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Circulation Journal
Official Journal of the Japanese Circulation Society
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Validity of Using Body Mass Index as a Surrogate Measure of Abdominal Obesity

To the Editor:

We read the recent article by Irie et al[1] with great interest. The study showed the association between the clustering of metabolic risk factors and cardiovascular mortality in a population of community-dwelling men and women in Japan. They concluded that the clustering of metabolic risk factors increases the risk of cardiovascular disease, irrespective of the presence or absence of overweight. While we agree with their conclusion, we are concerned about the rationale for using the body mass index (BMI) ≥25.0 kg/m^2 as a surrogate criterion for the waist circumference (WC) ≥90 cm (ie, abdominal obesity) in men. They stated that these values are reported to correspond well in Asian men, but the cited reports do not appear to mention this issue. In this regard, according to our data, which were obtained from male workers (age range; 40–65 years) during a health examination at 2 companies in Japan, the BMI closely correlated with the WC (r=0.89) and a linear regression analysis showed the BMI levels corresponding to the WC of 90 cm in men to be 25.6 kg/m^2 (Figure 1). A receiver operating characteristic curve analysis also revealed the optimal cutoff level of BMI to be 25.0 kg/m^2 for identifying participants with a WC ≥90 cm (Figure 2). Although our data were not collected from the general population, these findings at least partially support the methodology in the report by Irie et al.

The Japanese criteria of metabolic syndrome define abdominal obesity as the WC ≥85 cm in men.[2] However, a recent study demonstrated a WC of 90 cm to represent both the visceral fat area of 100 cm^2 and the clustering of metabolic risk factors in Japanese men.[3] Moreover, the Hisayama study showed the optimal cutoff level of WC to be 90 cm in men for predicting cardiovascular events.[4] We therefore accept the concept by Irie et al, which adopted the WC ≥90 cm for the diagnosis of abdominal obesity. However, when diagnosing abdominal obesity using the BMI as a surrogate measure of WC, it is necessary to demonstrate its validity.

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(Released online December 26, 2009)

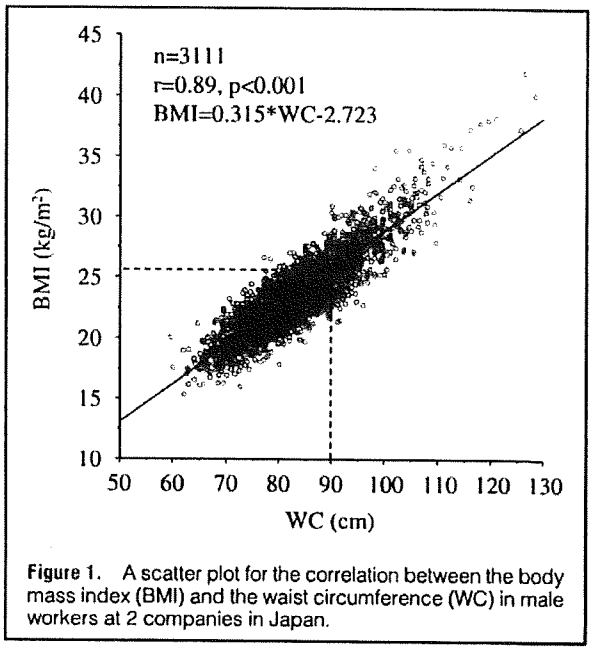

Figure 1. A scatter plot for the correlation between the body mass index (BMI) and the waist circumference (WC) in male workers at 2 companies in Japan.

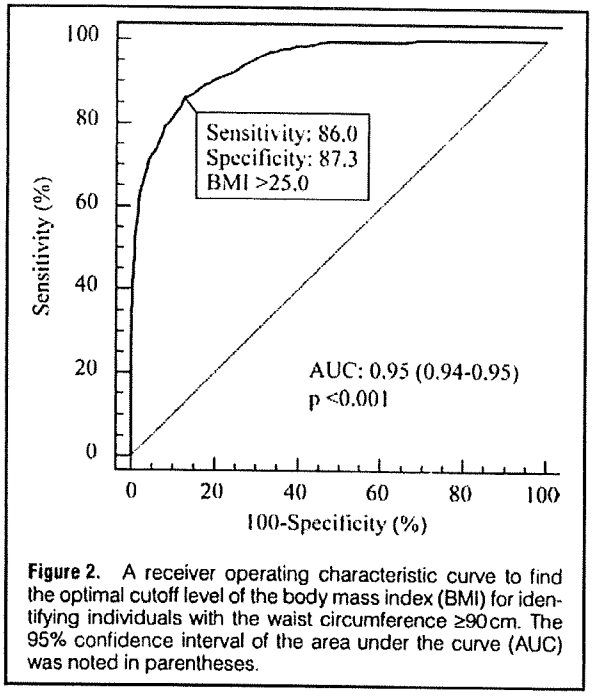

Figure 2. A receiver operating characteristic curve to find the optimal cutoff level of the body mass index (BMI) for identifying individuals with the waist circumference ≥90 cm. The 95% confidence interval of the area under the curve (AUC) was noted in parentheses.

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Validity of Using Body Mass Index as a Surrogate Measure of Abdominal Obesity: Reply

We used body mass index (BMI) ≥25 kg/m² as a surrogate criterion for abdominal obesity[1] because that cutoff value corresponds to waist circumference (WC) ≥90 cm in men or ≥80 cm in women of Asian populations, as we cited,[2] and as also reported by the WHO Western Pacific Region, International Association for the Study of Obesity and the International Obesity Task Force,[3] which recommended new diagnostic criteria to identify overweight and obesity for the Asia-Pacific region because the WHO criteria established in 1998 may not be appropriate for Asian populations based on their risk factors and morbidities.[4] They proposed that the cut-off for obesity in Asians (BMI ≥25 kg/m²) was lower than that in Europeans (BMI ≥30 kg/m²). They also mentioned the Asian criteria of waist circumference (WC) as the measure of abdominal obesity because body fat distribution determines the risk associated with obesity. The WHO report in 1998 suggested that 94 cm in men and 80 cm in women should be the appropriate measures in Europeans, but these cut-offs were not suitable for Asian populations; 90 cm for men and 80 cm for women were suggested as interim values for Asians.

BMI and WC correlate well in both men and women and these 2 obesity measures related to the metabolic risk factors in a community-based population in Japan.[5] We considered that the use of BMI as surrogate measure of WC is acceptable when WC was not routinely obtained. Further, prospective studies examining the association between each obesity measure and cardiovascular endpoints are needed to evaluate validity.

The recent report in the Korean population investigated the appropriate visceral adipose tissue (VAT) cut-off values for predicting metabolic risk factors. They indicated that the appropriate VAT cut-offs for metabolic risk factors were 100 cm² in men and 70 cm² in women using receiver-operating characteristic analysis. Regression lines indicated that VAT of 100 cm² corresponded to WC of 88.1 cm and BMI of 24.9 kg/m² in men, and VAT of 70 cm² corresponded to WC of 84.0 cm and BMI of 25.1 kg/m² in women.[6]

We appreciate your comparable data, indicating that BMI ≥25 kg/m² corresponds to WC ≥90 cm in Japanese men.

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(Released online December 26, 2009)

Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2009.02183.x

Gender difference of association between LDL cholesterol concentrations and mortality from coronary heart disease amongst Japanese: the Ibaraki Prefectural Health Study

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Abstract. Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Ohta H (Osaka University, Osaka, Japan; Harvard School of Public Health, Cambridge, MA, USA; Ibaraki Prefectural Office, Ibaraki; Dokkyo Medical University School of Medicine, Tochigi; Ibaraki Health Service Association, Ibaraki; Japan). Gender difference of association between LDL cholesterol concentrations and mortality from coronary heart disease amongst Japanese: the Ibaraki Prefectural Health Study. *J Intern Med* 2010;**00**: 000–000

Objective. The aim of this study was to examine whether LDL cholesterol raises the risk of coronary heart disease in a dose–response fashion in a population with low LDL-cholesterol levels.

Design. Population-based prospective cohort study in Japan.

Subjects and main outcome measures. A total of 30 802 men and 60 417 women, aged 40 to 79 years with no history of stroke or coronary heart disease, completed a baseline risk factor survey in 1993. Systematic mortality surveillance was performed through 2003 and 539 coronary heart disease deaths were identified.

Results. The mean values for LDL-cholesterol were 110.5 mg dL^{-1} (2.86 mmol L^{-1}) for men and 123.9 mg dL^{-1} (3.20 mmol L^{-1}) for women. Men with LDL-cholesterol ≥140 mg dL^{-1} (≥3.62 mmol L^{-1}) had two-fold higher age-adjusted risk of mortality from coronary heart disease than did those with LDL-cholesterol <80 mg dL^{-1} (<2.06 mmol L^{-1}), whereas no such association for women was found. The multivariable hazard ratio for the highest versus lowest categories of LDL-cholesterol was 2.06 (95 percent confidence interval: 1.34 to 3.17) for men and 1.16 (0.64 to 2.12) for women.

Conclusion. Higher concentrations of LDL-cholesterol were associated with an increased risk of mortality from coronary heart disease for men, but not for women, in a low cholesterol population.

Keywords: coronary heart disease, gender, LDL.

Introduction

Low-density lipoprotein cholesterol (LDL-cholesterol) is one of the major atherogenic lipoproteins and has been identified by the National Cholesterol Educational Program (NCEP) Expert Panel as a primary target for prevention of coronary heart disease [1, 2].

Previous studies [3–6] showed that high concentrations of LDL-cholesterol were associated with increased risk of coronary heart disease mainly for obese populations with higher concentrations of LDL-cholesterol, whereas little evidence is available for less obese populations with lower concentrations of LDL-cholesterol. It therefore remains unclear whether a similar association as for obese populations is also observed at lower ranges of LDL-cholesterol levels.

As the metabolism of obese populations is affected by different environmental factors than those affecting less obese population, it is of major importance to examine the effect of LDL-cholesterol on the risk of coronary heart disease for populations with its lower ranges. First, it is difficult to examine the threshold values in the lower ranges of LDL-cholesterol amongst obese populations,

because of their higher concentrations of LDL-cholesterol. Seven countries study confirmed the positive association between total cholesterol and mortality from coronary heart disease for high cholesterol populations, including Americans, but not for Japanese, who had the lowest population mean levels of total cholesterol levels [7]. Previous studies [3–6] of participants with a higher mean level of LDL-cholesterol could not examine the effect of LDL-cholesterol amongst individuals in the lower LDL-cholesterol ranges. Thus, the report of Adults Treatment Panel III (ATP III) could not make any recommendations for further reduction of LDL-cholesterol for populations with low mean LDL-cholesterol levels [2].

Secondly, obese populations were found to be more likely to show a mixture of multiple metabolic abnormalities [8], which may lead to high LDL-cholesterol levels, and thus make it more likely for such populations to be at high risk. In fact, a previous study showed that almost all persons (>95%) enrolled in the Third National Health and Nutrition Examination Survey (NHANES III) had border line or higher levels of coronary risk factors [9].

To examine whether LDL-cholesterol raises the risk of coronary heart disease for a less obese population with low LDL-cholesterol levels, we conducted a population-based cohort study of Japanese men and women, who had lower means of total cholesterol and body mass index in comparison with Western populations [7, 10].

Materials and methods

Study cohort and population

In 1993, the Ibaraki Prefectural government initiated a community-based cohort study, known as the Ibaraki Prefectural Health Study, to obtain information on health status for the purpose of health education and policy making [11–13]. The participants in the cohort were 98 196 individuals (33 414 men and 64 782 women) aged 40–79 years, living in Ibaraki Prefecture, who underwent an annual health check-up in 1993, which included the examination of blood lipids for 96 610 individuals (32 984 men and 63 626 women).

We excluded 5391 persons (2182 men and 3209 women) from our analysis because of a previous history of stroke and coronary heart disease at the time of baseline inquiry. Thus, a total of 91 219 individuals (30 802 men and 60 417 women) were enrolled in the study presented here.

Informed consent was obtained from the community representatives for conducting an epidemiological study based on guidelines of the Council for International Organizations of Medical Science [14]. The Ethics Committee of Ibaraki Prefecture approved this study.

Measurement of risk factors

Serum total cholesterol and triglycerides were measured with enzymatic methods using an RX-30 device (Nihon Denshi, Tokyo, Japan) and HDL cholesterol levels were measured with phosphotungstic acid-magnesium methods using an MTP-32 (Corona Electric, Ibaraki, Japan). These measurements were performed on the premises of the Ibaraki Health Service Association, and were standardized by the Osaka Medical Center for Health Science and Promotion under the aegis of the US National Cholesterol Reference Method Laboratory Network (CRMLN). The laboratory of the Osaka Medical Center for Health Science and Promotion has been standardized since 1975 by the CDC-NHLBI Lipid Standardization Program provided by the Center for Disease Control and Prevention (Atlanta, GA) and has met all the criteria for both precision and accuracy of lipid measurements [15]. LDL-cholesterol was calculated using the Friedewald formula as follows: LDL-cholesterol (mg dL^{-1}) = total cholesterol (mg dL^{-1})–HDL-cholesterol (mg dL^{-1})–0.2*triglycerides (mg dL^{-1}) [16]. A previous study showed no bias related to LDL-cholesterol levels amongst persons with <802 mg dL^{-1} (<8.8 mmol L^{-1}) of triglycerides in fasting blood samples [17]. As 83% of subjects were nonfasting, we compared LDL-cholesterol measured by direct method as golden standard and values estimated from the Friedewald formula amongst serum samples from 15 743 men and 13 143 women aged 40–79 years who participated in health check-ups by Osaka Medical Center for Health Science and Promotion [15]. We found that the values by Friedewald formula were comparable with LDL-cholesterol levels measured by direct method when triglycerides were <802 mg dL^{-1} (<8.8 mmol L^{-1}) in both fasting and nonfasting blood samples. The Spearman's rank correlation coefficients between directly measured and estimated LDL-cholesterol values were 0.96 (0.96 for men and 0.97 for women) in fasting and 0.94 (0.93 for men and 0.95 for women) in nonfasting

subjects. Non-HDL-cholesterol was calculated as follows; Non-HDL-cholesterol (mg dL^{-1}) = total cholesterol (mg dL^{-1})–HDL-cholesterol (mg dL^{-1}).

Mild hypertension was defined as systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg, and the corresponding values were 160–179 mmHg or 100–109 mmHg for moderate hypertension and ≥180 mmHg or ≥110 mmHg for severe hypertension. Diabetes was defined as a plasma glucose level of ≥126 mg dL^{-1} (≥7.0 mmol L^{-1}) during fasting or ≥200 mg dL^{-1} (≥11.1 mmol L^{-1}) during nonfasting, or as use of medication for diabetes, and impaired glucose tolerance was defined as a plasma glucose level of 110–125 mg dL^{-1} (6.1–6.9 mmol L^{-1}) at fasting or 140–199 mg dL^{-1} (7.8–11.0 mmol L^{-1}) at nonfasting and no use of medication for diabetes. Kidney dysfunction was defined as a serum creatinine level of ≥1.2 mg dL^{-1} (≥110 μmol L^{-1}) for men or of ≥1.0 mg dL^{-1} (≥90 μmol L^{-1}) for women and/or as a history of kidney disease. Height in stocking feet and weight in light clothing were measured and body mass index (BMI) was calculated as weight (kg) per height $(m)^2$. An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual weekly intake of alcohol in *go* units (a Japanese traditional unit of alcohol intake converted to grams of ethanol per day at 23 g ethanol per *go* unit) and histories of stroke and heart disease. Current drinkers were defined as occasional and habitual drinkers.

Follow-up surveillance

To ascertain deaths in the cohort, the investigators conducted a systematic review of death certificates, which in Japan are all forwarded to the local public health centre of every community. It is believed that all deaths that occurred in the cohort were ascertained, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. Mortality data are centralized at the Ministry of Health and Welfare, where the underlying causes of death are coded for the National Vital Statistics according to the International Classification of Disease, 9th (1993–1994) and 10th (1995–2004) revisions (410–414 for International Classification of Disease, 9th revision and code I20 to I25 for 10th revision).

The follow-up inquiry for this study was conducted until the end of 2003 and the median of follow-up was 10.3 years. Only 3.2% of the subjects had moved out of their respective communities and were treated as censored.

Statistical analysis

Statistical analysis was based on mortality rates from coronary heart disease divided by clinical categories of LDL-cholesterol (<80, 80–99, 100–119, 120–139, ≥140 mg dL^{-1} or <2.06, 2.06–2.57, 2.58–3.09, 3.10–3.61, ≥3.62 mmol L^{-1}). Person-years of follow-up were calculated from the date of the baseline survey to the date of death, exit from the community, or the end of 2003, whichever occurred first.

Sex-specific age-adjusted means and proportions of selected cardiovascular risk factors at baseline were determined in terms of the LDL-cholesterols categories. The *t*-test or chi-squared test was used to examine differences in age-adjusted mean values and proportions of baseline characteristics from those of the lowest LDL-cholesterol category. The age-adjusted and multivariable hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated with the Cox proportional hazards model after adjustment for age and potential confounding factors. These potential confounding factors included body mass index (sex-specific quintiles), blood pressure categories (normal, mild hypertension, moderate hypertension or severe hypertension), anti-hypertensive medication use (yes or no) diabetes status (normal, impaired glucose tolerance or diabetes), gamma-glutamyl transferase (sex-specific quintiles), kidney dysfunction (yes or no), smoking status (never, ex-smoker and current smokers of one to 19 or ≥20 cigarettes per day), alcohol intake category (never or ex-drinkers, occasional drinkers and habitual drinkers consuming <69 g day^{-1} and ≥69 g day^{-1} of ethanol respectively), HDL-cholesterol (<40, 40–49, 50–59, 60–69, ≥70 mg dL^{-1} or <1.03, 1.03–1.28, 1.29–1.54, 1.55–1.80, ≥1.81 mmol L^{-1}) and triglycerides (<100, 100–149, 150–199, 200–249, 250–299, ≥300 mg dL^{-1} or <1.12, 1.12–1.68, 1.69–2.24, 2.25–2.81, 2.82–3.37, ≥3.38 mmol L^{-1}). We also calculated the HR per 1 SD increment of LDL-cholesterol (32.5 mg dL^{-1} or 0.84 mmol L^{-1}). We tested the assumption of proportional hazards for LDL-cholesterol categories [18] and found no violation of proportionality. Tests for effect modification by sex or other variables were conducted with an interaction term generated by multiplying the continuous variables of LDL-cholesterol by sex or other variables. As the Friedewald formula introduces biased data for LDL-cholesterol [17], we conducted an additional analysis after the exclusion of persons with

hypertriglyceridaemia (triglycerides ≥802 mg dL^{-1}) at baseline survey (55 men and 23 women), and after exclusion of persons used lipid lowering medication at baseline survey (370 men and 1903 women). Furthermore, we analysed the data excluding deaths within the first 2 years after the baseline (399 men and 264 women) to examine the potential effect by any existing preclinical disorders.

We further analysed the data with Cox proportional hazard model with the time-dependent covariates, using the additional data of LDL-cholesterol and confounding factors for 80 578 persons (88.3% of the participants) whose blood lipids had been examined additionally more than once during follow-ups. The median duration between the date of the latest examination and the date of the end of the follow-up was 0.7 years.

As the presence of competing risks may lead to biased results, we also analysed using proportional hazard model for the subdistribution of competing risks [19]. We also examined possible effects of cut-offs on the significant associations nonparametrically by using restricted cubic splines method [20]. Tests for nonlinearity were examined by the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

All statistical tests were two-sided and a *P*-value <0.05 was regarded as statistically significant and a *P*-value 0.05 to 0.10 was regarded as borderline significant. All statistical analyses except for proportional hazard model for the subdistribution of competing risks were conducted using sas, version 9.13 (SAS Institute, Inc., Cary, NC, USA). r version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for calculations pertaining to the proportional hazard model for the subdistribution of competing risks.

Results

A total of 91 219 persons (30 802 men and 60 417 women) were followed up for a median of 10.3 years, during which time 295 men and 244 women died from coronary heart disease. The mean (standard deviation: SD) LDL-cholesterol level was 110.5 mg dL^{-1} (31.6) for men and 123.9 mg dL^{-1} (31.9) for women. The prevalence of obesity (BMI≥30.0 kg m^{-2}) was 1.7% for men and 3.3% for women.

Table 1 shows selected cardiovascular risk factors by LDL-cholesterol concentration category. Compared with men who had the lowest levels of LDL-cholesterol (<80 mg dL^{-1}: <2.06 mmol L^{-1}), those who had the highest levels (≥140 mg dL^{-1}: ≥3.62 mmol L^{-1}) were younger, more fasted, more likely to use medication for lipid abnormality and less likely to use medication for hypertension, smoke or drink heavily. They also tended to have kidney dysfunction, higher mean body mass index and total cholesterol level, and lower mean systolic blood pressure, gamma-glutamyl transferase, HDL-cholesterol and triglyceride levels. Except for certain risk factors, similar associations were observed for women. Compared with women who had the lowest LDL-cholesterol levels, women with the highest levels were older, more likely to have diabetes and had higher mean systolic and diastolic blood pressure and gamma-glutamyl transferase level. Compared with women, men had higher means of systolic and diastolic blood pressure, gamma-glutamyl transferase and triglyceride levels, and lower means of body mass index, and total, HDL, non-HDL and LDL-cholesterol levels (not shown in the table). Men were likely to have diabetes mellitus and kidney dysfunction, smoke, drink heavily and use medication for lipid abnormality.

Age-adjusted mortality from coronary heart disease was twice as high for the highest than for the lowest LDL-cholesterol category for men, whilst there was no such association for women (Table 2). Adjustment for potential confounding factors did not alter these associations materially. The multivariable HR (95% CI) of coronary heart disease mortality for the highest versus the lowest concentrations of LDL-cholesterol was 2.06(1.34–3.17), $P = 0.001$, for men and 1.16(0.64–2.12), $P = 0.62$, for women. The corresponding multivariable HR (95% CI) associated with a 1 SD increment in LDL-cholesterol was 1.27(1.13–1.43), $P < 0.0001$ and 1.06(0.93–1.21), $P = 0.36$. There was a borderline significant interaction for gender difference in the association between LDL-cholesterol and mortality from coronary heart disease (*P* for interaction = 0.06).

These associations did not alter substantially after the exclusion of persons with hypertriglyceridaemia, persons who used lipid lowering medication or deaths within the first 2 years, for analysis with the time-dependent covariates Cox proportional hazard model or for analysis with proportional hazard model for the subdistribution of competing risks (not shown in the table). The HR (95% CI) of coronary heart disease mortality for the highest versus lowest LDL-cholesterol levels was 2.05(1.33–3.15), $P = 0.001$ for men and 1.16(0.64–2.10), $P = 0.64$ for women after the

Table 1 *Gender-specific age-adjusted mean values or prevalence of cardiovascular risk factors according to LDL-cholesterol levels*

	Men					Women				
	LDL-cholesterol, mg dL^{-1}					LDL-cholesterol, mg dL^{-1}				
	<80	80–99	100–119	120–139	140+	<80	80–99	100–119	120–139	140+
Range, mmol L^{-1}	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	3.62+	<2.06	2.06–2.57	2.58–3.09	3.10–3.61	3.62+
Number of persons	4685	6918	8112	6030	5057	4103	9858	14 728	14 327	17 401
Age, year	60.1	60.6*	60.5**	60.3	59.4*	54.2	55.5*	57.0*	58.7*	59.9*
Systolic blood pressure, mmHg	138	136*	136*	136*	136*	131	131	131	132*	133*
Diastolic blood pressure, mmHg	81	81*	81*	81	82	76	77	77*	78*	79*
Hypertensive medication use, %	21	20	19**	20	20	19	19	19	20	20
Diabetes, %	9	7*	7*	8	8	4	3**	4	4	5**
Body mass index, kg m^{-2}	22.6	22.9*	23.3*	23.7*	24.0*	22.9	23.0	23.4*	23.7*	24.1*
Gamma-glutamyl transferase, U L^{-1}	56	36*	34*	33*	35*	17	15*	16*	17**	19*
Kidney dysfunction, %	11	11	13**	14*	17*	9	8	8	8	9
Current smoker, %	59	54*	50*	48*	46*	6	5*	5*	4*	5*
Heavy drinkers, %	13.7	8.4*	6.2*	5.2*	3.8*	0.4	0.2*	0.1*	0.1*	0.1*
Lipid medication use, %	0.7	0.7	1.0	1.4*	2.5*	2.0	1.7	2.5	2.8*	5.1*
Total cholesterol, mg dL^{-1}	155	173*	190*	209*	240*	157	175*	194*	213*	246*
HDL-cholesterol, mg dL^{-1}	55	54*	52*	51*	50*	57	58*	58*	57	56*
Triglycerides, mg dL^{-1}	180	142*	141*	145*	151*	162	131*	129*	131*	137*
Fasting (≥8 h after last meal)	10.3	13.2*	16.5*	21.2*	27.0*	9.7	11.8	14.9*	17.6*	22.9*

Test for difference from the lowest category; *P < 0.01 **P < 0.05.

exclusion of persons with hypertriglyceridaemia, 2.22(1.43–3.46), P = 0.0004 for men and 1.09(0.60–1.99), P = 0.78 for women after the exclusion of persons who used lipid lowering medication, 2.16(1.35–3.45), P = 0.001 for men and 1.29(0.67–2.46), P = 0.44 for women after excluding deaths within the first 2 years, 1.55(1.02–2.34), P = 0.04 for men and 1.01(0.58–1.76), P = 0.97 for women, when we used the Cox proportional hazard model with time-dependent covariates and 1.82(1.20–2.76), P = 0.005 for men and 1.11(0.62–1.99), P = 0.72 for women when we used proportional hazard model for the subdistribution of competing risks.

To examine a potential effect modification by menopausal status, we conducted age-stratified analysis (aged <50 years vs. aged ≥50 years) for women, because we did not have the data on menopausal status. There was a significant age interaction although the number of cases was only five amongst women aged <50 years; the HR (95% CI) of coronary heart disease mortality for 30 mg dL^{-1} increment of LDL-cholesterol levels was 2.45(1.27–4.75), P = 0.009 for women aged <50 years and 1.05(0.92–1.19), P = 0.49 for women aged ≥50 years (P for interaction was 0.004).

We confirmed the gender difference of associations between LDL-cholesterol and mortality from coronary heart disease using nonparametric analysis (Fig. 1). The hazard ratios was linearly increased amongst men (P for linearity was P = 0.0003), whilst there was no linear association for women (P for linearity was 0.70). However, its graph suggested that the mortality from coronary heart disease may start to increase around 160 mg dL^{-1} of LDL-cholesterol levels (corresponding to 243 mg dL^{-1} of total cholesterol levels) amongst women.

To examine an effect of higher levels of LDL-cholesterol on mortality from coronary heart disease, we divided persons with ≥140 mg dL^{-1} into persons with

Table 2 *Gender-specific age-adjusted and multivariable hazard ratio (HR) and 95% confidence interval (95% CI) of mortality from coronary heart disease and all-causes according to LDL-cholesterol levels*

	LDL-cholesterol, mg dL^{-1}					HR per 1 SD increment
	<80	80–99	100–119	120–139	140+	
Men						
Person-years	44 532	67 098	79 049	58 858	49 213	298 750
Coronary heart disease						
No	35	56	74	62	68	295
Age-adjusted HR	1.0	0.99 (0.65–1.51)	1.11 (0.74–1.66)	1.28 (0.84–1.93)	1.78 (1.18–2.67)	1.24 (1.10–1.39)
Multivariable HR[a]	1.0	1.09 (0.71–1.68)	1.29 (0.85–1.95)	1.47 (0.95–2.26)	2.06 (1.34–3.17)	1.27 (1.13–1.43)
All-causes						
No	801	951	996	671	550	3969
Age-adjusted HR	1.0	0.73 (0.66–0.80)	0.65 (0.59–0.71)	0.60 (0.54–0.67)	0.63 (0.56–0.70)	0.84 (0.81–0.87)
Multivariable HR[a]	1.0	0.78 (0.71–0.86)	0.72 (0.66–0.80)	0.68 (0.61–0.75)	0.71 (0.64–0.80)	0.88 (0.85–0.91)
Women						
Person-years	40 539	97 681	146 571	142 469	172 472	599 731
Coronary heart disease						
No	13	40	56	47	88	244
Age-adjusted HR	1.0	1.15 (0.61–2.14)	0.97 (0.53–1.77)	0.74 (0.40–1.37)	1.10 (0.61–1.96)	1.07 (0.94–1.22)
Multivariable HR[a]	1.0	1.29 (0.69–2.43)	1.10 (0.60–2.03)	0.83 (0.44–1.55)	1.16 (0.64–2.12)	1.06 (0.93–1.21)
All-causes						
No	248	539	731	751	906	3175
Age-adjusted HR	1.0	0.81 (0.70–0.94)	0.67 (0.58–0.77)	0.63 (0.55–0.73)	0.60 (0.52–0.69)	0.88 (0.85–0.92)
Multivariable HR[a]	1.0	0.85 (0.73–0.99)	0.71 (0.61–0.82)	0.68 (0.58–0.78)	0.64 (0.55–0.73)	0.90 (0.86–0.93)

Potential confounding factors: blood pressure categories, anti-hypertensive medication use, diabetes mellitus, lipid medication use, body mass index, gamma-glutamyl transferase, smoking status, alcohol consumptions, kidney dysfunction and categories of HDL-cholesterol and triglycerides. 1SD of LDL-cholesterol was 32.5 mg dL^{-1} (0.84 mmol L^{-1}). [a]HR (95% CI) adjusted for age and potential confounding factors.

140–159 mg dL^{-1}, 160–179 mg dL^{-1} and ≥180 mg dL^{-1} (not shown in the table). The multivariable hazard ratio of mortality from coronary heart disease was 1.90(1.18–3.06), $P = 0.008$ (no of persons = 3130, no of events = 40) for 140–159 mg dL^{-1}, 2.32(1.32–4.09), $P = 0.004$ (no of persons = 1316, no of events = 20), for 160–179 mg dL^{-1}, 2.37(1.07–5.22), $P = 0.03$ (no of persons = 611, no of events = 8) for ≥180 mg dL^{-1} amongst men. The respective hazard ratio was 1.04(0.55–1.97), $P = 0.89$, (no of persons = 9695, no of events = 44) for 140–159 mg dL^{-1}, 1.19(0.60–2.36), $P = 0.62$, (no of persons = 4897, no of events = 25), for 160–179 mg dL^{-1}, 1.56(0.76–3.21), $P = 0.23$, (no of persons = 2809, no of events = 19) for ≥180 mg dL^{-1} amongst women.

On the other hand, higher levels of LDL-cholesterol were associated with reduced risk of all-cause mortality for both men and women (Table 2). The multivariable HR (95% CI) of all-cause mortality for the highest versus lowest LDL-cholesterol levels was 0.71(0.64–0.80), $P < 0.0001$ for men and 0.64(0.55–0.73), $P < 0.0001$ for women.

We observed no interaction of fasting/nonfasting status in the association between LDL-cholesterol and mortality from coronary heart disease (Table 3). When we stratified the data on the sub-population by fasting status, the associations did not differ substantially. No statistically significant interaction of the association between LDL-cholesterol and mortality from coronary heart disease was observed for other potential risk factors ($P > 0.20$) except for gender difference (Table 3).

We observed a weaker gender interaction in non-HDL-cholesterol and total cholesterol that that in LDL-cholesterol, although we showed significant

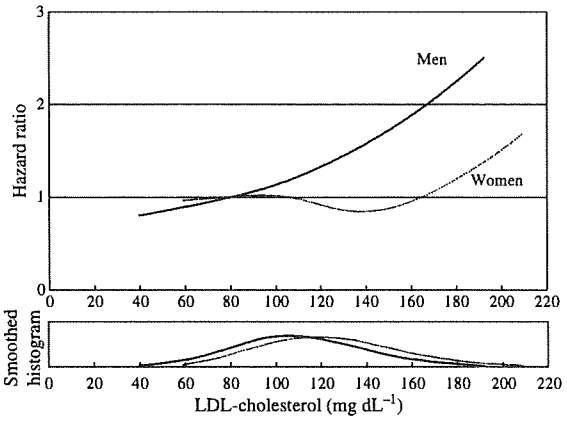

Fig. 1 *Multivariable hazard ratios of mortality from coronary heart disease in relation to LDL-cholesterol levels amongst men (solid line) and women (dotted line). 80 mg dL^{-1} of LDL-cholesterol were selected as reference. The values of the four knots correspond to 64.4 mg dL^{-1}, 98.0 mg dL^{-1}, 120.4 mg dL^{-1} and 161.0 mg dL^{-1} of LDL-cholesterol levels for men, and 78.0 mg dL^{-1}, 110.4 mg dL^{-1}, 134.0 mg dL^{-1} and 175.6 mg dL^{-1} for women. Smoothed histogram showed the distribution of LDL-cholesterol levels. We did not graph predictions from the top and bottom 1% of the analytical distribution to avoid undue visual influence of sparse tail data.* *P*-values for nonlinearity was $P = 0.93$ for men and $P = 0.23$ and *P*-values for linearity was $P = 0.0003$ for men and $P = 0.70$.

associations for men, but not for women (Table 4). The *P* for interaction was $P = 0.06$ for LDL-cholesterol, $P = 0.13$ for non-HDL-cholesterol and $P = 0.26$ for total cholesterol.

Discussion

In the large population-based prospective study of Japanese reported here, we observed, in a less obese population, significant positive associations of high LDL-cholesterol levels as well as non-HDL-cholesterol and total cholesterol levels, with increased risk of mortality from coronary heart disease for men, but not for women, whereas the gender interaction was more significant for LDL-cholesterol than that for total and non-HDL-cholesterol. These associations did not alter substantially after adjustment for potential confounding factors and after the exclusion of persons with hypertriglyceridaemia or the use of time-dependent covariates.

For this study population, the mean LDL-cholesterol level was 111 mg dL^{-1} for men and 124 mg dL^{-1} for women at baseline. Previous studies involving participants with higher mean LDL-cholesterol levels, showed an association with risk of coronary heart disease for higher LDL-cholesterol ranges. For example, the Framingham study (mean LDL-cholesterol at baseline: 139 mg dL^{-1} for men and 138 mg dL^{-1} for women) [3], the Chin-Shan Community Cardiovascular Cohort study (133 mg dL^{-1} and 142 mg dL^{-1} respectively) [5] and a cholesterol lowering clinical trial of high-risk patients (162 mg dL^{-1}) [21] demonstrated the relationship between higher concentrations of LDL-cholesterol and increased risk of coronary heart disease. The lowest LDL-cholesterol category of these studies comprised persons with over 100 mg dL^{-1} of LDL-cholesterol, who were classified in the middle and higher categories in our study.

A recent Japanese prospective cohort study in urban area [22] showed the relationship between higher concentration of LDL-cholesterol and increased risk of myocardial infarction (the means of LDL-cholesterol was 125 mg dL^{-1} for men and 135 mg dL^{-1} for women) amongst Japanese population, whose LDL-cholesterol levels was higher than that in our study. However, they could not show the relationship amongst women due to small number of case in women (cases of myocardial infarction was 24).

Another previous Japanese cohort study showed a significant association between LDL-cholesterol and incident coronary heart disease amongst men and women [23]. That study showed 1.68 (95% CI 0.99–2.84) times higher multivariable hazard ratio for persons with 125–150 mg dL^{-1} of LDL-cholesterol in comparison with persons with ≤102 mg dL^{-1}, whereas the risk was plateaued under 125 mg dL^{-1}. However, they did not conduct gender-specific analysis, probably due to the small number of cases. Our findings thus extend the previous evidence applying for the lower ranges of LDL-cholesterol.

We observed a gender difference in the associations of LDL-cholesterol with mortality from coronary heart disease. The possible mechanisms of the gender difference interaction are as follows. First, men develop atherosclerosis more often than women [24], which may lead to accelerating the atherogenic effect of LDL-cholesterol. Secondly, there may be a gender difference in the cumulative burden from LDL-cholesterol during atherosclerosis development due to lag time to an increase in LDL-cholesterol levels over a lifespan. Premenopausal women have lower total cholesterol levels than men of the same age group [25], which may result in a lower cumulative burden of atherosclerosis development for women than for

Table 3 *Multivariable hazard ratio (HR)[a] and 95% confidence interval (95% CI) of coronary heart disease according to LDL-cholesterol levels, stratified by gender and other risk factors*

		LDL-cholesterol, mg dL^{-1}					HR per 1 SD	*P* for
		<80	80–99	100–119	120–139	140+	increment	interaction
Men	No	35	56	74	62	68	295	
	Multivariable HR[a]	1.0	1.09 (0.71–1.68)	1.29 (0.85–1.95)	1.47 (0.95–2.26)	2.06 (1.34–3.17)	1.27 (1.13–1.43)	
Women	No	13	40	56	47	88	244	
	Multivariable HR[a]	1.0	1.29 (0.69–2.43)	1.10 (0.60–2.03)	0.83 (0.44–1.55)	1.16 (0.64–2.12)	1.06 (0.93–1.21)	0.06
Aged 40–59 years	No	5	12	13	11	18	59	
	Multivariable HR[a]	1.0	1.81 (0.62–5.27)	1.63 (0.56–4.75)	1.69 (0.56–5.13)	2.43 (0.84–7.08)	1.30 (1.02–1.66)	
Aged 60–79 years	No	43	84	117	98	138	480	
	Multivariable HR[a]	1.0	1.12 (0.77–1.63)	1.21 (0.84–1.73)	1.12 (0.77–1.63)	1.52 (1.05–2.19)	1.16 (1.05–1.27)	0.56
Nonhypertensive	No	13	31	32	24	39	139	
	Multivariable HR[a]	1.0	1.26 (0.66–2.44)	0.97 (0.50–1.88)	0.86 (0.43–1.74)	1.38 (0.71–2.69)	1.10 (0.92–1.31)	
Hypertensive[b]	No	35	65	98	85	117	400	
	Multivariable HR[a]	1.0	1.15 (0.76–1.75)	1.36 (0.91–2.03)	1.32 (0.88–1.99)	1.71 (1.14–2.57)	1.20 (1.09–1.33)	0.40
Normal glucose	No	32	74	92	77	108	383	
	Multivariable HR[a]	1.0	1.28 (0.84–1.95)	1.23 (0.82–1.85)	1.17 (0.76–1.78)	1.61 (1.07–2.44)	1.15 (1.04–1.28)	
Impaired glucose	No	16	22	38	31	47	154	
tolerance/Diabetic	Multivariable HR[a]	1.0	0.86 (0.45–1.64)	1.15 (0.63–2.09)	0.99 (0.53–1.84)	1.29 (0.71–2.34)	1.14 (0.97–1.33)	0.30
Nonsmoker	No	22	53	78	71	112	336	
	Multivariable HR[a]	1.0	1.19 (0.72–1.97)	1.23 (0.76–1.99)	1.16 (0.71–1.90)	1.61 (1.00–2.59)	1.20 (1.07–1.34)	
Current smoker	No	26	43	52	38	44	203	
	Multivariable HR[a]	1.0	1.16 (0.71–1.92)	1.29 (0.79–2.10)	1.19 (0.71–2.01)	1.63 (0.97–2.75)	1.15 (1.00–1.32)	0.77
Nondrinker	No	24	53	84	64	121	346	
	Multivariable HR[a]	1.0	0.97 (0.59–1.57)	1.05 (0.66–1.66)	0.82 (0.51–1.32)	1.33 (0.84–2.10)	1.16 (1.04–1.29)	
Current drinker	No	23	38	40	38	29	168	
	Multivariable HR[a]	1.0	1.34 (0.79–2.27)	1.36 (0.80–2.31)	1.81 (1.05–3.11)	1.78 (1.00–3.18)	1.20 (1.02–1.41)	0.69
BMI<23.3 kg m^{-2}[c]	No	34	55	70	48	73	280	
	Multivariable HR[a]	1.0	0.99 (0.64–1.53)	1.05 (0.68–1.60)	0.86 (0.54–1.36)	1.34 (0.86–2.08)	1.09 (0.96–1.24)	
BMI≥23.3 kg m^{-2}[c]	No	13	40	58	61	80	252	
	Multivariable HR[a]	1.0	1.79 (0.95–3.38)	1.88 (1.02–3.48)	2.06 (1.11–3.82)	2.46 (1.33–4.55)	1.27 (1.12–1.43)	0.50
HDL-cholesterol	No	26	37	49	47	60	219	
≥54 mg dL^{-1}[c]								

Table 3 (Continued)

		LDL-cholesterol, mg dL^{-1}					HR per 1 SD	*P* for
		<80	80–99	100–119	120–139	140+	increment	interaction
Multivariable HR[a]	1.0	0.86 (0.52–1.43)	0.92 (0.56–1.50)	1.01 (0.61–1.68)	1.25 (0.76–2.07)	1.12 (0.97–1.29)		
HDL-cholesterol	No	22	59	81	62	96	320	
<54 mg dL^{-1}[c]	Multivariable HR[a]	1.0	1.51 (0.92–2.48)	1.60 (0.99–2.59)	1.36 (0.83–2.25)	1.99 (1.22–3.23)	1.20 (1.08–1.35)	0.73
Triglycerides	No	27	52	54	50	61	244	
<118 mg dL^{-1}[c]	Multivariable HR[a]	1.0	0.95 (0.59–1.52)	0.79 (0.49–1.27)	0.93 (0.57–1.51)	1.30 (0.80–2.10)	1.10 (0.95–1.27)	
Triglycerides	No	21	44	76	59	95	295	
≥118 mg dL^{-1}[c]	Multivariable HR[a]	1.0	1.34 (0.79–2.27)	1.73 (1.06–2.84)	1.38 (0.83–2.30)	1.85 (1.13–3.02)	1.21 (1.08–1.35)	0.61
Fasting (≥8 h	No	3	10	11	16	29	69	
after last meal)	Multivariable HR[a]	1.0	1.28 (0.35–4.76)	0.85 (0.23–3.12)	1.20 (0.34–4.25)	1.62 (0.47–5.61)	1.16 (0.91–1.50)	
Nonfasting (<8 h	No	45	86	119	93	127	470	
after last meal)	Multivariable HR[a]	1.0	1.18 (0.82–1.70)	1.32 (0.92–1.88)	1.18 (0.81–1.71)	1.64 (1.14–2.37)	1.19 (1.08–1.31)	0.94

[a]HR (95% CI) adjusted for gender, age and potential confounding factors. [b]Hypertensive was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 and/or as use of medication for hypertension. [c]Median value was used for cut-off point.

men. Our study showed a statistically significant age interaction (<50 years vs. ≥50 years) amongst women, whereas the number of cases was small (only five cases) amongst women aged <50 years. This result suggests an important role of menopause on the gender difference. Thirdly, men were more likely to have unhealthy lifestyles and unfavourable psychosocial factors compared with women and these risk factors may accelerate the effect of LDL-cholesterol on atherosclerosis development. In the present study, men were more likely to smoke and drink heavily compared with women.

It has remained a matter of debate in recent recommendations what range is optimal for LDL-cholesterol levels. A review article [26] declared that the optimal level of LDL-cholesterol is 50 to 70 mg dL^{-1}, because this range is observed amongst native hunter-gathers, healthy human neonates, free-living primates or wild mammals, all without atherosclerosis. Further, atherosclerosis progression and coronary heart disease events were minimized amongst participants in a cholesterol lowering trial to reduce the level to less than 70 mg dL^{-1}. However, NCEP-ATPIII [1, 2] recommended the clinical management and dietary therapy for low risk populations with ≥160 mg dL^{-1} of LDL-cholesterol and high risk populations with ≥100 mg dL^{-1} of LDL-cholesterol, because it was estimated that low cholesterol populations gain less absolute benefit from cholesterol lowering therapy than do high cholesterol populations. We identified an increased risk of mortality from coronary heart disease only in men with ≥140 mg dL^{-1} of LDL-cholesterol amongst this low cholesterol population. Our findings of men thus support the current suggestions by the NCEP-ATPIII that there may be an LDL-cholesterol threshold above 140 mg dL^{-1} for increased risk of coronary heart disease.

It is also a matter of debate why low LDL-cholesterol is associated with increased risk of all-cause mortality. A previous review showed the association between low total cholesterol levels and increased mortality from cancer and intraparenchymal haemorrhage [27]. Low LDL-cholesterol may be caused by cancer in most cases [27], but low LDL-cholesterol *per se* may increase the risk of intraparenchymal haemorrhage through the development of arteriolosclerosis [28].

A limitation of the current study is that we estimated LDL-cholesterol levels by using the Friedewald formula, which was formulated in fasting subjects without hypertriglyceridaemia [17]. However, there

Table 4 *Gender-specific multivariable hazard ratio (HR)[a] and 95% confidence interval (95% CI) of coronary heart disease according to lipid profiles*

	Lipid categories (Lower)				(Higher)	HR per 1 SD increment	*P* for interaction
LDL-cholesterol							
Range, mg dL^{-1}	<80	80–99	100–119	120–139	140+		
No for men	35	56	74	62	68	295	
Multivariable HR[a] for men	1.0	1.09 (0.71–1.68)	1.29 (0.85–1.95)	1.47 (0.95–2.26)	2.06 (1.34–3.17)	1.27 (1.13–1.43)	
No for women	13	40	56	47	88	244	
Multivariable HR[a] for women	1.0	1.29 (0.69–2.43)	1.10 (0.60–2.03)	0.83 (0.44–1.55)	1.16 (0.64–2.12)	1.06 (0.93–1.21)	0.06
Non-HDL-cholesterol							
Range, mg dL^{-1}	<110	110–129	130–149	150–169	170+		
No for men	48	57	56	52	82	295	
Multivariable HR[a] for men	1.0	1.17 (0.79–1.73)	1.10 (0.73–1.64)	1.42 (0.93–2.18)	2.15 (1.42–3.26)	1.28 (1.13–1.46)	
No for women	23	34	43	47	97	244	
Multivariable HR[a] for women	1.0	0.80 (0.47–1.37)	0.65 (0.39–1.09)	0.66 (0.39–1.11)	0.83 (0.50–1.37)	1.08 (0.94–1.25)	0.13
Total cholesterol							
Range, mg dL^{-1}	<160	160–179	180–199	200–219	220+		
No for men	50	57	56	53	79	295	
Multivariable HR[a] for men	1.0	1.02 (0.70–1.51)	0.90 (0.60–1.33)	1.18 (0.78–1.78)	1.89 (1.27–2.82)	1.26 (1.12–1.43)	
No for women	22	24	40	55	103	244	
Multivariable HR[a] for women	1.0	0.52 (0.29–0.93)	0.50 (0.29–0.85)	0.57 (0.34–0.95)	0.61 (0.37–1.00)	1.08 (0.94–1.25)	0.26

1SD of lipid profiles was 32.5 mg dL^{-1} (0.84 mmol L^{-1}) for LDL-cholesterol, 35.9 mg dL^{-1} (0.93 mmol L^{-1}) for non-HDL-cholesterol and 35.2 mg dL^{-1} (0.91 mmol L^{-1}) for total cholesterol. [a]HR (95% CI) adjusted for age and potential confounding factors.

was no change in the association between LDL-cholesterol and coronary heart disease after the exclusion of nonfasting subjects or persons with hypertriglyceridaemia at baseline, probably because the magnitude of subjects with hypertriglyceridaemia may be small in our cohort. Secondly, we used the mortality data based on death certificate diagnoses, not the incidence data. Thirdly, we did not measure menopausal status, which may have an important role in the mechanisms of gender difference. There was an age interaction (aged <50 years vs. aged ≥50 years) amongst women, suggesting that menopause may contribute to the gender difference. Finally, we did not measure psychosocial factors, which may contribute to gender-difference of association with risk of coronary heart disease [29–31]. The residual confounding and unmeasured effect modifier may affect the gender difference.

The strength of the present study is that we used lipid measurement values standardized in a single laboratory, which in turn was standardized by the CDC-NHLBI Lipid Standardized Program [15]. This justifies our assumption that misclassification bias due to errors in lipid measurement have been adequately reduced, and that the resultant accuracy lipid measurements are comparable with the results of previous well-standardized studies. The other strength is a statistical power sufficient to detect the association between LDL-cholesterol and mortality from coronary heart disease after the gender stratification. A previous Japanese study had too small number of cases to detect the association in women [22].

In conclusion, our large cohort study provides epidemiological evidence that, in a less obese population, higher concentrations of LDL-cholesterol are associated with increased risk of mortality from coronary heart disease for men, but not for women.

Conflict of interest statement

None declared.

Acknowledgements

This research was supported by Grant-in-Aid from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan (Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou[Seishuu]-Ippan-013). Hiroyuki Noda was also supported by the postdoctoral fellowship programme of the Uehara Memorial Foundation (Tokyo, Japan).

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ORIGINAL ARTICLE

Relationship Between Obesity and Incident Diabetes in Middle-Aged and Older Japanese Adults: The Ibaraki Prefectural Health Study

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OBJECTIVE: **To investigate the age-specific relationship between body mass index (BMI) and risk of diabetes in a Japanese general population.**

PARTICIPANTS AND METHODS: **A cohort of Japanese men (N=19,926) and women (N=41,489) (aged 40-79 years) who underwent community-based health checkups in 1993 and were free of diabetes was followed up by annual examinations with measurement of blood glucose concentrations until the end of 2006. *Incident diabetes mellitus* was defined as a blood glucose concentration of 126 mg/dL or greater under fasting conditions, 200 mg/dL or greater under nonfasting conditions, or diabetic medication use at baseline. Hazard ratios (HRs) for diabetes according to BMI were estimated using a Cox proportional hazard model. The model was adjusted for possible confounding variables.**

RESULTS: **A total of 4429 participants (7.2%) developed diabetes (2065 men and 2364 women) during a mean follow-up of 5.5 years. Compared with those with a BMI of less than 25.0, the multivariate HRs for diabetes among participants with a BMI of 30.0 or greater were 1.40 (95% confidence interval [CI], 0.89-2.20) for men aged 40 to 59 years and 1.26 (95% CI, 0.81-1.96) for men aged 60 to 79 years (*P*=.002 for interaction). The HRs were 2.50 (95% CI, 2.01-3.11) for women aged 40 to 59 years and 1.80 (95% CI, 1.41-2.30) for women aged 60 to 79 years (*P*=.04 for interaction).**

CONCLUSION: **The effect of obesity on the risk of diabetes is greater for middle-aged than for older adults.**

***Mayo Clin Proc.* 2010;85(1):36-40**

BMI = body mass index; CI = confidence interval; HR = hazard ratio

Diabetes mellitus is one of the major public health problems in Western countries and in Japan as a risk factor of cardiovascular diseases.[1,2] Many previous prospective studies have shown that obesity or being overweight is related to the risk of diabetes mellitus.[3-11] The Health Professionals' Follow-up Study[8] of 51,529 US male dentists, veterinarians, osteopaths, podiatrists, optometrists, and pharmacists aged 40 to 75 years reported that the risk of diabetes mellitus increased continuously with increasing body mass index (BMI; calculated as the weight in kilograms divided by height in meters squared) among men with a BMI of 23 or greater. The Nurses' Health Study[6] of 113,861 US female nurses aged 30 to 55 years also reported similar results among women with a BMI of 22 or greater. Because treating long-term diabetes mellitus is costly, the best approach to control diabetes is primary prevention. Examining the modifiable risk factors for diabetes mellitus, including obesity, is important because of its public health implications.

The relationship between obesity and diabetes mellitus has been reported to be age-dependent. A recent meta-analysis has shown an age-dependent relationship between BMI and the incidence of diabetes mellitus throughout the entire Asia-Pacific region.[12] However, this age-dependent relationship has not been extensively studied in a large cohort of the general population in Japan only. Clarification of this issue may help by implementation of more effective public health and clinical efforts aimed at primary prevention of diabetes mellitus via weight control. The increasing prevalence of diabetes mellitus in all age groups in Japan highlights the need for such data. The purpose of the current study was to investigate whether aging affects the relationship between the degree of obesity and incident diabetes mellitus in a large Japanese cohort.

PARTICIPANTS AND METHODS

In this prospective cohort study, we enrolled 97,079 Japanese adults (33,139 men and 63,940 women) who underwent community-based health checkups conducted by the Ibaraki Health Service Association in 1993. These checkups were in accordance with regulations by local governments. Data were collected by the Ibaraki prefectural government from local governments after depersonalizing participant data to ensure anonymity. Data were collected regarding anthropometric measurements, blood pressure, blood samples, and interview questionnaires on smoking habits, daily alcohol intake, and medical history. We excluded 2624 adults (451 men and 2173 women) with incomplete data and 5101 adults (2557 men and 2544 women) with a fasting blood glucose concentration of 126 mg/dL or greater (to convert to

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This work was supported in part by a grant-in-aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences Research Grants, Japan (Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou [Seishuu]-Ippan-012; and H20-Junkankitou [Seishuu]-Ippan-013). These financial supports played an important role in the design and conduct of the study.

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mmol/L, multiply by 0.05551), a nonfasting blood glucose concentration of 200 mg/dL or greater, or diabetic medication use at baseline. Moreover, we excluded 27,939 adults (10,205 men and 17,734 women) who did not participate in the 1994 survey, thereby ensuring that the participants were followed up for at least 1 year. Of note, mean blood glucose concentrations were almost identical between participants who were and were not followed up.[13]

Thus, the study sample consisted of 61,415 adults (63.3% of initially recruited participants; 19,926 men and 41,489 women). These participants were followed up by annual examinations until diabetes mellitus had been diagnosed or until the end of 2006. Blood glucose concentrations were measured at annual follow-up examinations. Participants who did not undergo annual checkups during the follow-up periods were censored on the date of their latest checkup. The protocol for this cohort study was approved by the Ibaraki Epidemiology Study Union Ethics Review Committee.

Baseline Examinations

Height of participants in stocking feet and weight in light clothing were measured at baseline. With participants seated, blood samples were drawn into 2 polyethylene terephthalate tubes: 1 with an accelerator and 1 with sodium fluoride and ethylenediaminetetraacetic acid. Overnight fasting (≥8 hours) was not necessarily required. The blood glucose concentration was measured by means of a glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan) in a single laboratory of the Ibaraki Health Service Association. Serum total cholesterol and serum triglyceride values were measured by means of an enzyme method with an RX-30 device (Nihon Denshi, Tokyo, Japan). High-density lipoprotein cholesterol values were measured in the same laboratory by means of a phosphotungstic acid magnesium method with an MTP-32 device (Corona Electric, Ibaraki, Japan). The laboratory participated in external standardization and successfully met the criteria for precision accuracy for the measurement of blood samples by the Japan Medical Association, the Japanese Association of Medical Technologists, and the Japan Society of Health Evaluation and Promotion.

Baseline blood pressure was measured from the right arm of seated participants who had rested for more than 5 minutes, by trained observers using standard mercury sphygmomanometers. When systolic blood pressure was greater than 150 mm Hg or diastolic blood pressure was greater than 90 mm Hg, the second measurement was performed after several deep breaths, and the lower values, which were almost always observed after the second measurement, were used for analyses. An interview was conducted to ascertain medical history, smoking status (never, ex-smoker, and current smoker <20 cigarettes/day or ≥20 cigarettes/day), and alcohol intake (none, occasionally, or daily <66 g/d or ≥66 g/d).

End Point Determination

The blood glucose concentration was measured by the glucose oxidase electrode method with a GA1140 device in 1994-1996 and by the hexokinase/glucose-6-phosphate dehydrogenase method with a H7170 device (Hitachi, Tokyo, Japan) from 1997-2006. Blood glucose concentrations determined by means of the glucose oxidase electrode method were compared with those determined by the hexokinase method, using 237 random samples of blood drawn in 1996. Comparability between blood glucose concentrations based on the 2 methods was excellent. In the linearity test, the regression line was $Y = 1.017 \times X + 0.802$, in which Y is a hexokinase method value (mg/dL) and X is a glucose oxidase electrode method value (mg/dL) (r=0.999). The slope coefficient of 1.017 and the intercept of 0.802 were not statistically significantly different from 1.0 and 0, respectively. On the basis of the linearity test, calibration was performed every day.

Incident diabetes mellitus was defined as a fasting blood glucose concentration of 126 mg/dL or greater, a nonfasting blood glucose concentration of 200 mg/dL or greater, or initiation of treatment for diabetes mellitus. Fasting was defined as not having had a meal for at least 8 hours.

Statistical Analyses

Participants were classified with regard to their BMI as less than 25.0, 25.0 to 29.9, and 30.0 or greater according to the World Health Organization classification.[14] Hazard ratios (HRs) with the corresponding 95% confidence interval (CI) for diabetes mellitus according to BMI were calculated with reference to BMI as less than 25.0 using a Cox proportional hazards regression model. Analyses were stratified by sex and age groups (40-59 and 60-79 years). We applied this age cut-point to maintain sufficient incidence data. Covariates included age, baseline blood glucose concentration, fasting status (yes/no), systolic blood pressure, antihypertensive medication use (yes/no), total cholesterol, high-density lipoprotein cholesterol, log-transformed triglyceride, lipid medication use (yes/no), smoking status (never, ex-smoker, current <20 cigarettes/day or ≥20 cigarettes/day), alcohol intake (none, occasionally, daily <60 g/d or ≥60 g/d), and BMI change from baseline to the end of the year of follow-up. The analysis was repeated with an interaction term of age groups and sex times BMI categories. P<.05 was regarded as statistically significant. All statistical analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Of the 61,415 adults (19,926 men and 41,489 women), 4429 (2065 men and 2364 women [7.2%]) developed diabetes mellitus during a mean 5.5 years of follow-up (5.1 years for men and 5.7 years for women).

TABLE 1. **Sex-Stratified Baseline Characteristics According to BMI Among Study Participants**

Baseline characteristic	Men (N=19,926)				Women (N=41,489)			
	BMI (kg/m²)				BMI (kg/m²)			
	<25.0	25.0-29.9	≥30.0	*P* value	<25.0	25.0-29.9	≥30.0	*P* value
No. of participants	14,474	5163	289		8812	11,443	1234	
Age (y)	61.5 (9.7)	59.5 (9.6)	58.0 (10.1)	<.001	57.2 (10.1)	59.0 (9.3)	58.1 (9.3)	<.001
Fasting blood glucose (mg/dL)	99.1 (10.8)	100.9 (10.8)	99.1 (12.6)	<.001	95.5 (10.8)	99.1 (10.8)	99.1 (10.8)	<.001
Nonfasting blood glucose (mg/dL)	111.7 (25.2)	113.5 (25.2)	115.3 (25.2)	.12	106.3 (19.8)	108.1 (21.6)	111.7 (23.4)	<.001
Fasting participants (%)	15.1	14.5	14.2	.57	16.1	14.0	12.6	<.001
Systolic blood pressure (mm Hg)	135.0 (17.1)	138.9 (16.8)	142.6 (17.8)	<.001	129.2 (17.4)	136.0 (16.7)	141.1 (17.2)	<.001
Diastolic blood pressure (mm Hg)	79.7 (10.4)	83.3 (10.4)	86.6 (12.0)	< 001	76.2 (10.2)	80.6 (10.0)	84.7 (10.7)	<.001
Antihypertensive medication use (%)	18.6	26.4	33.9	<.001	14.9	27.7	40.4	<.001
Total cholesterol (mg/dL)	189.5 (30.9)	201.1 (30.9)	204.9 (34.8)	<.001	204.9 (34.8)	212.7 (34.8)	216.6 (34.8)	<.001
HDL cholesterol (mg/dL)	54.1 (15.5)	46.4 (11.6)	42.5 (11.6)	<.001	58.0 (15.5)	54.1 (11.6)	50.3 (11.6)	<.001
Triglyceride (mg/dL)	132.9 (79.7)	186.0 (106.3)	212.6 (124.0)	<.001	124.0 (70.9)	159.4 (88.6)	168.3 (88.6)	<.001
Lipid medication use (%)	1.1	1.6	3.1	.001	3.0	4.2	5.3	<.001
Smoking status (%)				<.001				.002
Never	22.1	26.1	28.4		95.2	95.6	93.3	
Ex-smoker	26.6	32.8	27.3		0.6	0.6	1.3	
Current								
<20 cigarettes/d	17.0	11.0	10.7		2.9	2.5	3.6	
≥20 cigarettes/d	34.3	30.1	33.6		1.4	1.2	1.9	
Alcohol intake (%)				<.001				<.001
None	34.9	33.5	42.6		90.5	91.7	92.1	
Occasionally	13.0	16.2	18.3		6.0	5.4	5.1	
Daily								
<60 g/d	46.4	43.7	31.8		3.4	2.8	2.5	
≥60 g/d	5.7	6.6	7.3		0.1	0.1	0.3	

Values are mean (SD) for continuous variables. BMI = body mass index; HDL = high-density lipoprotein. SI conversion factors: To convert blood glucose concentrations to mmol/L, multiply by 0.05551; to convert cholesterol values to mmol/L, multiply by 0.02586; to convert triglyceride values to mmol/L, multiply by 0.01129.

Sex-stratified baseline characteristics according to BMI categories are shown in Table 1. Approximately 15% of participants were in a fasting state at baseline. All covariates, except for nonfasting blood glucose in men and percentage of fasting male participants, were associated with BMI in both sexes.

Table 2 presents sex- and age-stratified HRs for diabetes mellitus according to BMI categories. In men aged 40 to 59 years, compared with participants who had a BMI lower than 25.0, the multivariate HR for diabetes mellitus was significantly increased among participants who had a BMI of 25.0 to 29.9 but did not differ significantly among participants who had a BMI of 30.0 or greater. In men aged 60 to 79 years, compared with participants who had a BMI lower than 25.0, the multivariate HR for diabetes mellitus did not differ significantly among participants in either of the other BMI groups. The effect of BMI on risk of diabetes mellitus was significantly greater for men aged 40 to 59 years compared with men aged 60 to 79 years (P=.002 for interaction).

In women aged 40 to 59 years and in women aged 60 to 79 years, compared with participants who had a BMI lower than 25.0, the multivariate HRs for diabetes mellitus were significantly greater among participants in each of the higher BMI groups. The effect of BMI on risk of diabetes was significantly greater for women aged 40 to 59 years compared with women aged 60 to 79 years (P=.04 for interaction).

Among participants aged 60 to 79 years, the effect of BMI on risk of diabetes was significantly greater for women compared with men (P=.002 for interaction). Among participants aged 40 to 59 years, the effect of BMI on risk of diabetes did not differ significantly between women and men (P=.15 for interaction).

DISCUSSION

The current large cohort study showed that the effect of BMI on diabetes mellitus, of which 99% was type 2 in Japan according to the published statistics,[15] was significantly greater among middle-aged adults than among older adults. To our knowledge, this is the first large prospective cohort study to show that the relationship of the degree of obesity and the risk of diabetes mellitus is different between Japanese middle-aged and older adults. As judged by their HRs, this relationship might be more prominent in women than in men.

As we expected, a significant relationship between obesity and diabetes mellitus was observed in our cohort. This relationship was consistent with previous studies in white and Asian populations.[2-10] Previous studies investigating the age-specific relationship between obesity and diabetes mellitus reported inconsistent results. Ishikawa-Takata et al[3] found no age-specific relationship in Japanese male workers aged 18 to

TABLE 2. **Hazard Ratios (HRs) for Type 2 Diabetes Mellitus According to Body Mass Index (BMI) Among Study Participants, Stratified by Sex and Age**

Variable	No. of participants	Person-years	Incidence rates per 1000 person-years	Age-adjusted HRs (95% CI[a])	Multivariate HRs[b] (95% CI[a])	Interaction analysis[c]
Men (N=19,926)						
Age 40-59 (y)						
BMI (kg/m^2)						
<25.0	4914	26,569	14.9	1.00 (Reference)	1.00 (Reference)	
25.0-29.9	2268	11,791	25.3	1.68 (1.44-1.95)	1.42 (1.21-1.67)	
≥30.0	147	718	29.2	1.96 (1.26-3.03)	1.40 (0.89-2.20)	−0.27±0.09, *P*=.002
Age 60-79 (y)						
BMI (kg/m^2)						
<25.0	9560	47,223	20.5	1.00 (Reference)	1.00 (Reference)	
25.0-29.9	2895	14,029	25.7	1.24 (1.10-1.40)	1.13 (0.99-1.29)	
≥30.0	142	619	33.9	1.62 (1.05-2.49)	1.26 (0.81-1.96)	−0.16±0.08, *P*=.15
Women (N=41,489)						−0.23±0.07, *P*=.002
Age 40-59 (y)						
BMI (kg/m^2)						
<25.0	15,878	100,461	6.3	1.00 (Reference)	1.00 (Reference)	
25.0-29.9	5441	32,439	11.4	1.68 (1.47-1.91)	1.20 (1.05-1.37)	
≥30.0	640	3096	34.2	4.91 (3.99-6.03)	2.50 (2.01-3.11)	−0.14±0.07, *P*=.04
Age 60-79 (y)						
BMI (kg/m^2)						
<25.0	12,934	68,069	10.2	1.00 (Reference)	1.00 (Reference)	
25.0-29.9	6002	30,041	15.9	1.55 (1.38-1.74)	1.30 (1.15-1.47)	
≥30.0	594	2511	30.7	2.88 (2.28-3.65)	1.80 (1.41-2.30)	

[a] CI = confidence interval.
[b] Adjusted for age, blood glucose, fasting status (yes/no), systolic blood pressure, antihypertensive medication use (yes/no), total cholesterol, high-density lipoprotein cholesterol, log-transformed triglycerides, lipid medication use (yes/no), smoking status (never, ex-smoker, current <20 or ≥20 cigarettes/day), alcohol intake (none, occasionally, daily <60 or ≥60 g/d), and BMI change from baseline to the end of the year follow-up.
[c] Multivariate regression coefficients ± SE and *P* value for interaction.

59 years. Nagaya et al[4] showed that for each 1-year increment of age, there was a 4% to 5% increased risk of developing diabetes mellitus in men and women aged 30 to 59 years. Our data did not corroborate the findings of these studies partly because of differences in age range. The Asia Pacific Cohort Studies Collaboration demonstrated age-specific relationships between BMI and risk of diabetes mellitus, showing stronger proportional relationships in younger age groups.[12] The study reported that, for each reduction in BMI of 2.0, there was a 31% lower risk of diabetes mellitus in those younger than 60 years and a 19% lower risk in those aged 70 years or older. The Cardiovascular Health Study[16] also revealed the effect of age and BMI on the development of diabetes mellitus in older adults (≥65 years). McNeely et al[17] reported that overweight (BMI ≥25.0) Japanese Americans younger than 55 years, but not those aged 55 years or older, were at a significantly high risk of diabetes mellitus. These data corroborate with those in the current study. Because our study enrolled a larger sample population with a wide age range compared with previous studies, our results might provide stronger evidence of the effect of age on incident diabetes mellitus.

Several possible explanations exist for why an age-specific relationship between obesity and diabetes mellitus was observed. First, lower adiponectin levels in middle-aged adults may contribute to the age-specific effect on incident diabetes mellitus.[18] Adiponectin is a novel cytokine specifically secreted from fat cells and has an antidiabetic effect by suppressing tumor necrosis factor α activity.[19] Second, effects of genetic predisposition on differences in body weight might exist to a greater extent among middle-aged vs older adults.[20] To the extent that diabetes mellitus and obesity share common genetic risk factors, being overweight in middle-age would seem to confer risk in itself. Third, recent work by our group showed that leanness in the elderly, but not in middle-aged adults, was also a risk factor for developing diabetes mellitus.[21] Therefore, the relatively higher effect of obesity on diabetes mellitus in middle-aged adults may be evident because of an attenuated relative risk in obese elderly people. Fourth, the weaker relationship between obesity and the risk of diabetes mellitus in older age groups might be due in part to elevated risk among nonobese older individuals because of the effects of aging, such as increased fat mass and reduced physical activity.

We unexpectedly observed that the effects of obesity on incident diabetes mellitus were significantly greater in women than men. This might be accounted for by health risks induced by decreased production of sex hormones in postmenopausal women. However, the finding is inconsistent with a previous study,[16] which reported that relative risks for diabetes were more prominent in older (≥65 years) men than in women. Possible explanations for this discrepancy might

be differences in ethnicity or age range of participants (aged 40-79 years vs ≥65 years).

The strength of the current study is that it consists of a cohort large enough to allow subgroup analyses. Moreover, all blood samples were measured by the same laboratory, which was acknowledged by a known quality control program.[22] We also ascertained the incidence of diabetes mellitus primarily by blood glucose concentrations, in contrast to many previous large cohort studies that used self-administered questionnaires.[6,8]

Our study has several limitations. First, external validity for the study may not be high because participants were community residents of a single prefecture in Japan. Second, the follow-up rates were moderate. However, mean blood glucose concentrations did not differ between individuals who were and were not followed up. Thus, the potential selection bias might have been small. Third, potential confounding variables were present that we could not assess, including fat distribution, physical activity, nutritional status, family history of diabetes mellitus, and duration of obesity. Physical activity is known to not substantially alter the relationship between BMI and the risk of diabetes mellitus.[23] Fourth, even though the age-BMI interaction was statistically significant, the magnitude of differences showed that clinical importance was not necessarily high, especially in men. The HRs were 1.40 for obese men aged 40 to 59 years and 1.26 for obese men aged 60 to 79 years. However, the magnitude of differences in women may be clinically important because HRs for obese women aged 40 to 59 years and obese women aged 60 to 79 years were 2.50 and 1.80, respectively. Fifth, the diagnosis of diabetes was based on a single blood glucose measurement. Sixth, there were approximately 1-year differences in mean follow-up times between lean and obese participants. This was also observed between participants aged 40 to 59 years and those aged 60 to 79 years. Thus, screening bias might modify the differences in the effects of obesity on developing diabetes mellitus between participants aged 40 to 59 years and those aged 60 to 79 years.

Our results provide a better understanding of the age-specific relationship between obesity and the risk of diabetes mellitus and should guide public health and clinical efforts aimed at primary prevention by weight control. These results also highlight the importance of weight control for primary prevention of diabetes mellitus in middle-aged adults, even though the incidence rate was higher in older adults than in middle-aged adults.

CONCLUSION

This study shows that the effect of BMI on diabetes mellitus is greater among middle-aged than older adults. Moreover, we suggest that the relationship is more prominent in women than in men.

We thank all those who participated in this study.

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