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Different age-related impacts of lean and obesity on cardiovascular prognosis in Japanese patients with cardiovascular risks: The J-HOP (Japan Morning Surge-Home Blood Pressure) Study

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Abstract

The relationship between lean and cardiovascular events has been shown to vary with age, but the relationship between age-related lean and cardiovascular events in Asia has not been established. We divided patients enrolled in the J-HOP (Japan Morning Surge-Home Blood Pressure) study with one or more cardiovascular disease risks into three groups based on their body mass index (BMI): lean (BMI < 21), normal-weight (21 ≤ BMI <27), and obese (BMI ≥ 27). We stratified the risk of cardiovascular events of lean and obesity compared to normal weight into the patients < 65 years old and those aged ≥ 65 years. A total of 286 cardiovascular disease events were observed during the follow-up period (73 ± 46 months). Regarding the relationship between BMI and cardiovascular disease risk, both lean and obesity were independent prognostic factors: lean: hazard ratio (HR) 1.43, 95% confidence interval (CI): 1.02-2.01, p = .040; obesity: HR 1.55, 95%CI: 1.13-2.12, p = .006. In patients < 65 years old, the risk of cardiovascular disease of the lean patients was lower than that of the normal-weight patients (HR 0.39, 95%CI: 0.12-1.29, p = .124) and the risk of obesity patients was significantly higher (HR 1.77, 95%CI: 1.08-2.92, p = .024). In the patients aged ≥ 65 years, lean was a significant independent factor of cardiovascular events compared to normal-weight (lean: HR 1.70, 95%CI: 1.18-2.47, p = .005). In conclusion, lean was an independent predictor of cardiovascular events in patients aged ≥ 65 years.

1 | INTRODUCTION

Many reports have already established that obesity is a predictor of cardiovascular events, although the relationship between body mass index (BMI) and cardiovascular events does not show a linear correlation.[1-8] In addition, despite the significant association reported between lean and cardiovascular events,[1-3,6] few investigations of these associations in Asia have been conducted.

Age is one of the important confounding factors in the association between BMI and mortality risk. The mortality risk varies not

only with the degree of lean and obesity but also with age.[5,8] Very few studies have analyzed the effects of age that contribute to cardiovascular events by setting the endpoints related to obesity and lean not as whole death but as cardiovascular disease events,[8] and no such study has been conducted in Asia. We conducted the present study to clarify the risks of cardiovascular disease of lean and obesity, with a division of patients into those aged < 65 years and those aged ≥ 65 years.

2 | METHODS

2.1 | Patients

This study was performed as part of the J-HOP (Japan Morning Surge-Home Blood Pressure) study.[9] The recruitment of the patients for the J-HOP study was consecutively conducted from January 2005 to May 2012, by 75 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and four specialized university hospitals) throughout Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. The study protocol was registered on the clinical trials registration site: University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR): #UMIN000000894. Written informed consent was obtained from all patients who were enrolled in the study.

Briefly, the J-HOP study is a prospective observational study conducted to evaluate the predictive values of home measurements of blood pressure (BP) for cardiovascular (CV) events in Japanese patients with any of the following CV risk factors: hypertension, diabetes mellitus, hyperlipidemia, smoking (including those with chronic obstructive pulmonary disease), chronic renal disease, atrial fibrillation, metabolic syndrome, and sleep apnea syndrome.

The BMI was calculated as body weight divided by height squared (kg/m^2). We divided the patients into three groups based on their BMI: lean (BMI < 21), normal-weight (21 ≤ BMI <27), and obese (BMI ≥ 27). The cutoff points were based on the literature targeting Japanese people.[3,6]

2.2 | Blood examinations and echocardiographic measurements

Blood samples were collected upon each patient's hospital arrival in the morning in a fasting state, at enrollment, and at the end of the study. The blood samples were centrifuged at 3000g for 15 min at room temperature. Plasma/serum samples after separation were stored at 4°C in refrigerated containers and sent to a commercial laboratory (SRL, Tokyo) within 24 hr All assays were performed within the next 24 hr at this single laboratory center. For the definition of anemia by Hb, the World Health Organization (WHO)-defined criteria (Hb < 13.0 for men, Hb < 12.0 for women) were used.[10] The

plasma level of brain natriuretic peptide (BNP) was measured by using a chemiluminescent enzyme.

Echocardiography was performed at each participating institute by a trained technician, and the results were checked by a trained echocardiologist. Two-dimensional M-mode or B-mode images were obtained using an ultrasound machine according to the guidelines of the American Society of Echocardiology (ASE) and the European Association of Echocardiography (EAE). The left ventricular mass was obtained using the formula validated by the ASE: left ventricular mass = 0.8 (1.04 ([diastolic left ventricular dimension + diastolic posterior wall diameter + diastolic interventricular septal diameter]3 − [diastolic left ventricular dimension]3)) + 0.6 g. The left ventricular mass index (LVMI) was calculated as the left ventricular mass/body surface area. These measurements and definitions were based on the guidelines of the ASE and EAE.[11]

2.3 | Follow-up and outcome ascertainment

The primary endpoint was defined as a composite endpoint that combines fatal events (cardiovascular death and sudden death) and nonfatal events (acute myocardial infarction, angina, congestive heart failure, stroke, subarachnoid hemorrhage, and aortic dissection). The outcomes were categorized as follows[1]: fatal and nonfatal stroke, defined as the sudden onset of a neurologic deficit that persisted for ≥ 24 hr in the absence of another disease that could account for the symptoms, with the findings of brain computed tomography or magnetic resonance imaging; transient ischemic attack was not included. [2] fatal and nonfatal coronary artery disease, defined as acute myocardial infarction, angina pectoris that required percutaneous coronary intervention, and sudden death within 24 hr of the abrupt onset of symptoms. [3] fatal and nonfatal heart failure and artery disease that required admission. The endpoint committee adjudicated all events by reviewing patient files and source documents or requesting more detailed written information from investigators. The committee was blinded to the individual clinical characteristics, including home BP data. A final follow-up survey to reconfirm the clinical outcomes was performed from September 2014 to March 2015. In this study, the first event was used for the analyses.

2.4 | Statistical analyses

Data are presented as the mean (±standard deviation) or percentage. Because the distribution of the plasma BNP levels was highly skewed, it is presented as the median value together with the 25th and 75th percentiles (25%, 75%) and was log-transformed before the statistical analysis. Comparisons between groups were based on the chi-square test of independence for categorical variables and an analysis of variance (ANOVA) for continuous variables. We performed a one-way ANOVA to detect differences among groups. To evaluate the cumulative occurrence of primary endpoints over time, a survival time analysis method (Kaplan–Meier method) was applied

and analyzed nonparametrically. The hazard ratio (HR) and 95% confidence interval (CI) of the primary endpoint in the lean and obese groups were calculated by Cox proportional hazard model analysis after adjusting for age, gender, smoking, hypertension, dyslipidemia, diabetes, use of antihypertensive medication, history of ischemic heart disease, history of heart failure, and history of stroke in model 1; fasting glucose, high-density lipoprotein (HDL)-cholesterol, log-BNP, and hematocrit were added in model 2, and the pulse pressure was added in model 3. A probability (p)-value < .05 was considered significant. All statistical analyses were performed with IBM SPSS Statistics ver. 25 software (Chicago, IL).

3 | RESULTS

The follow-up period was 73 ± 46 months, during which a total of 286 cardiovascular disease events were observed. Table 1 summarizes the patients' backgrounds stratified by BMI. The mean age, proportion of women in the group, pulse pressure, HDL cholesterol, and BNP were significantly higher in the lean group compared to the normal-weight group (Table 1). The proportion of hypertension, that of dyslipidemia, the diastolic blood pressure, the LVMI, and the hematocrit were significantly lower in the lean group compared to the normal-weight group. The proportion of patients with anemia was

TABLE 1 Patient characteristics

	Lean BMI < 21 (n = 665)	Normal-weight 21 ≤ BMI<27 (n = 2850)	Obesity 27 ≤ BMI (n = 795)
Age, yrs	67.9 ± 10.6[**]	65.2 ± 10.5	61.1 ± 11.7[**]
Male, %	42[**]	49	44[*]
Body mass index, kg/m^2	19.5 ± 1.2[**]	23.9 ± 1.6	29.6 ± 2.7[**]
Hypertension, %	86[**]	92	95[*]
Dyslipidemia, %	34[**]	41	45
Diabetes, %	22	23	25
Smoking, %	13	12	12
History of IHD, %	9.8	9.4	9.3
History of CHF, %	1.9	1.1	1.3
History of stroke, %	3.2	4.6	3.0
Antihypertensive medication, %	70[**]	79	82
Lipid-lowering medication, %	20	24	26
Office systolic BP, mmHg	139.7 ± 17.0	140.2 ± 16.3	140.0 ± 16.3
Office diastolic BP, mmHg	79.0 ± 10.7[**]	81.0 ± 10.5	82.3 ± 10.6[**]
Office pulse pressure , mmHg	61.8 ± 14.6[*]	60.0 ± 14.3	58.5 ± 14.6[*]
Office pulse rate, bpm	71.6 ± 11.0	70.8 ± 10.9	71.9 ± 10.7
HDL cholesterol, mg/dl	63.0 ± 17.3[**]	56.0 ± 14.5	51.0 ± 13.7[**]
Fasting glucose, mg/dl	97.0 ± 27.2	100.0 ± 26.0	104.0 ± 31.8[**]
Left ventricular mass index, g/m^2	90.1 ± 26.3[**]	96.6 ± 29.2	98.2 ± 24.3
eGFR, mL/min/1.73m^2	74.0 ± 16.4	72.9 ± 17.3	73.8 ± 18.7
Hematocrit, %	40.0 ± 4.6[**]	41.4 ± 4.5	41.9 ± 4.3[*]
Anemia (%)	23.2[**]	13.1	9.8[*]
BNP, pg/ml	24.8 (12.3-52.2)[**]	18.5 (9.4-37.3)	14.3 (6.7-29.2)[**]

Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IHD, ischemic heart disease.

*p < .05 vs. normal-weight group;

**p < .01 vs. normal-weight group.
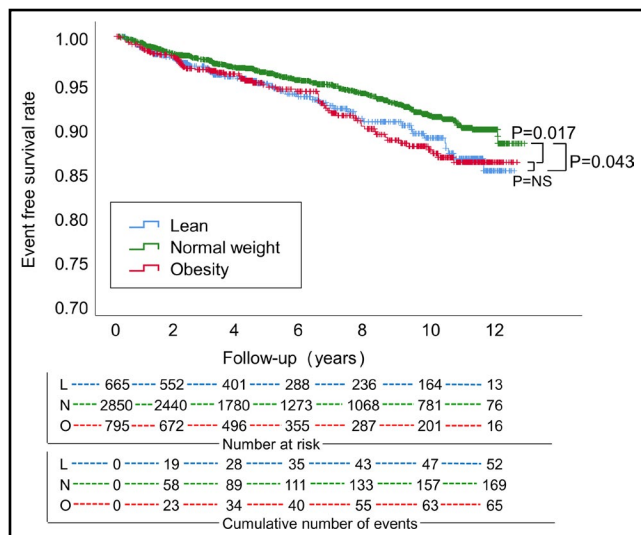
FIGURE 1 The Kaplan–Meier curves for cardiovascular events. The number at risk and the cumulative number of events are listed under the table. L: lean. N: normal-weight. O: obesity

also significantly higher in the lean group compared to the normal-weight group (23.2% vs 13.1%, $p < .001$, Table 1).

Figure 1 shows the Kaplan–Meier curves for cardiovascular events. Both the lean and obese patients suffered significantly more cardiovascular events compared to the normal-weight patients (lean vs. normal-weight $p = .043$, obesity vs. normal-weight $p = .017$). Table 2 shows the results of the Cox proportional hazard model analysis for the main endpoints. Lean and obesity were independent predictors of cardiovascular events after adjusting for model 3 (lean: HR 1.43, 95%CI: 1.02-2.01 $p = .040$; obesity: HR 1.55, 95%CI: 1.13-2.12, $p = .006$). We compared the three groups stratified by BMI dividing into the patients aged < 65 years and those aged ≥ 65 (supplemental Table S1 and S2). Significantly low levels of hematocrit were observed in the lean patients compared to the normal-weight patients in both age groups (patients < 65 years old: 41.2 ± 4.1% vs. 42.3 ± 4.2%, $p = .001$, patients aged ≥ 65:39.3 ± 4.8% vs. 40.7 ± 4.6%, $p < .001$). In addition, the BNP values in the lean group were similar to those of the normal-weight patients < 65 years old, but the BNP values in the lean group were significantly higher than those of the normal-weight patients aged ≥ 65 (median BNP: 32.7 vs. 27.0 pg/ml, $p = .003$). Kaplan–Meier curves of the patients < 65 years and those aged ≥ 65 are shown in Figure 2A and B. Among the patients < 65 years, the incidence of cardiovascular events was significantly lower in the lean group and significantly higher in the obese group compared to the normal-weight group (lean vs. normal-weight $p = .027$, obese vs. normal-weight $p = .030$). Among the patients aged ≥ 65, the incidence of cardiovascular events was significantly higher in the lean group compared to the normal-weight group (lean vs. normal-weight $p = .003$). We also compared the incidence of cardiovascular events in subgroups of BMI according to World Health Organization classification (supplemental figure).

TABLE 2 Hazard ratios for cardiovascular events

	Hazard ratio	95%CI	p value
Lean (vs. normal-weight)			
Model 1	1.41	1.03 - 1.93	$p = .035$
Model 2	1.43	1.02 - 2.01	$p = .039$
Model 3	1.43	1.02 - 2.01	$p = .040$
Obesity (vs. normal-weight)			
Model 1	1.61	1.20 - 2.16	$p = .002$
Model 2	1.56	1.14 - 2.14	$p = .005$
Model 3	1.55	1.13 - 2.12	$p = .006$

Note: Model 1: adjusting for age, gender, smoking, hypertension, dyslipidemia, diabetes, use of antihypertensive medication, history of ischemic heart disease, history of congestive heart failure, history of stroke. Model 2: adjusting for model 1 + hematocrit, logBNP, HDL cholesterol, and fasting glucose. Model 3: adjusting for model 2 + clinic pulse pressure.
Abbreviation: CI, confidence interval.

Table 3 shows the results of the Cox proportional hazard model analysis for key endpoints in the patients < 65 years and those aged ≥ 65. The lean group was significantly associated with cardiovascular events compared to the normal-weight group (lean vs. normal-weight, HR 1.70, $p = .005$) among the patients aged ≥ 65, whereas lean was not associated with cardiovascular events compared to the normal-weight group (lean vs. normal-weight, HR 0.39, $p = .124$) in the patients < 65 years. The average age of onset of a cardiovascular event was 73.4 years (n = 52) in the lean group, 69.0 years (n = 169) in the normal-weight group, and 65.0 years (n = 65) in the obese group, indicating that the lean group developed cardiovascular events at significantly older ages than the normal-weight group ($p = .007$) and that the obese group developed cardiovascular events at significantly younger ages than the normal-weight group ($p = .011$).

4 | DISCUSSION

The main findings of this study of patients in Asia (Japan) were that: (i) lean was an independent predictor of cardiovascular events in lean patients aged ≥ 65 years; (ii) the percentages of anemia and BNP were higher in the lean patients aged ≥ 65 years.

In this patient cohort, lean was an independent predictor of cardiovascular events in patients aged ≥ 65. In the only prior study that conducted an age-specific analysis of the risks of lean and obesity with cardiovascular death as the endpoint, the lean group was at significant higher risk compared to the normal-weight group only in the elderly female group (aged ≥ 85 years) and with a BMI < 19.[8] Studies conducted in Japan showed that the risk of cardiovascular disease and the all-cause mortality was significantly higher in the group with BMI values of 18.5-21 kg/m2 compared to the group with 23-25 kg/m2.[3,6] The threshold of lean might different according to racial difference.
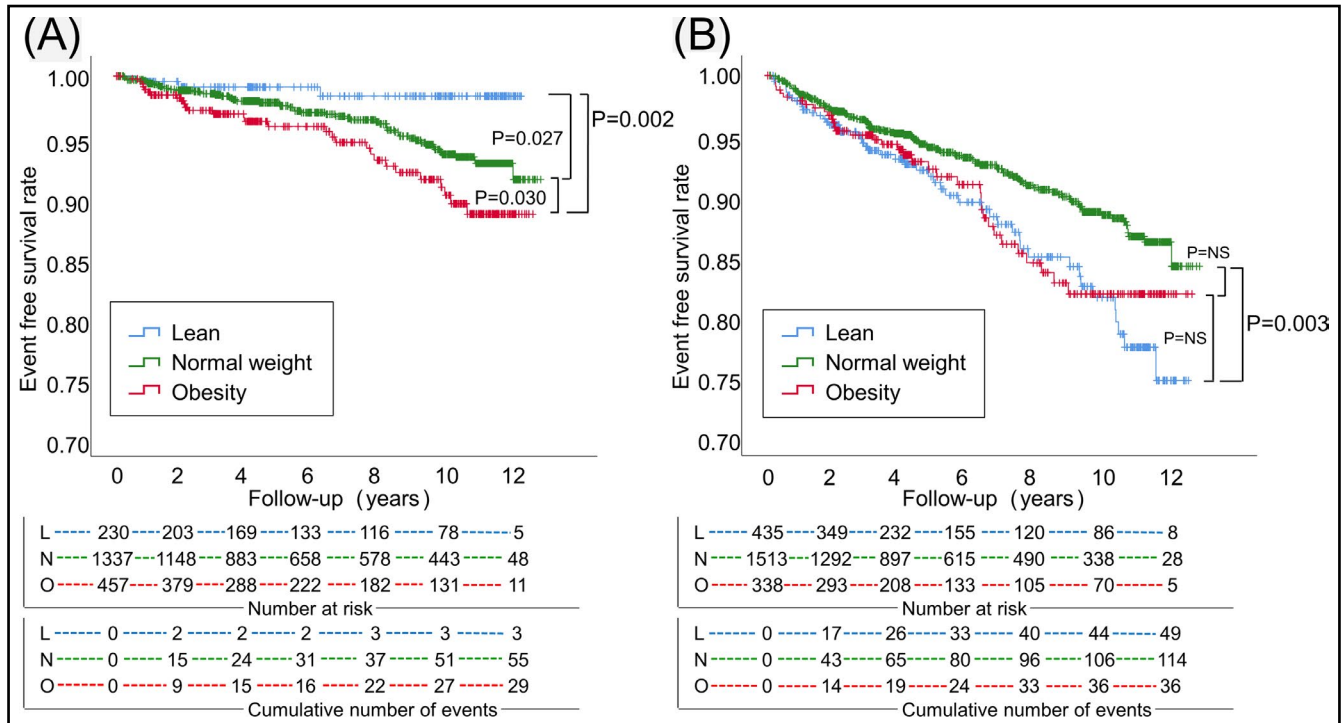
FIGURE 2 The Kaplan–Meier curves for cardiovascular events dividing into the patients aged < 65 years and those aged ≥ 65. (A) patients aged < 65 years, (B) patients aged ≥ 65 years. The number at risk and the cumulative number of events are listed under the table. L: lean. N: normal-weight. O: obesity

In the present analyses, anemia was associated with lean. Appetite decreases physiologically with aging.[12,13] In a 12-year observational study of a general population aged 40-79 years conducted in Japan, the energy intake rate and the body weight tended to decrease with aging, and the risk of undernutrition gradually increased from middle age to old age.[14] Such malnutrition is reportedly common in outpatients with heart failure and is strongly associated with increased mortality.[15]

Anemia was associated with cardiovascular events,[16-18] was a factor in the development of heart failure,[19] and was an independent predictor of readmission and death of patients with heart failure.[20,21] In a recent study,[22] risk factors associated with poor outcomes in anemia patients include decreased BMI.

There are reports on the relationship between anemia and high BNP levels,[23] the mechanism mediated by sympathetic nerve activity,[24] and the renin–angiotensin system activated by anemia and

TABLE 3 Hazard ratios for cardiovascular events in patients < 65 years and patients aged ≥ 65

	Patients < 65 years			Patients aged ≥ 65		
	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Lean (vs. normal-weight)						
Model 1	0.36	0.11-1.17	p = .090	1.71	1.22-2.41	p = .002
Model 2	0.39	0.12-1.28	p = .122	1.72	1.19-2.49	p = .004
Model 3	0.39	0.12-1.29	p = .124	1.70	1.18-2.47	p = .005
Obesity (vs. normal-weight)						
Model 1	1.77	1.11-2.82	p = .016	1.55	1.05-2.28	p = .028
Model 2	1.78	1.08-2.93	p = .024	1.48	0.98-2.25	p = .065
Model 3	1.77	1.08-2.92	p = .024	1.50	0.96-2.22	p = .076

Note: Model 1: adjusting for age, gender, smoking, hypertension, dyslipidemia, diabetes, use of antihypertensive medication, history of ischemic heart disease, history of congestive heart failure, and history of stroke. Model 2: adjusting for model 1 + hematocrit, logBNP, HDL cholesterol, and fasting glucose. Model 3: adjusting for model 2 + clinic pulse pressure.

Abbreviation: CI, confidence interval.

the mechanism of a reduced clearance of natriuretic peptide.[25] The relationship between anemia and BNP should be considered in lean patients with cardiovascular risk.

We already showed the association between lean and an increase in cardio-ankle vascular index in the Cardiovascular Prognostic COUPLING Study in Japan (the COUPLING Registry).[26,27] The atherosclerotic factor might play a role in an increase cardiovascular events in lean patients aged 65 years or older.

Our present investigation has some limitations to address. Regarding the BMI cutoff, it has been reported that BMI-related risks vary due to racial and regional differences. This study examined only Japanese patients with cardiovascular risks, and the results of this study cannot be directly applied to other populations. In addition, the analysis of background factors may have been insufficient. Not all of the patients had undergone a thorough medical examination, and the presence of various underlying diseases for which lean individuals are prone to develop, such as aspiration pneumonia and cancer, could not be evaluated.

5 | CONCLUSIONS

Lean was an independent predictor of cardiovascular events, and the percentages of anemia and high BNP were higher in the lean patients aged ≥ 65 years.

CONFLICT OF INTEREST

K. Kario has received research grants from Omron Healthcare and A&D Co. All other authors report no potential conflicts of interest in relation to this article.

AUTHORS CONTRIBUTIONS.

Kario K takes primary responsibility for this paper. Toriumi S wrote the manuscript and did the statistical analysis. Kario K, Kabutoya T, and Hoshide S collected the patients' data. Kario K acquired research grants for the J-HOP study. Toriumi S, Kabutoya T, Hoshide S, and Kario K reviewed/edited the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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