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

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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

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Abbreviation

HOMA-IR HOMA of insulin resistance

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, $\text{HbA}_{1c} \geq 5.8\%$ 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) $\text{HOMA-IR} < 1.00$; (2) $1.00 \leq \text{HOMA-IR} < 1.50$; (3) $1.50 \leq \text{HOMA-IR} < 2.00$; (4) $2.00 \leq \text{HOMA-IR} < 2.50$; and (5) $2.50 \leq \text{HOMA-IR}$. Hazard ratios in each HOMA-IR group were calculated in a multivariate Cox model, with the $\text{HOMA-IR} < 1.00$ 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 pmol/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 pmol/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 $1.00 \leq \text{HOMA-IR} < 1.50$ ($n = 620$), 2.92 for $1.50 \leq \text{HOMA-IR} < 2.00$ ($n = 349$), 3.37 for $2.00 \leq \text{HOMA-IR} < 2.50$ ($n = 151$) and 8.15 for $2.50 \leq \text{HOMA-IR}$ ($n = 163$), 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 $1.00 \leq \text{HOMA-IR} < 1.50$, 2.07 (0.97–4.43) for $1.50 \leq \text{HOMA-IR} < 2.00$, 2.37 (0.89–6.32) for $2.00 \leq \text{HOMA-IR} < 2.50$ and 5.83 (2.90–11.74) for $2.50 \leq \text{HOMA-IR}$; 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				<i>p</i> 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 (<i>n</i>)	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 obe-

sity 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 log₃ 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 1 SD (0.61) increment	<i>p</i> value for interaction ^c
	1st+2nd (0.18–1.01)	3rd (1.02–1.51)	4th (1.52–18.73)		
Overall					
Events/participants (<i>n/n</i>)	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 (<i>n/n</i>)	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					
Events/participants (<i>n/n</i>)	11/392	10/231	11/284		0.42
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 (<i>n/n</i>)	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					
Events/participants (<i>n/n</i>)	5/217	7/198	11/324		0.26
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 (<i>n/n</i>)	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					
Events/participants (<i>n/n</i>)	3/164	4/191	14/315		0.91
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 (<i>n/n</i>)	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					
Events/participants (<i>n/n</i>)	16/815	12/345	15/342		0.76
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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