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"Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and Diabetes: 5-year Japanese Cohort Study

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Abstract

Objective—Whether obesity without metabolic syndrome (i.e., "metabolically healthy" obesity) confers similar or less metabolic risk remains controversial.

Methods—We conducted a retrospective 5-year cohort study of 9,721 Japanese subjects (48.5±10.5 years, 4,160 men) in 2004 and reevaluated 5 years later. Subjects were excluded if they were hypertensive, diabetic, or were receiving medications for dyslipidemia and/or gout or hyperuricemia in 2004. Study subjects were categorized according to baseline BMI of ≥25 kg/m^2(overweight/obesity) and <25 kg/m^2(lean/normal) and also whether they had metabolic syndrome. The cumulative incidences of hypertension and diabetes over 5 years between groups were assessed. A second analysis evaluated whether baseline hyperuricemia provided additional risk.

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Author contributions: MK, RK, IH and RJJ designed the study; MK and KN collected the data; MK analyzed the data; and MK, JOH, and RJJ were responsible for writing the manuscript. All authors read and approved the final manuscript. MK had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Results—Subjects with overweight/obesity but without metabolic syndrome carried increased cumulative incidences of hypertension(14.6% vs 7.2%, p<0.001) and diabetes(2.6% vs 1.1%, p=0.004) over 5 years compared to lean/normal subjects without metabolic syndrome. Overweight/obesity conferred an increased risk for diabetes even in individuals with normal fasting blood glucose. Hyperuricemia became an independent risk factor for developing hypertension over 5 years in lean/normal subjects without metabolic syndrome. A 1 mg/dL increase in serum uric acid carried increased risk for hypertension(19%) and diabetes(27%).

Conclusions—"Metabolically healthy" obesity and hyperuricemia confers increased risk for hypertension and diabetes.

Keywords

Obesity; Metabolic Syndrome; Cardiovascular Risk; Epidemiology

Introduction

Metabolic syndrome is an important risk factor for cardiovascular disease (1), but current definitions of metabolic syndrome do not consider body mass index (BMI) (2, 3, 4, 5) because waist circumference is a better predictor of total body fat than BMI (6). While obesity is recognized as an independent risk factor for hypertension and diabetes mellitus (DM) (7, 8, 9, 10), the classical approach in obesity research is to control for the various metabolic risk factors, many of which may be causally linked to obesity. An alternative approach would be to perform longitudinal analyses in which subjects with obesity are stratified at baseline into those with or without metabolic syndrome. This is especially important as the concept of a metabolically healthy population with obesity is widely recognized (11, 12, 13, 14, 15).

We tested the hypothesis that "metabolically healthy" obesity, defined as obesity in the absence of metabolic syndrome, still carried increased risk for hypertension and DM by a longitudinal study design. Moreover, we performed a second analysis to determine if hyperuricemia provided an additional risk for developing hypertension or DM because of the strong relationship of serum uric acid with obesity, hypertension, and DM (16).

Methods

Study design and study subjects

This study was a large-scale, single-center, retrospective cohort study in Japan. We used the database at the Center for Preventive Medicine, St. Luke's International Hospital, Tokyo, Japan. This study population was considered as an 'apparently healthy population' since they came to the center by themselves to have annual regular health checkup without specific complaints, and also provided a general history of comorbidities. We have previously published studies using this database (17, 18, 19, 20, 21, 22, 23). The study subjects were similar to our previous studies, but this study design, inclusion and exclusion criteria, and outcomes were different from our previous studies.

We enrolled study subjects between ages 30 and 85 years old whose data were available at 2004 and 2009. Of 13,201 subjects who enrolled in 2004 and had follow-up data in 2009, 5 subjects were excluded due to missing waist circumference data, age <30 (n=121), age >85 (n=10), the presence of hypertension (2,599 subjects), DM (575 subjects), or treatment for dyslipidemia (658 subjects) or hyperuricemia and/or gout (373 subjects). A total of 9,721 study subjects were analyzed (Figure 1). The subjects were cross-classified into four groups as 'BMI of ≥25 kg/m^2 (overweight/obesity) and BMI of <25 kg/m^2 (lean/normal) and those with and without metabolic syndrome, defined using a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention (IDF); National Heart, Lung, and Blood Institute (NHLBI); American Heart Association (AHA); World Heart Federation (WHF); International Atherosclerosis Society (IAS); and International Association for the Study of Obesity (IASO) (2). Thus, four groups were followed, consisting of: 1) lean/normal without metabolic syndrome group, 2) overweight/obesity without metabolic syndrome group, 3) lean/normal with metabolic syndrome group, and 4) overweight/obesity with metabolic syndrome group at the baseline (in 2004) (Figure 1). We compared cumulative incidences of hypertension and DM over 5 years among the four groups, and calculated odds ratios (ORs) for each disease by crude analysis and after adjustments for age, sex, smoking and drinking habits, chronic kidney disease, BMI and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (or serum uric acid levels). Moreover, we performed a second analysis to determine if hyperuricemia and elevated serum uric acid provided an additional risk for developing hypertension or DM.

Definition of metabolic syndrome, hypertension, diabetes mellitus, hyperuricemia, and chronic kidney disease

Metabolic syndrome was defined according to a joint interim statement of IDF; NHLBI; AHA; WHF; IAS; and IASO (2). Metabolic syndrome definition was a condition when a person had three or more of the following five measurements: 1) Abdominal obesity: IDF and WHO recommended waist circumference of 90 cm or above in men, and 80 cm or above in women for Japanese, 2) Triglyceride level of 150 mg/dL of blood or greater, 3) High-density lipoprotein (HDL) cholesterol of less than 40 mg/dL in men or less than 50 mg/dL in women, 4) Systolic blood pressure of 130 mmHg or greater, or diastolic blood pressure of 85 mmHg or greater, 5) Fasting glucose of 100 mg/dL or greater.

Hypertension was defined as the subjects who were on current antihypertensive medication and/or systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg according to the Japanese Society of Hypertension guidelines (JSH 2014) (24). Blood pressure readings were obtained using an automatic brachial sphygmomanometer (OMRON Corporation, Kyoto, Japan). Two blood pressure examinations were taken after the participant had been seated and resting quietly for more than five minutes with feet on the ground and back supported. The mean systolic and diastolic blood pressure of each of the subjects were calculated from the recorded measurements. DM was defined as the subjects who had current DM on medication and/or HbA1c (National Glycohemoglobin Standardization Program) of ≥6.5% according to International Expert Committee. Hyperuricemia was defined as >7.0 mg/dL of serum uric acid in men and ≥6.0 mg/dL in

women as the standard definition for most studies (25). The definition in men was attributed to Japanese guideline for the management of hyperuricemia and gout: second edition (26). However, compared to men, serum uric acid levels are lower in women because female hormones decrease serum uric acid levels (27). Thus, we defined hyperuricemia in women as ≥6.0 mg/dL as is commonly used in many other study populations (28, 29, 30, 31). Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. We calculated eGFR using the Japanese GFR equation: eGFR (mL/min/1.73m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 if woman) (32). Drinking habits was defined as positive if the individual drank habitually (daily), while an absence of drinking or social drinking was considered negative. Smoking habits defined both current smokers and past smokers as positive.

Statistical analysis

The statistically significant level was set α =0.05, and all statistical analyses were two-sided. Data are expressed as mean ± standard derivation or as percent frequency unless otherwise specified. Comparisons between two groups were performed with Student *t*-tests for normally distributed variables, and χ^2 analyses for categorical data. Multiple comparisons based on Tukey's method were performed for pairwise comparisons. The risk factors for incident hypertension and DM over 5 years were evaluated both by crude models and by multivariable logistic regression models with adjustments for age, sex, smoking and drinking habits, chronic kidney disease, BMI and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (or serum uric acid), and the ORs for each disease were analyzed in each group. All analyses were also stratified by sex because the distribution of serum uric acid levels differed between men and women. We also compared the cumulative incidences of hypertension and DM between hyperuricemia and normouricemia in each group. All the statistical analyses were performed by the SPSS Statistics software (IBM SPSS Statistics version 22 for Windows; IBM, New York, USA).

Ethical considerations

We adhered to the principles of the Declaration of Helsinki. Consents were obtained from all subjects by a comprehensive agreement method provided by St. Luke's International Hospital. All data were collected and compiled in a protected computer database. Individual data were anonymous without identifiable personal information. St. Luke's International Hospital Ethics Committee approved the protocol for this study. No patients were involved in setting the research question or outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Results

Demographics

Subjects were divided into four groups; 7,927 lean/normal without metabolic syndrome, 966 overweight/obesity without metabolic syndrome, 364 lean/normal with metabolic syndrome, and 464 overweight/obesity with metabolic syndrome (Table 1). Lean/normal with metabolic syndrome group was significantly older than the other groups (p<0.001), but the other three

groups had no significant differences of age. Overweight/obesity groups had significantly higher height, weight, BMI, waist circumference, higher prevalence of smoking and drinking habits, and higher levels of CRP and serum uric acid compared to lean/normal groups ($p<0.001$). Subjects with metabolic syndrome had significantly higher systolic and diastolic blood pressure, and higher levels of fasting blood glucose hemoglobin A1c, low-density lipoprotein cholesterol, and triglyceride but lower high-density lipoprotein cholesterol compared to subjects without metabolic syndrome ($p<0.001$) (Table 1 Total). When we compared the baseline characteristics of subjects stratified by sex, the results were similar (Table 1 Men and Women).

Cumulative incidences of hypertension and diabetes mellitus among lean/normal and overweight/obesity with and without metabolic syndrome

The cumulative incidences of hypertension and DM over 5 years are shown in Table 2. Lean/normal subjects without metabolic syndrome group had lowest cumulative incidence of hypertension and DM among the four groups ($p<0.001$). Overweight/obesity without metabolic syndrome group had significantly higher cumulative incidence of hypertension (14.6% vs 7.2%, $p<0.001$) and DM (2.6% vs 1.1%, $p=0.004$) compared to lean/normal without metabolic syndrome group, but significantly lower cumulative incidence of hypertension (14.6% vs 28.0%, $p<0.001$) and DM (2.6% vs 7.1%, $p<0.001$) compared to lean/normal with metabolic syndrome group. Lean/normal with metabolic syndrome group did not have significant differences of cumulative incidence of hypertension (28.0% vs 28.4%, $p=1.00$) and DM (7.1% vs 9.5%, $p=0.057$) compared to overweight/obesity with metabolic syndrome group. We also conducted the same analyses stratified by sex, the results were almost the same, but there was no significant differences of cumulative incidences of DM between lean/normal without metabolic syndrome group and overweight/obesity without metabolic syndrome group both in men (1.8% vs 3.0%, $p=0.38$) and women (0.6% vs 1.7%, $p=0.25$).

Effect of hyperuricemia and normouricemia on outcomes

We compared the cumulative incidences of hypertension and DM over 5 years between hyperuricemia and normouricemia in each group by χ^2 analyses (Figure 2). Only in the lean/normal without metabolic syndrome group, was hyperuricemia a significant risk factor for incident hypertension (12.6% vs 6.7%, $p<0.001$) and DM (2.0% vs 1.0%, $p=0.014$) compared to normouricemia. Stratified by sex, hyperuricemia had a significantly higher cumulative incidence of hypertension both in men (12.5% vs 9.6%, $p=0.050$) and women (12.9% vs 5.2%, $p<0.001$), but hyperuricemia carried a significant risk for DM only in women (2.0% vs 0.5%, $p=0.031$) (Figure 3). We also calculated the cumulative incidence of hypertension and DM over 5 years for each serum uric acid level by sex (Figure 4). Levels of more than 6.0 mg/dL of serum uric acid in men and 5.0 mg/dL in women are associated with higher risk for developing hypertension and DM compared to mean prevalence of these conditions in the overall population. The results suggest a threshold of 5.0 mg/dL of serum uric acid in women and 6.0 mg/dL in men that carries an increased risk for developing hypertension and DM.

Multivariable analyses

We calculated ORs for hypertension and DM by crude analysis and after adjustments for age, sex, smoking and drinking habits, chronic kidney disease, BMI and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (or serum uric acid levels) (Table 3). Male sex is an independent risk for hypertension [OR: 1.31; 95% confidence interval (CI), 1.10-1.55] and DM (OR: 1.89; 95% CI, 1.28-2.78) after multivariable adjustments. Compared with lean/normal without metabolic syndrome group, overweight/obesity without metabolic syndrome group had a 1.93-fold greater odds for hypertension (95% CI, 1.57-2.38) and a 1.94-fold greater odds for DM (95% CI, 1.22-3.10), lean/normal with metabolic syndrome group had a 3.53-fold greater odds for hypertension (95% CI, 2.75-4.55) and a 4.68-fold greater odds for DM (95% CI, 2.93-7.46), and overweight/obesity with metabolic syndrome group had a 4.27-fold greater odds for hypertension (95% CI, 3.38-5.39) and a 7.10-fold greater odds for DM (95% CI, 4.47-10.6) after multivariable adjustments. Every 1 mg/dL increase in serum uric acid was associated with a 19% increased risk for developing hypertension (95% CI, 1.11-1.27) and a 27% increased risk for developing DM (95% CI, 1.10-1.45) in adjusted analyses. We also performed the same analyses stratified by sex. In men, we observed a 12% increased risk for developing hypertension (95% CI, 1.03-1.21) and a 21% increased risk for developing DM (95% CI, 1.03-1.43) for every 1 mg/dL increase in serum uric acid in adjusted analyses. In women, we observed a 29% increased risk for developing hypertension (95% CI, 1.14-1.45) and a 34% increased risk for developing DM (95% CI, 1.01-1.79) for every 1 mg/dL increase in serum uric acid in adjusted analyses.

Risk for hypertension in subjects with normal blood pressure and for DM in subjects with normal fasting blood glucose

Since a baseline elevated blood pressure may increase the risk for hypertension, and since a baseline impaired fasting glucose level might predict development of DM, we performed a separate analysis in which we evaluated whether obesity without these findings could predict hypertension and DM, respectively.

Of 9,721 subjects (4,160 men) in this study, 8,411 subjects (3,365 men) had normal blood pressure (<130/85 mmHg) and 6,502 subjects (2,073 men) had normal blood glucose (<100 mg/dL). We calculated ORs for hypertension in the 8,411 subjects with normal blood pressure and for DM in the 6,502 subjects with normal blood glucose after adjustments for age, sex, smoking and drinking habits, chronic kidney disease, BMI and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (Table 4). In the subjects with normal blood pressure, the overweight/obesity without metabolic syndrome group were not a risk for hypertension compared with lean/normal subjects without metabolic syndrome after multivariable adjustments (p=0.59). In contrast, in the subjects with normal blood glucose, the presence of overweight/obesity without metabolic syndrome still carried an 11.4-fold greater odds for developing DM (95% CI, 2.49-51.9) compared with lean/normal subjects without metabolic syndrome after multivariable adjustments.

Discussion

The primary finding of this study was that “metabolically healthy” obesity, defined as overweight/obesity without metabolic syndrome, carried increased cumulative incidences of hypertension (14.6% vs 7.2%, p<0.001) and DM (2.6% vs 1.1%, p=0.004) over 5 years compared to lean/normal without metabolic syndrome. This result confirms other studies (7, 8, 9, 10) and suggests that “metabolically healthy” obesity is a misnomer as it is still associated with increased risk for hypertension and DM. Second, our study documented that hyperuricemia is an independent risk factor for developing hypertension and DM in the overall population. However, when stratified by the four groups as BMI of ≥25 kg/m^2 (overweight/obesity) and BMI of < 25 kg/m^2 (lean/normal) and those with and without metabolic syndrome, hyperuricemia was only an independent risk for the development of hypertension and DM only in the lean/normal without metabolic syndrome group. The result may relate to hyperuricemia being causally linked with obesity and metabolic syndrome, and therefore not independent of its components (33, 34).

While overweight/obesity was an important risk factor for hypertension and DM in the group without metabolic syndrome, it did not confer independent risk for incident hypertension and DM in subjects with metabolic syndrome. This may be ascribed to BMI and increased abdominal circumference (a feature of metabolic syndrome) both reflecting a state of increased fat storage. In the group without metabolic syndrome, overweight/obesity carried a nearly 2-fold risk for incident hypertension and DM after multivariable adjustments.

An important observation was that in subjects without metabolic syndrome, the presence of overweight/obesity carried increased risk for the development of hypertension and DM (Table 2 and 3). However, the subjects who were overweight/obesity and/or had metabolic syndrome had higher baseline blood pressure and fasting blood glucose than lean/normal subjects without metabolic syndrome (Table 1), which may increase the risk for hypertension and DM. Some of these subjects with overweight/obesity had elevated blood pressure despite not qualifying as having metabolic syndrome, which might be expected to predict the development of hypertension. Likewise, some subjects with overweight/obesity who did not qualify as having metabolic syndrome also had elevated fasting blood glucose that might influence the risk for DM. Thus, to address this, we performed a separate analysis to determine if subjects with overweight/obesity who did not have metabolic syndrome and had normal blood pressure (defined as <130/85 mmHg on no antihypertensive agent) still carried risk for hypertension, and similarly, whether a normal blood glucose (defined as fasting blood glucose <100 mg/dL) in subjects with overweight/obesity but without metabolic syndrome carried risk for DM (Table 4). The primary finding was that overweight/obesity with a normal blood glucose still conveyed an 11-fold risk for developing DM after multivariable adjustments but that the risk for developing hypertension in subjects with overweight/obesity and with normal blood pressure at baseline was not significant. This emphasizes the key role obesity itself has in driving DM. In contrast, baseline blood pressure in subjects overweight/obesity but without metabolic syndrome is more important for developing hypertension compared to overweight/obesity itself.

In subjects who were lean/normal and without metabolic syndrome, hyperuricemia became an important risk factor for hypertension and DM. Thus, our studies show the importance of BMI and serum uric acid in identifying people at risk for developing hypertension and DM with hyperuricemia carrying a more important role in lean/normal subjects, whereas once overweight/obesity and metabolic syndrome develop, the latter factors become dominant.

This study has some limitations. First, there are two definitions for abdominal obesity using in Japan. Japanese Obesity Society (JOS) recommended waist circumference of 85 cm or above in men, and 90 cm or above in women (35). However, this study used abdominal obesity definition per IDF and WHO recommendation; waist circumference of 90 cm or above in men, and 80 cm or above in women (4, 36). A sensitivity analysis using JOS definition rather than IDF and WHO definition provided similar results. Second, this study was a retrospective, single center study, which may have introduced selection bias. Furthermore, since subjects were those who sought a health examination, the study subjects may have more interested in health issues than the general population, especially since the health checkup was not covered by insurance. However, our medical check-up systems is open to everyone and the number of our study subjects was large, which suggests that we can generalize our results to Japanese. Our study was based on a homogenous population, and further studies of other ethnicities are needed. Third, our study did not assess the risk for developing dyslipidemia due to it being part of the diagnostic criteria for metabolic syndrome. This is different from predicting hypertension or DM, as the criteria for metabolic syndrome involves prehypertension and impaired fasting blood glucose rather than hypertension and DM per se. However, high blood pressure, hyperglycemia and lipid abnormality have mutual influences, and we should account for the importance of lipid abnormality. Finally, this longitudinal study lacks time-to-event data which precluded survival analysis.

The results of this study add to the growing evidence base demonstrating that being obesity is associated with increased risk of metabolic disease as compared to matched individuals without obesity. We do not believe the use of the term “metabolically healthy” obesity is useful either for understanding the development of chronic disease or for prioritizing treatment of obesity. Designating some individuals as “metabolically healthy” suggests that intervention in these individuals should not be prioritized compared to metabolically unhealthy obesity. Given that “metabolically healthy” obesity have a higher risk of developing metabolic disease than their lean counterparts, and that obesity increases risks of other many non-metabolic conditions such as orthopedic problems (37) and increased risk of depression and other mood disorders (38), it is inappropriate to suggest that this group is healthy. In fact, this group might present a very cost-effect opportunity for intervention since it is possible that less intense interventions may be effective in this population. We think it is time to stop thinking of any individuals with obesity as healthy.

Conclusion

“Metabolically healthy” obesity, defined as obesity in the absence of metabolic syndrome, confers increased risk for hypertension and diabetes mellitus. An elevated serum uric acid

levels also confers a risk for hypertension and diabetes mellitus in lean/normal subjects, but not in subjects with overweight/obesity or those with metabolic syndrome.

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Abbreviations list

BMI	body mass index
DM	diabetes mellitus
ORs	odds ratios
IDF	the International Diabetes Federation Task Force on Epidemiology and Prevention
NHLBI	National Heart, Lung, and Blood Institute
AHA	American Heart Association
WHF	World Heart Federation
IAS	International Atherosclerosis Society
IASO	International Association for the Study of Obesity
eGFR	estimated glomerular filtration rate

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What is already known about this subject?

Obesity is recognized as an independent risk factor for hypertension and diabetes.

However, the concept of a metabolically healthy population with obesity is widely recognized.

Metabolic syndrome is an important risk factor for cardiovascular disease, but many of metabolic risk factors are causally linked with obesity.

What does this study add?

This study is to clarify whether subjects with obesity in the absence of metabolic syndrome confers similar or less compared to subjects without obesity.

Subjects with obesity but without metabolic syndrome carried more than 2-fold increased cumulative incidences of hypertension and diabetes mellitus over 5 years compared to lean/normal subjects without metabolic syndrome.

Hyperuricemia was an independent risk factor for developing hypertension in the lean/normal subjects without metabolic syndrome but not in subjects with obesity those with metabolic syndrome.

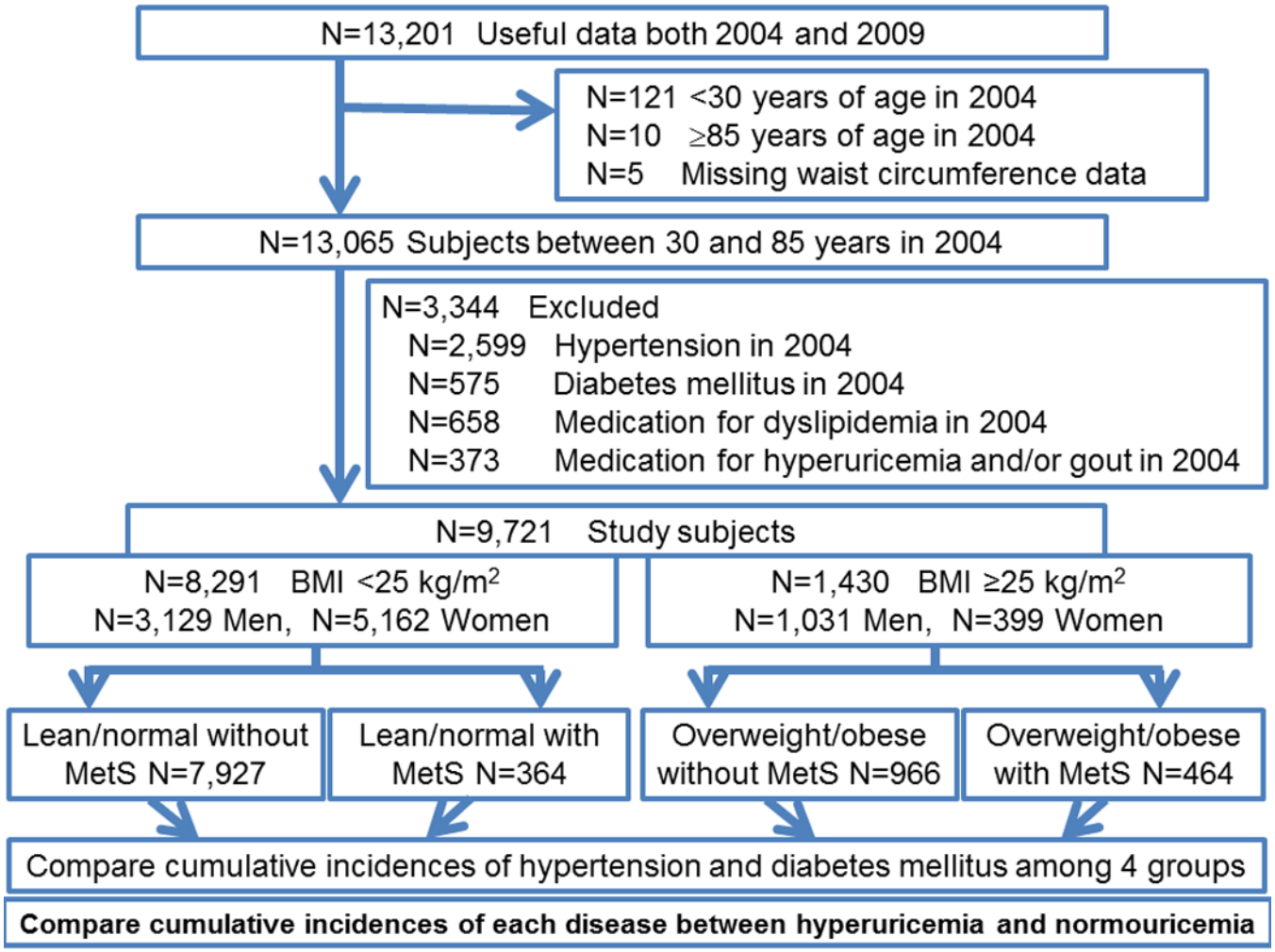

Figure 1. Flow diagram of study enrollment

N: number of subjects; BMI: body mass index

1935 subjects had only hypertension. 275 subjects had only diabetes mellitus. 125 subjects had only medication for dyslipidemia. 273 subjects had only medication for hyperuricemia and/or gout.261 subjects had both hypertension and diabetes mellitus. 93 subjects had medication for dyslipidemia and hyperuricemia and/or gout. 322 subjects had hypertension and medication for dyslipidemia. 204 subjects had hypertension and medication for hyperuricemia and/or gout. 58 subjects had hypertension and medication for dyslipidemia and hyperuricemia and/or gout. 84 subjects had diabetes mellitus and medication for dyslipidemia. 36 subjects had diabetes mellitus and medication for hyperuricemia and/or gout. 16 subjects had diabetes mellitus and medication for dyslipidemia and hyperuricemia and/or gout. 54 subjects had hypertension, diabetes mellitus and medication for dyslipidemia. 25 subjects had hypertension, diabetes mellitus and medication for hyperuricemia and/or gout. 14 subjects had hypertension, diabetes mellitus and medication for dyslipidemia and hyperuricemia and/or gout.

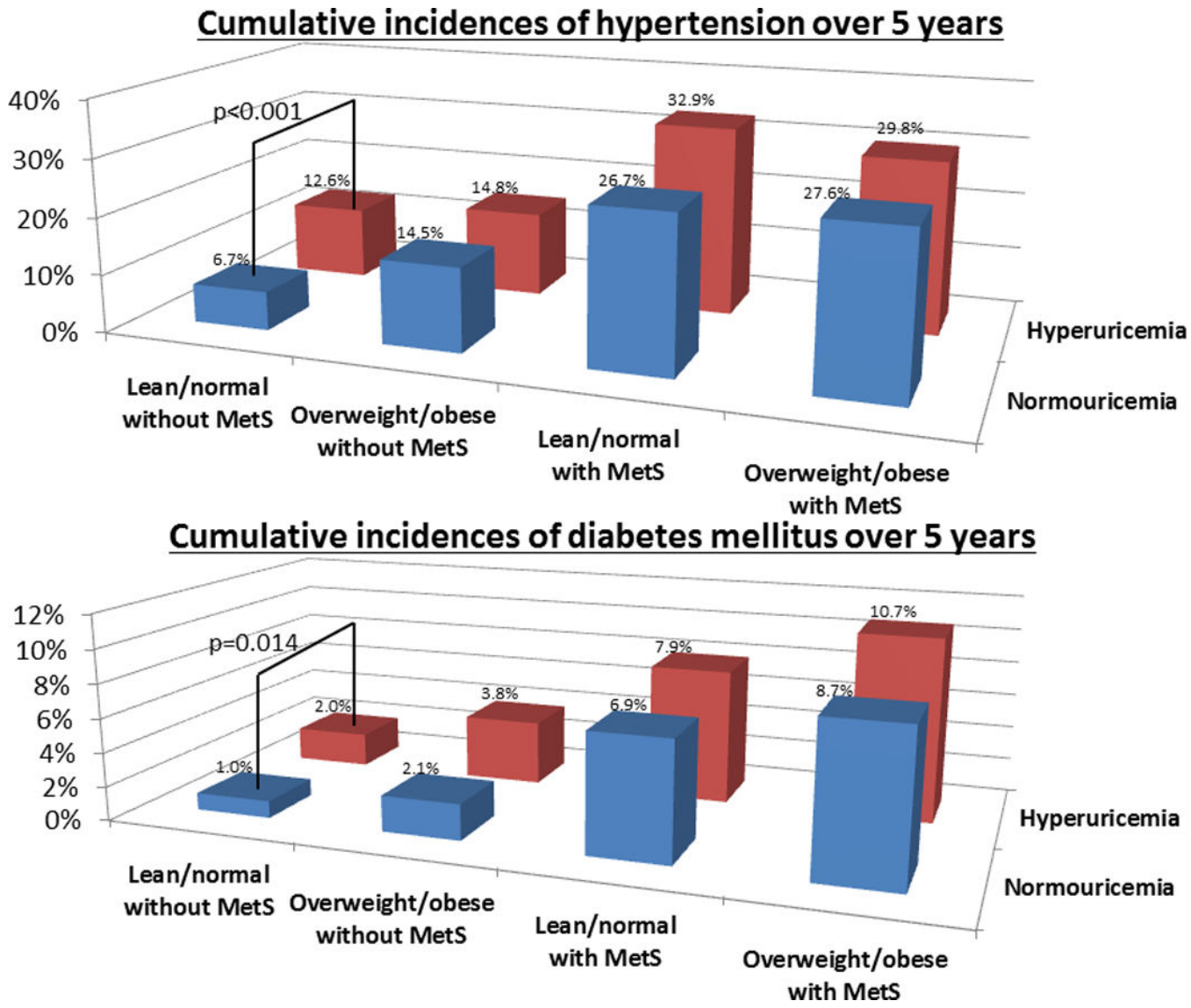

Figure 2. Cumulative incidences of hypertension and diabetes mellitus over 5 years between hyperuricemia and normouricemia in each group

MetS: metabolic syndrome

The number of subjects in normouricemia: 7,173 subjects in lean/normal without metabolic syndrome, 702 subjects in overweight/obesity without metabolic syndrome, 288 subjects in lean/normal with metabolic syndrome, and 286 subjects in overweight/obesity with metabolic syndrome.

The number of subjects in hyperuricemia: 754 subjects in lean/normal without metabolic syndrome, 264 subjects in overweight/obesity without metabolic syndrome, 76 subjects in lean/normal with metabolic syndrome, and 178 subjects in overweight/obesity with metabolic syndrome.

The bars show significant difference of cumulative incidences of hypertension and diabetes mellitus between hyperuricemia and normouricemia by χ^2 analyses.

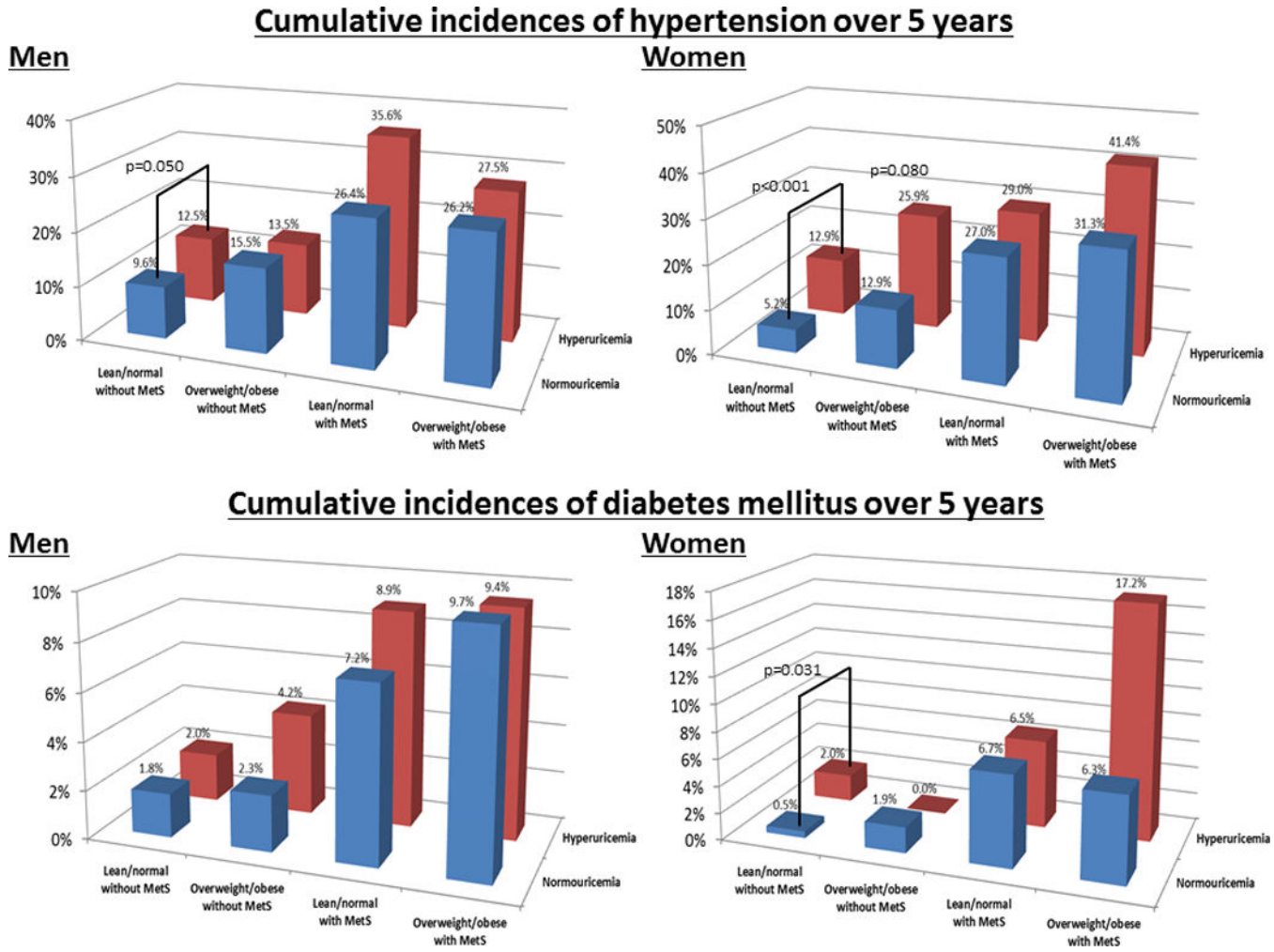

Figure 3. Cumulative incidences of hypertension and diabetes mellitus over 5 years between hyperuricemia and normouricemia in each group by sex

The number of subjects in normouricemia: 2,406 men and 4,767 women in lean/normal without metabolic syndrome, 439 men and 263 women in overweight/obesity without metabolic syndrome, 125 men and 163 women in lean/normal with metabolic syndrome, and 206 men and 80 women in overweight/obesity with metabolic syndrome.

The number of subjects in hyperuricemia: 553 men and 201 women in lean/normal without metabolic syndrome, 237 men and 27 women in overweight/obesity without metabolic syndrome, 45 men and 31 women in lean/normal with metabolic syndrome, and 149 men and 29 women in overweight/obesity with metabolic syndrome.

The bars show significant difference of cumulative incidences of hypertension and diabetes mellitus between hyperuricemia and normouricemia by χ^2 analyses.

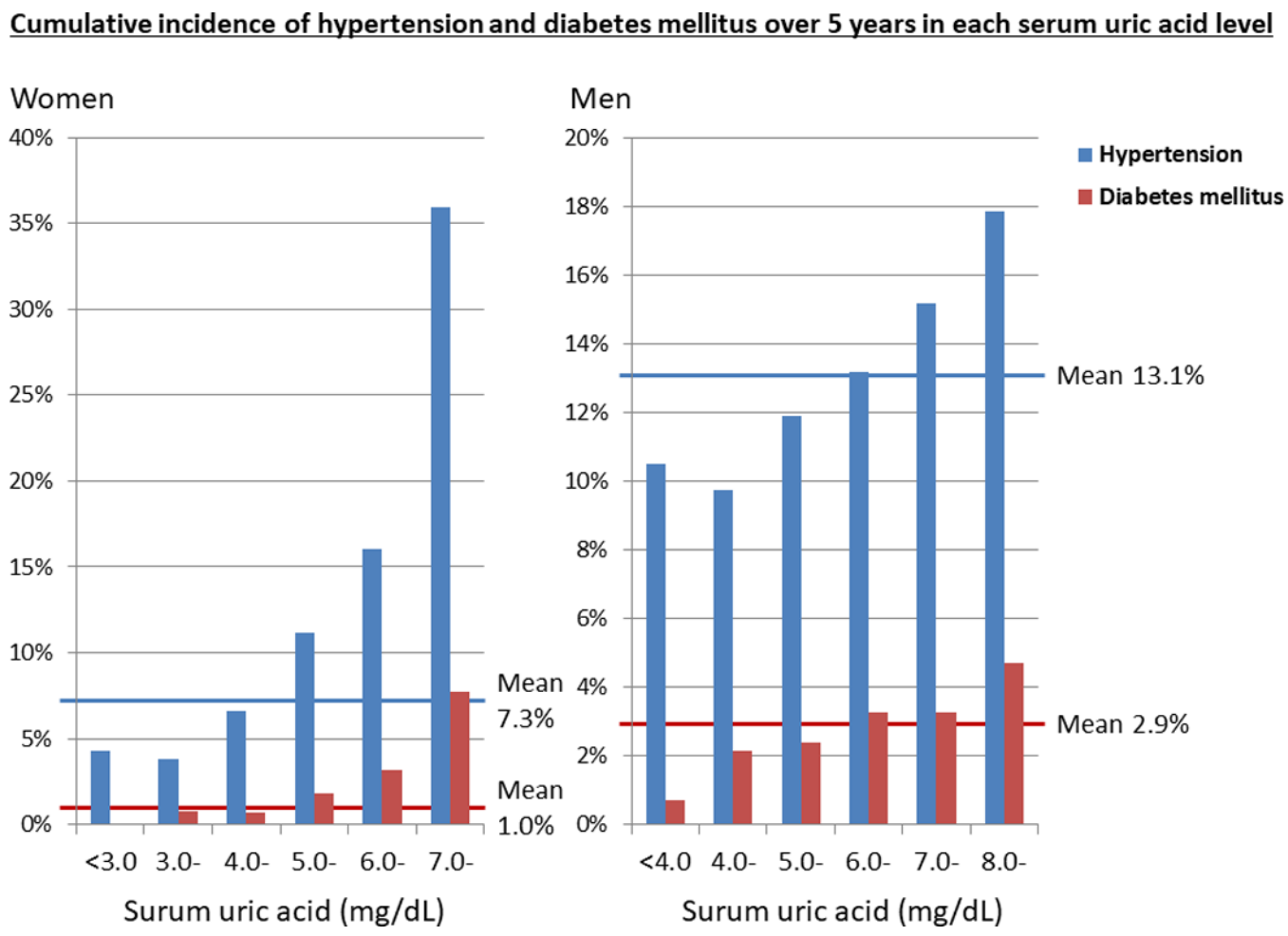

Figure 4. Cumulative incidences of hypertension and diabetes mellitus over 5 years in each serum uric acid level by sex

The number of women in serum uric acid of <3.0, 3.0-3.9, 4.0-4.9, 5.0-5.9, 6.0-6.9, and 7.0- were 256, 1,451, 2,503, 1,063, 249, and 39, respectively. The number of men in serum uric acid of <4.0, 4.0-4.9, 5.0-5.9, 6.0-6.9, 7.0-7.9, and 8.0- were 143, 421, 1,178, 1,323, 798, and 297, respectively. Blue lines show mean cumulative incidence of hypertension (women 7.3%, men 13.1%) and red lines shows mean cumulative incidence of diabetes mellitus (women 1.0%, men 2.9%).

Table 1

Demographics of study subjects

The baseline characteristics of subjects are shown following stratification by cross-classified four groups as 'BMI of ≥25 kg/m2 (overweight/obesity) and BMI of < 25 kg/m2 (lean/normal) and those with and without metabolic syndrome.

Total	**Total**	**Lean/normal without MetS**	**Overweight/obesity without MetS**	**Lean/normal with MetS**	**Overweight/obesity with MetS**	**p**
Number of subjects	9,721	7,927	966	364	464	
Male sex	42.8%	37.3%	70.0%	46.7%	76.5%	
Age	48.5±10.5	48.1±10.5	48.3±10.0	55.9±9.5	49.2±10.6	<0.001
Height (cm)	163.3±8.5	162.7±8.2	166.0.±8.5	163.0±9.8	168.4±8.5	<0.001
Weight (kg)	58.9±11.3	55.8±9.0	73.6±8.3	61.4±9.1	78.1±9.7	<0.001
Body mass index (kg/m^2)	21.9±2.9	21.0±2.1	26.7±1.6	23.0±1.4	27.5±2.1	<0.001
Waist circumference (cm)	79.6±8.6	77.1±7.0	90.6±5.8	85.7±4.7	94.3±5.6	<0.001
Systolic BP (mmHg)	112.8±13.1	110.8±12.6	117.8±10.7	125.4±11.8	126.2±10.2	<0.001
Diastolic BP (mmHg)	70.3±8.8	69.1±8.5	73.6±7.2	77.5±8.0	79.0±6.8	<0.001
Pulse rate (bpm)	72.8±10.1	73.0±10.2	70.0±8.7	75.9±11.5	73.0±9.1	<0.001
Smoking	35.9%	33.2%	47.3%	41.2%	55.8%	<0.001
Drinking habits	41.5%	40.2%	48.0%	40.9%	49.4%	<0.001
Fasting blood glucose (g/dL)	96.8±8.5	95.5±7.9	99.4±8.2	105.6±8.6	106.0±8.3	<0.001
Hemoglobin A1c (%)	4.94±0.33	4.92±0.32	4.99±0.32	5.17±0.35	5.15±0.35	<0.001
Total cholesterol (mg/dL)	204.4±33.3	202.5±33.0	209.1±32.0	219.6±36.5	214.0±33.4	<0.001
LDL cholesterol (mg/dL)	116±29	117.9±29.7	115.3±29.1	129.8±28.6	129.3±30.4	<0.001
HDL cholesterol (mg/dL)	64.0±15.9	66.7±15.4	55.6±11.9	51.5±14.2	47.1±11.3	<0.001
Triglyceride (mg/dL)	92.1±66.1	79.7±47.3	111.8±57.0	179.8±120.3	193.1±125.0	<0.001
BUN (mg/dL)	13.7±3.3	13.7±3.3	13.9±3.1	14.2±3.2	14.0±3.0	0.003
Serum creatinine (mg/dL)	0.671±0.177	0.659±0.180	0.735±0.150	0.671±0.144	0.745±0.144	<0.001
eGFR (mL/min/1.73m2)	87.0±15.2	87.5±15.3	85.2±14.8	84.1±14.7	85.0±14.7	<0.001
CRP (mg/dL)	0.140±0.260	0.133±0.238	0.162±0.311	0.157±0.343	0.206±0.389	<0.001
Serum uric acid (mg/dL)	5.17±1.37	4.97±1.29	6.04±1.38	5.67±1.24	6.40±1.38	<0.001
Men	Total	Lean/normal without MetS	Overweight/obesity without MetS	Lean/normal with MetS	Overweight/obesity with MetS	p
Number of subjects	4,160	2,959	676	170	355	

Total	**Total**	**Lean/normal without MetS**	**Overweight/obesity without MetS**	**Lean/normal with MetS**	**Overweight/obesity with MetS**	**p**
Age	49.5±11.0	49.7±11.2	48.1±10.3	55.1±10.1	48.0±10.1	<0.001
Height (cm)	170.5±6.0	170.4±6.0	169.9±6.1	170.6±7.0	171.9±5.8	<0.001
Weight (kg)	68.0±9.2	64.4±6.8	76.6±7.1	68.7±6.3	81.1±7.8	<0.001
Body mass index (kg/m^2)	23.4±2.6	22.1±1.8	26.5±1.4	23.6±1.1	27.4±1.9	<0.001
Waist circumference (cm)	83.8±7.4	80.8±5.7	90.4±5.3	87.3±4.5	94.3±5.0	<0.001
Systolic BP (mmHg)	116.9±11.9	114.9±11.7	118.6±10.3	126.5±11.0	125.8±10.2	<0.001
Diastolic BP (mmHg)	73.4±8.0	72.2±7.9	74.4±7.0	78.7±7.5	79.1±6.8	<0.001
Pulse rate (bpm)	70.5±9.5	70.6±9.6	68.8±8.7	73.1±10.3	71.8±8.9	<0.001
Smoking	67.9%	59.7%	59.5%	72.4%	67.9%	<0.001
Drinking habits	60.2%	60.3%	60.5%	61.2%	58.0%	0.85
Fasting blood glucose (g/dL)	100.5±8.7	99.3±8.2	100.7±8.1	108.2±9.2	106.5±8.5	<0.001
Hemoglobin A1c (%)	4.97±0.33	4.94±0.32	4.98±0.32	5.18±0.35	5.12±0.35	<0.001
Total cholestrol (mg/dL)	203.6±31.9	201.5±31.3	206.2±31.1	212.3±37.4	211.4±33.3	<0.001
LDL cholesterol (mg/dL)	122.1±28.9	120.0±28.3	128.5±28.6	122.3±32.0	127.1±30.2	<0.001
HDL cholesterol (mg/dL)	55.7±13.3	58.2±13,3	52.8±11.0	45.8±11.7	44.9±9.7	<0.001
Triglyceride (mg/dL)	119.0±83.1	101.8±60.5	121.7±61.8	223.0±146.1	207.4±132.9	<0.001
BUN (mg/dL)	14.5±3.2	14.6±3.3	14.2±3.0	14.4±3.1	14.2±3.0	0.003
Serum creatinine (mg/dL)	0.794±0.120	0.792±0.121	0.804±0.115	0.786±0.109	0.797±0.116	0.089
eGFR (mL/min/1.73m2)	84.3±14.5	84.5±14.6	83.7±14.4	82.3±14.1	84.6±14.6	0.17
CRP (mg/dL)	0.159±0.310	0.152±0.301	0.169±0.363	0.144±0.176	0.201±0.327	0.030
Serum uric acid (mg/dL)	6.20±1.20	6.04±1.16	6.56±1.23	6.42±1.07	6.74±1.30	<0.001
Women	Total	Lean/normal without MetS	Overweight/obesity without MetS	Lean/normal with MetS	Overweight/obesity with MetS	p
Number of subjects	5,561	4,968	290	194	109	
Age	47.7±10.1	47.2±9.9	48.9±9.3	56.6±9.0	53.2±11.4	<0.001
Height (cm)	157.9±5.5	158.0±5.4	156.7.±5.5	156.3±6.4	157.0±5.1	<0.001
Weight (kg)	52.1±7.2	50.7±5.6	66.6±6.6	55.0±5.7	68.3±8.8	<0.001
Body mass index (kg/m^2)	20.9±2.7	20.3±2.0	27.1±1.9	22.5±1.5	27.6±2.6	<0.001
Waist circumference (cm)	76.5±8.1	74.9±6.7	90.8±6.7	84.3±4.4	94.2±7.2	<0.001
Systolic BP (mmHg)	109.7±13.1	108.3±12.5	116.0±11.4	124.5±12.4	127.5±10.1	<0.001
Diastolic BP (mmHg)	68.0±8.6	67.3±8.3	71.7±7.5	76.4±8.2	78.6±6.9	<0.001

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Total	Total	Lean/normal without MetS	Overweight/obesity without MetS	Lean/normal with MetS	Overweight/obesity with MetS	p
Pulse rate (bpm)	74.6±10.2	74.5±10.2	72.9±7.9	78.4±12.0	77.0±8.7	<0.001
Smoking	17.3%	17.3%	19.0%	13.9%	16.5%	0.54
Drinking habits	27.4%	28.2%	19.0%	23.2%	21.1%	0.001
Fasting blood glucose (g/dL)	94.0±7.3	93.3±6.8	96.4±7.5	103.3±7.4	104.5±7.4	<0.001
Hemoglobin A1c (%)	4.92±0.33	4.90±0.32	5.03±0.32	5.17±0.35	5.24±0.32	<0.001
Total cholesterol (mg/dL)	205.0±34.3	203.2±33.9	215.7±33.3	226.0±34.4	222.4±32.6	<0.001
LDL cholesterol (mg/dL)	114.8±29.9	112.5±29.2	132.7±28.4	135.9±29.0	136.5±30.2	<0.001
HDL cholesterol (mg/dL)	70.3±14.7	71.7±14.3	62.0±11.5	56.4±14.3	54.1±13.1	<0.001
Triglyceride (mg/dL)	71.9±39.0	66.6±30.6	88.8±34.0	141.9±93.7	146.6±78.7	<0.001
BUN (mg/dL)	13.2±3.2	13.1±3.2	13.2±3.3	13.9±3.3	13.5±3.0	0.003
Serum creatinine (mg/dL)	0.578±0.155	0.579±0.161	0.573±0.080	0.570±0.080	0.577±0.086	0.80
eGFR (mL/min/1.73m2)	89.1±15.4	89.3±15.4	88.9±15.0	85.7±15.0	86.5±14.9	0.003
CRP (mg/dL)	0.126±0.214	0.122±0.190	0.146±0.116	0.168±0.440	0.225±0.55	<0.001
Serum uric acid (mg/dL)	4.40±0.90	4.34±0.87	4.84±0.89	5.00±0.97	5.27±0.96	<0.001

BMI: body mass index; BP: blood pressure, bpm: beats per minute, LDL: low density lipoprotein, HDL: high density lipoprotein, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, p: probability

Data are presented as mean ± standard deviation.

Table 2

Cumulative incidences of hypertension and diabetes mellitus over 5 years between study groups

Total	N	Incidence of hypertension	Incidence of diabetes
1) Lean/normal without MetS (presence of 0-2 risk factors)	7,927	7.2%	1.1%
2) Overweight/obesity without MetS (presence of 0-2 risk factors)	966	14.6%	2.6%
3) Lean/normal with MetS	364	28.0%	7.1%
4) Overweight/obesity with MetS	464	28.4%	9.5%
p value	9,721	<0.001	<0.001
Men			
1) Lean/normal without MetS (presence of 0-2 risk factors)	2,959	10.1%	1.8%
2) Overweight/obesity without MetS (presence of 0-2 risk factors)	676	14.8%	3.0%
3) Lean/normal with MetS	170	28.8%	7.6%
4) Overweight/obesity with MetS	355	26.8%	9.6%
p value	4,160	<0.001	<0.001
Women			
1) Lean/normal without MetS (presence of 0-2 risk factors)	4,968	5.5%	0.6%
2) Overweight/obesity without MetS (presence of 0-2 risk factors)	290	14.1%	1.7%
3) Lean/normal with MetS	194	27.3%	6.7%
4) Overweight/obesity with MetS	109	33.9%	9.2%
p value	5,561	<0.001	<0.001

BMI: body mass index, High BMI means BMI ≥25 kg/m^2

Total: There are significant differences of cumulative incidences of hypertension between 1) lean/normal without metabolic syndrome group and 2) overweight/obesity without metabolic syndrome group ($p<0.001$), between 1) and 3) lean/normal with metabolic syndrome group ($p<0.001$), between 1) and 4) overweight/obesity with metabolic syndrome group ($p<0.001$), between 2) and 3) ($p<0.001$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 3) and 4) ($p=1.0$) by analysis using Tukey's methods.

There are significant differences of cumulative incidences of diabetes mellitus between 1) and 2) ($p=0.004$), between 1) and 3) ($p<0.001$), between 1) and 4) ($p<0.001$), between 2) and 3) ($p<0.001$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 3) and 4) ($p=0.058$) by analysis using Tukey's methods.

Men: There are significant differences of cumulative incidences of hypertension between 1) and 2) ($p=0.006$), between 1) and 3) ($p<0.001$), between 1) and 4) ($p<0.001$), between 2) and 3) ($p<0.001$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 3) and 4) ($p=0.91$) by analysis using Tukey's methods.

There are significant differences of cumulative incidences of diabetes mellitus between 1) and 3) ($p<0.001$), between 1) and 4) ($p<0.001$), between 2) and 3) ($p=0.006$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 1) and 2) ($p=0.38$) and between 3) and 4) ($p=0.60$) by analysis using Tukey's methods.

Women: There are significant differences of cumulative incidences of hypertension between 1) and 2) ($p<0.001$), between 1) and 3) ($p<0.001$), between 1) and 4) ($p<0.001$), between 2) and 3) ($p<0.001$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 3) and 4) ($p=0.13$) by analysis using Tukey's methods.

There are significant differences of cumulative incidences of diabetes mellitus between 1) and 3) ($p<0.001$), between 1) and 4) ($p<0.001$), between 2) and 3) ($p<0.001$), and between 2) and 4) ($p<0.001$), but there is no significant differences between 1) and 2) ($p=0.25$) and between 3) and 4) ($p=0.17$) by analysis using Tukey's methods.

Table 3

Risk for developing hypertension and diabetes mellitus.

	Hypertension						Diabetes mellitus					
	Crude			Adjusted*			Crude			Adjusted*		
Total (n=9,721)	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Lean/normal without MetS	Reference			Reference			Reference			Reference		
Overweight/obesity without MetS	2.19	1.80–2.67	<0.001	1.93	1.57–2.38	<0.001	2.48	1.58–3.90	<0.001	1.94	1.22–3.10	0.005
Lean/normal with MetS	5.00	3.91–6.38	<0.001	3.53	2.75–4.55	<0.001	7.18	4.57–11.3	<0.001	4.68	2.93–7.46	<0.001
Overweight/obesity with MetS	5.10	4.10–6.35	<0.001	4.27	3.38–5.39	<0.001	9.78	6.80–14.3	<0.001	7.10	4.74–10.6	<0.001
Hyperuricemia	2.10	1.78–2.47	<0.001	1.36	1.13–1.63	0.001	2.64	1.89–3.68	<0.001	1.38	0.96–1.99	0.080
Serum uric acid (per 1 mg/dL increased)	1.36	1.30–1.43	<0.001	1.19	1.11–1.27	<0.001	1.55	1.40–1.72	<0.001	1.27	1.10–1.45	<0.001
Sex (men)	1.92	1.68–2.20	<0.001	1.31	1.10–1.55	0.002	2.84	2.07–3.90	<0.001	1.89	1.28–2.78	0.001
Men (n=4,160)												
Lean/normal without MetS	Reference			Reference			Reference			Reference		
Overweight/obesity without MetS	1.54	1.21–1.96	<0.001	1.60	1.25–2.06	<0.001	1.64	0.98–2.76	0.062	1.71	1.005–2.90	0.048
Lean/normal with MetS	3.59	2.52–5.11	<0.001	3.00	2.10–4.31	<0.001	4.45	2.38–8.33	<0.001	3.36	2.54–14.5	<0.001
Overweight/obesity with MetS	3.24	2.49–4.22	<0.001	3.43	2.61–4.52	<0.001	5.70	3.65–8.89	<0.001	5.86	0.090–5.96	<0.001
Hyperuricemia	1.38	1.13–1.69	0.002	1.24	1.002–1.53	0.048	1.56	1.06–2.30	0.025	1.24	0.82–1.88	0.30
Serum uric acid (per 1 mg/dL increased)	1.70	1.53–1.90	<0.001	1.12	1.03–1.21	0.006	1.30	1.12–1.51	<0.001	1.21	1.03–1.43	0.017
Women (n=5,561)												
Lean/normal without MetS	Reference			Reference			Reference			Reference		
Overweight/obesity without MetS	2.83	1.99–4.03	<0.001	2.71	1.89–3.90	<0.001	2.89	1.11–7.50	0.029	2.38	0.91–6.23	0.077
Lean/normal with MetS	6.46	4.61–9.07	<0.001	3.91	2.74–5.59	<0.001	11.8	6.06–23.0	<0.001	6.56	3.24–13.3	<0.001
Overweight/obesity with MetS	8.84	5.84–13.4	<0.001	6.28	4.01–9.78	<0.001	16.6	7.91–34.9	<0.001	9.46	4.21–21.3	<0.001
Hyperuricemia	3.25	2.37–4.45	<0.001	1.63	1.15–2.31	0.006	4.42	2.27–8.61	<0.001	1.75	0.84–3.65	0.138
Serum uric acid (per 1 mg/dL increased)	1.16	1.08–1.25	<0.001	1.29	1.14–1.45	<0.001	1.97	1.52–2.55	<0.001	1.34	1.01–1.79	0.042

n: number of subjects; MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval

*Data adjusted for age, sex, smoking and drinking habits, chronic kidney disease, body mass index and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (or serum uric acid).

Table 4

Risk for developing hypertension in subjects with normal blood pressure (a) and risk for developing diabetes mellitus in subjects with normal fasting blood glucose (b)

a) Normal blood pressure	**Hypertension**					
(n=8,411, 3,365 men)	**Crude**			**Adjusted***		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**P**
Lean/normal without MetS	Reference			Reference		
Overweight/obesity without MetS	2.04	1.57–2.66	<0.001	0.90	0.62–1.31	0.59
Lean/normal with MetS	2.72	1.62–4.56	<0.001	1.67	0.98–2.85	0.058
Overweight/obesity with MetS	3.33	2.20–5.03	<0.001	1.28	0.77–2.14	0.34

b) Normal fasting blood glucose	**Diabetes mellitus**					
(n=6,502, 2,073 men)	**Crude**			**Adjusted***		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**P**
Lean/normal without MetS	Reference			Reference		
Overweight/obesity without MetS	5.60	2.36–13.3	<0.001	11.4	2.49–51.9	0.002
Lean/normal with MetS	8.42	1.09–65.1	0.041	5.67	0.67–47.8	0.11
Overweight/obesity with MetS	5.53	0.72–42.5	0.10	15.1	1.25–182.5	0.033

n: number of subjects; MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval

*Data adjusted for age, sex, smoking and drinking habits, chronic kidney disease, body mass index and metabolic syndrome category (lean/normal and overweight/obesity with and without metabolic syndrome), and hyperuricemia (or serum uric acid).