、喫煙、生活活動強度を調整因子とした共分散分析を行った。女性では、多変量調整後もSDNN、RMSSD、LnLF、LnHFの4分位において、低群は高群に比べて収縮期・拡張期血圧値の平均値が有意に高く、LnLFHFの低群は高群よりも有意に収縮期・拡張期血圧の平均値が有意に低かった。しかしながら、男性では有意な関連は認めなかった。

3）飲酒別の高血圧症に対するオッズ比

収縮期血圧140 mm Hg以上または拡張期血圧90 mm Hg以上もしくは降圧薬服用者を高血圧とし、高血圧症に対する心拍変動指標と肥満（BMI25 kg/㎡以上）、降圧薬服用、飲酒、喫煙の交互作用を分析したところ（表3）、飲酒との交互作用が確認されたため、飲酒の有無により層別化し、高血圧症に対するオッズ比を求めた。

男性では、非飲酒者においてSDNN低群のオッズ比を1としたところ、高群のオッズ比が0.27まで低下し、SDNNと高血圧との間に有意な関連を認めた。

D．考察

3000人規模の地域集団を対象に、自律神経系機能指標と循環器疾患危険因子との関連について横断的研究を行った。年齢、降圧薬服用の有無、BMI、飲酒、喫煙、生活活動強度の指標を調整後も、女性においてSDNN等の心拍変動指標と血圧値との間に強い関連を認めた。つまり、心拍変動の低下、及び交感神経優位の状態が、高血圧症のリスクになることが示唆された。

男性においては、BMI等を調整したところ心拍変動と血圧値との間に有意な関連を認めなかったが、飲酒の影響が強く、非飲酒者についてみれば、女性と同様にSDNNと高血圧との間に有意な関連を認めた。

今後も引き続き調査を継続し、自律神経系機能がメタボリックシンドロームに与える影響について検討が必要であると考えられた。

E．健康危機情報

なし

F．研究発表

1．論文発表

なし

2.学会発表

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研究協力者

加藤匡宏　愛媛大学大学院教育学研究科
山内加奈子　愛媛大学教育実践センター
谷川　武　愛媛大学大学院医学系研究科
櫻井　進　愛媛大学大学院医学系研究科
森　浩実　愛媛大学大学院医学系研究科
白石恒子　大洲市保健センター