Original Article

Effect of Metabolically Healthy Obesity on the Development of Carotid Plaque in the General Population: A Community-Based Cohort Study

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Aim: Obesity and metabolic syndrome (MetS) frequently coexist and are both important risk factors for cardiovascular disease. However, the pathophysiological role of obesity without MetS, also referred to as metabolically healthy obesity (MHO), remains unclear. In this study, we aim to clarify the effect of MHO on the development of carotid plaque using a community-based cohort.

Methods: We examined 1,241 subjects who underwent health checkups at our institute. Obesity was defined as body mass index of ≥ 25.0 kg/m^2. Subjects were divided into three groups: non-obese, MHO, and metabolically unhealthy obesity (MUO).

Results: The prevalence of carotid plaque, defined as intima-media thickness (IMT) ≥ 1.1 mm, was higher in subjects with MUO and MHO than in non-obese subjects. Multivariable analysis demonstrated that MHO (odds ratio 1.6, $p = 0.012$) and MUO (odds ratio 1.9, $p = 0.003$) as well as age of ≥ 65 years, male sex, hypertension, and diabetes mellitus were independently associated with carotid plaque formation. A similar trend was observed in each subgroup according to age and sex.

Conclusions: MHO increased the prevalence of carotid plaque when compared with non-obese subjects, suggesting the potential significance of MHO in the development of subsequent cardiovascular diseases.

Key words: Metabolically healthy obesity, Metabolic syndrome, Carotid plaque, Carotid intima-media thickness, Atherosclerosis

Introduction

Obesity is a common and independent risk factor for all-cause mortality[1-3]. More specifically, obesity is a major component of atherosclerosis in association with metabolic disorders, including metabolic syndrome (MetS), hypertension[4-6], diabetes mellitus[4, 6-9], and dyslipidemia[6], resulting in the development of various cardiovascular diseases (CVDs)[4], such as coronary artery disease[10-12], ischemic stroke[11, 13], and peripheral artery disease[14]. Alternatively, obese subjects without MetS are also present and are referred to as subjects with metabolically healthy obesity (MHO)[15]. However, most preceding studies regarding MHO have been limited to small cohorts, and there are no consistent criteria for MHO. Therefore, the effect of MHO on atherosclerosis in the general population remains unclear. In this study, we aim to clarify the clinical significance of MHO in the development of subclinical CVD evaluated by carotid plaque formation using a community-based cohort.
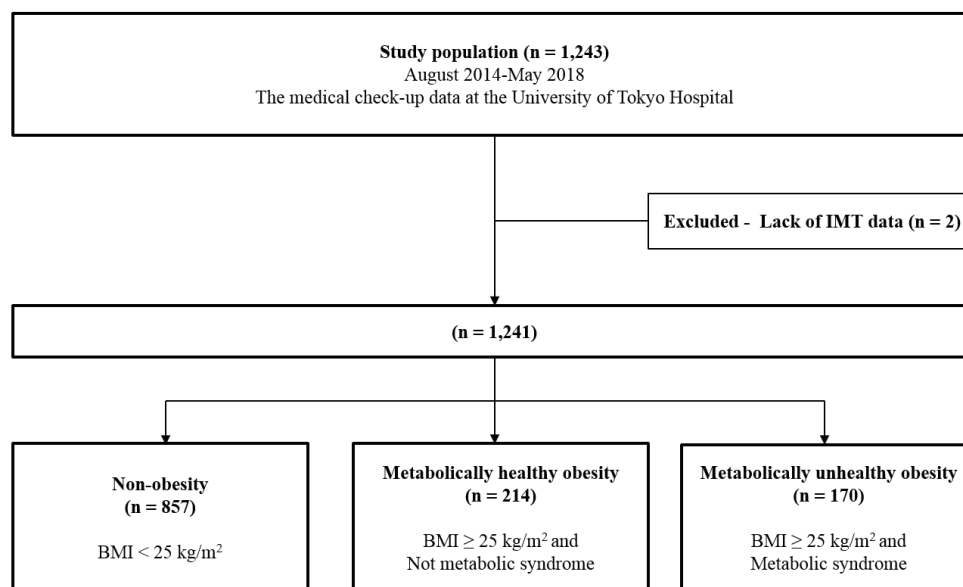
Fig. 1. Patient demographics

Among 1,243 subjects who underwent medical checkup at our institute, two subjects who lacked intima-media thickness data were excluded.

Methods

Study Population

We examined 1,243 subjects who underwent medical checkups at the University of Tokyo Hospital between August 2014 and May 2018 [16]. All subjects were at least 18 years old, and those who agreed to participate in this study were eligible. We excluded two subjects who lacked IMT data and included 1,241 subjects in this study. (Patient flowchart is shown in **Fig. 1**.)

Ethics

This study was approved by the Ethical Committee of the University of Tokyo (No. 2017-2424). This study was conducted in accordance with the Declaration of Helsinki.

Definiton

Obesity was defined as body mass index of ≥ 25.0 kg/m^2, according to the diagnostic criteria in Asian people[17, 18] and the guidlines of Japan Society for the Study of Obesity (JASSO:http://www.jasso.or.jp/contents/magazine/journal.html). Abdominal obesity, defined as waist circumstance at umbilical level ≥ 85 cm in men and ≥ 90 cm in women, was obligatory for diagnosis of MetS. In addition, any two of the following three anomalies should be observed for diagnosis of MetS: [1] high blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive medications; [2] hyperglycemia, fasting plasma glucose level ≥ 110 mg/dL, or use of insulin or oral antidiabetic medications; and [3] dyslipidemia, triglyceride level ≥ 150 mg/dL, HDL-C < 40 mg/dL, or use of lipid-lowering medications[19]. MHO was defined as obese subjects without MetS, whereas metabolically unhealthy obesity (MUO) was defined as obese subjects with MetS[15]. Hypertension was defined by blood pressure ≥ 140/90 mmHg or use of antihypertensive medications. Diabetes mellitus was defined by fasting glucose level ≥ 126 mg/dL or use of insulin or oral antidiabetic medications. Hypercholesterolemia was defined by total cholesterol level > 240 mg/dL or use of lipid-lowering medications.

Mesurement of Intima-Media Thickness (IMT) and Definition of Carotid Plaque

Images were obtained by multiple experts in carotid imaging using a Aplio 300 TUS-A300 or Xario SSA-660A ultrasound system (Toshiba Medical Systems, Otawara, Tochigi, Japan) equipped with a 7.5-MHz linear probe. Common carotid ultrasound examination was performed with the subjects in a supine position. Their necks were hyperextended and their heads were turned contralateral to the test side. The left common carotid arteries were visualized from a fixed lateral transducer angle. Bilateral measurement of the strain was performed from the images of the short axis of the common carotid artery at 1 cm infe-

rior to the carotid bulb. At least two consecutive beats were stored with a frame rate of 29–53 frames/s. Maximum IMT was defined as the distance between the leading edge of the luminal ultrasound and media/adventitia ultrasound. IMT of the common carotid artery was manually measured as the maximum thickness between the proximal and the common carotid bulb[20, 21]. We used the two right and left measurements on average to calculate IMT. Carotid plaque was defined as IMT ≥ 1.1 mm, as previously reported[22]. The reproducibility of the IMT was assessed using a similar technique that has already been previously reported[23-25].

Subgroup Analyses

The association between obesity category and carotid plaque formation was assessed in two subgroups according to age (< 65 and ≥ 65 years old) and sex.

Statistical Analyses

Categorical and consecutive data on the baseline clinical characteristics are presented as percentages (%) and mean ± standard deviation, respectively. Chi-square analysis was performed to compare categorical variables. Consecutive data were compared by one-way analysis of variance, whereas statistical significance of the difference was calculated using Tukey *t*-test. Univariate logistic regression analysis was used to identify the association between potential factors, including age, male gender, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, smoking, obesity category (non-obese, MHO, and MUO), and carotid plaque formation. Multivariable logistic regression analysis was performed to determine the independent predictors of carotid plaque formation. A probability value of < 0.05 was considered to indicate statistically significant difference. We performed statistical analysis using SPSS version 25 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Baseline demographics of study subjects are presented in **Table 1**. Among 1,241 subjects, 857 (69%) were categorized in the normal body weight group, whereas 214 (17%) were categorized as MHO and 170 (14%) were categorized as MUO. Subjects with obesity were more likely to be male, whereas those without obesity were older. Prevalence of classical cardiovascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, and cigarette smoking, was different in the three groups (non-obese, MHO, and MUO).

Prevalence of Carotid Plaque Formation

Fig. 2 shows the comparison of the prevalence of carotid plaque formation in the three groups. The prevalence increased in subjects with MHO subjects (41%) as compared with non-obese subjects (34%) and further increased in subjects with MUO (57%).

Determinants of Carotid Plaque Formation

Univariate logistic regression analysis showed that subjects with MHO [odds ratio (OR), 1.3; $p = 0.078$] as well as those with MUO (OR 2.6, $p < 0.001$) were associated with carotid plaque formation as compared with non-obese subjects (**Table 2**). Multivariable logistic regression analysis demonstrated that age, male gender, hypertension, diabetes mellitus, subjects with MHO (OR; 1.6, $p = 0.012$), and subjects with MUO (OR 1.9, $p = 0.003$) were independently associated with carotid plaque formation. There was no statistical difference in the risk of carotid plaque formation between subjects with MHO and MUO (**Table 2**).

Subgroup Analyses

The prevalence of carotid plaque formation was higher in subjects with MHO and MUO as compared with non-obese subjects having age < 65 years old or age ≥ 65 years old as well as in male non-obese subjects. A similar trend was also seen in the female subgroup (**Fig. 3**).

Discussion

The present study examines the general population who underwent health checkups at our institute, with a focus on the influence of MHO on IMT and carotid plaque formation. Three major findings were observed. First, obesity was observed in 31% of the general population, and 56% of the subjects with obesity were categorized as MHO. Second, the prevalence of carotid plaque formation was higher in subjects with MHO and MUO as compared with non-obese subjects. Third, the prevalence of carotid plaque was higher in subjects with MHO and MUO as compared with non-obese subjects, irrespective of age and sex.

Obesity is a worldwide pandemic public health problem[26, 27], and its prevalence is also increasing in Japan due to the westernized and industrialized lifestyle[28]. An excess of visceral adipose fat in subjects with obesity is known to be an important source of various molecules such as inflammatory cytokines inducing metabolic disorders. Therefore, obesity and MetS frequently coexist and accelerate the develop-

Table 1. Baseline clinical characteristics

Variable	Total	Non-obese (n = 857)	Metabolically healthy obesity (n = 214)	Metabolically unhealthy obesity (n = 170)	*P*-value
Demographics					
Age	62.6 ± 11.7	63.1 ± 11.7	61.0 ± 11.7	62.5 ± 11.7	0.067
Age ≥ 65 years old	598 (48.2%)	434 (50.6%)	83 (38.8%)	81 (47.6%)	0.008
Gender, Male	699 (56.3%)	421 (49.1%)	140 (65.4%)	138 (81.2%)	<0.001
Body mass index (kg/m²)	23.5 ± 3.6	21.7 ± 2.1	26.8 ± 1.8	28.6 ± 3.5	<0.001
Comorbidities					
Hypertension	449 (36.2%)	250 (29.2%)	63 (29.4%)	136 (80.0%)	<0.001
Diabetes mellitus	132 (10.6%)	70 (8.2%)	10 (4.7%)	52 (30.6%)	<0.001
Hypercholesterolemia	461 (37.1%)	322 (37.6%)	60 (28.0%)	79 (46.5%)	0.001
Coronary artery disease	32 (2.6%)	20 (2.3%)	3 (1.4%)	9 (5.3%)	0.041
Smoking	469 (37.8%)	299 (34.9%)	96 (44.9%)	74 (43.5%)	0.007
Metabolic syndrome	225 (18.1%)	55 (6.4%)	0 (0%)	170 (100%)	<0.001
Biochemistry					
Glucose (mg/dl)	100.0 ± 20.0	97.2 ± 16.7	98.4 ± 16.2	116.4 ± 29.7	<0.001
HbA1c (%)	5.9 ± 0.6	5.8 ± 0.5	5.8 ± 0.6	6.4 ± 0.9	<0.001
T-cholesterol (mg/dl)	205.1 ± 34.3	207.2 ± 34.2	207.3 ± 31.7	191.6 ± 35.1	<0.001
LDL-C (mg/dl)	124.1 ± 30.5	123.7 ± 30.5	131.9 ± 30.9	116.3 ± 29.6	<0.001
HDL-C (mg/dl)	65.4 ± 18.5	69.7 ± 18.7	58.7 ± 13.5	51.8 ± 13.4	<0.001
Triglyceride (mg/dl)	110.9 ± 80.0	99.1 ± 76.0	116.8 ± 67.9	163.1 ± 92.0	<0.001
Metabolic risk components					
Waist circumstance	478 (38.5%)	150 (17.5%)	158 (73.8%)	170 (100%)	<0.001
High blood pressure	574 (46.3%)	333 (38.9%)	89 (41.6%)	152 (89.4%)	<0.001
Hyperglycemia	222 (17.9%)	111 (13.0%)	15 (7.0%)	96 (56.5%)	<0.001
Dyslipidemia	477 (38.4%)	279 (32.6%)	59 (27.6%)	139 (81.8%)	<0.001
Number of metabolic risks components					
0	423 (34.1%)	355 (41.4%)	68 (31.8%)	0 (0%)	<0.001
1	452 (36.4%)	321 (37.5%)	131 (61.2%)	0 (0%)	
2	277 (22.3%)	141 (16.5%)	13 (6.1%)	123 (72.4%)	
3	89 (7.2%)	40 (4.7%)	2 (0.9%)	47 (27.6%)	

Data are expressed as mean ± standard deviation, or percentage (number).
LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
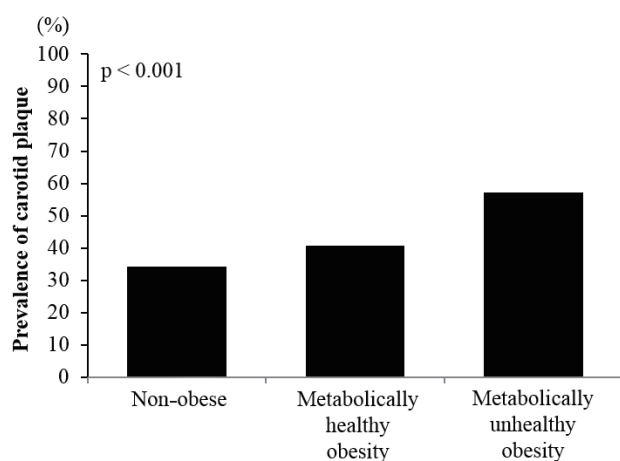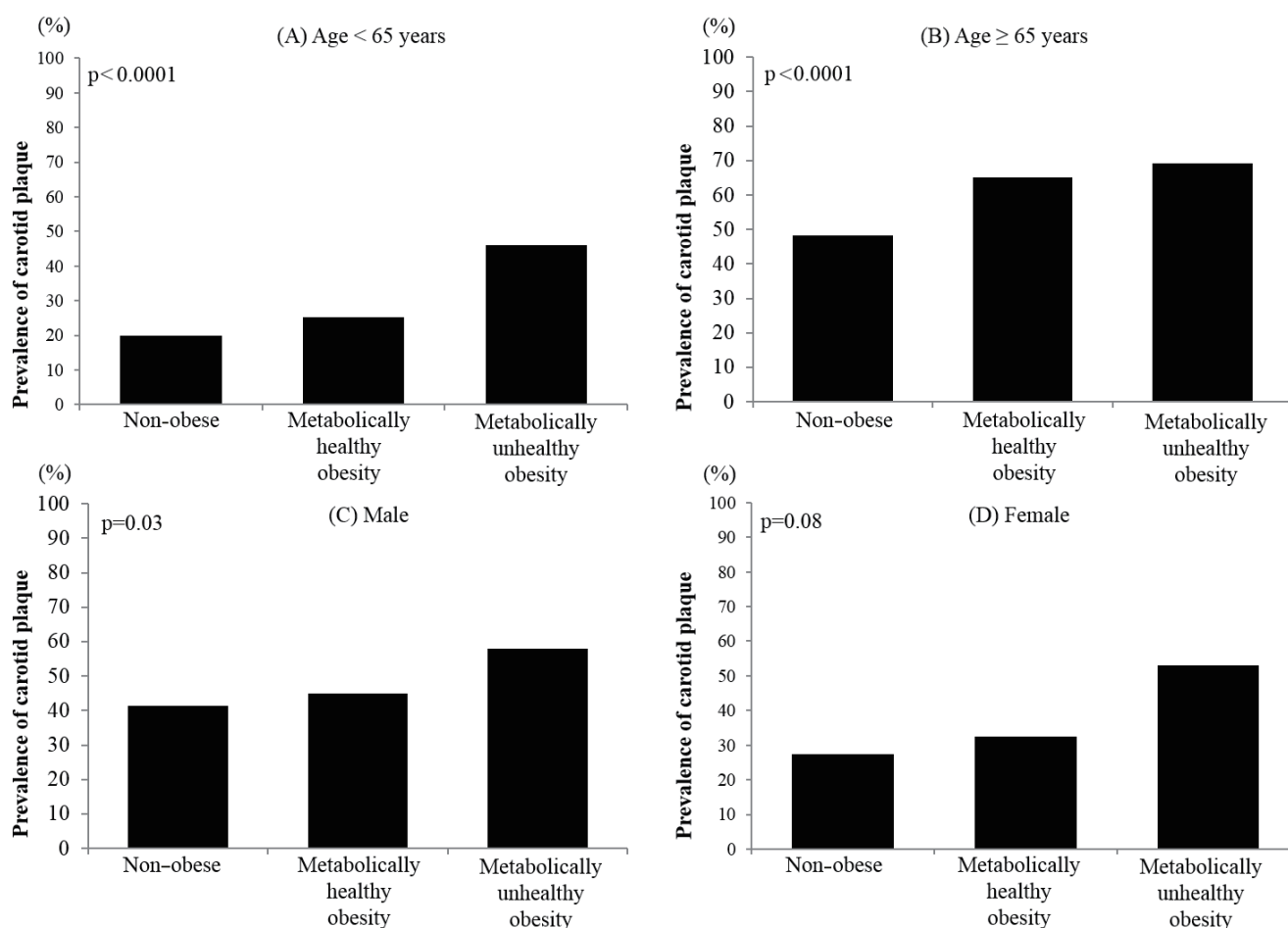

Fig. 2. Prevalence of carotid plaque

The prevalence of carotid plaque formation was higher in subjects with obesity (both metabolically healthy and metabolically unhealthy) than in non-obese subjects

Table 2. Determinants of carotid plaque

Variables	Univariate Analysis		Multivariable Analysis	
	P-value	OR (95% CI)	*P*-value	OR (95% CI)
Age	<0.001	1.084 (1.070 - 1.097)	<0.001	1.088 (1.073 - 1.103)
Gender, Male	<0.001	1.981 (1.563 - 2.511)	<0.001	2.325 (1.718 - 3.147)
Hypertension	<0.001	2.649 (2.085 - 3.367)	0.001	1.640 (1.236 - 2.178)
Diabetes mellitus	<0.001	3.074 (2.115 - 4.468)	0.047	1.540 (1.005 - 2.361)
Hypercholesterolemia	0.002	1.453 (1.148 - 1.839)	0.397	1.124 (0.857 - 1.475)
Coronary artery disease	0.088	1.845 (0.913 - 3.731)	0.841	0.922 (0.415 - 2.047)
Smoking	0.742	1.040 (0.822 - 1.317)	0.495	0.902 (0.671 - 1.213)
Stage				
Non-obese		Reference		Reference
MHO	0.078	1.319 (0.970 - 1.793)	0.012	1.564 (1.102 - 2.222)
MUO	<0.001	2.558 (1.830 - 3.575)	0.003	1.857 (1.226 - 2.811)

OR, odds ratio; CI, confidence interval, MHO, Metabolically healthy obesity, MUO, Metabolically unhealthy obesity

Fig. 3. Prevalence of carotid plaque in subjects with age <65 years (A), ≥ 65 years (B), male sex (C), and female sex (D)

The prevalence of carotid plaque formation was significantly higher in subjects with obesity (both metabolically healthy and metabolically unhealthy) than in non-obese subjects in subgroups of age <65 years (A), age ≥ 65 years (B), and male sex (C). A similar trend was observed in the female subgroup (D)

ment of subsequent CVD. However, recent studies have identified a phenotype, i.e., so-called MHO, which has a low burden of metabolic disorders[29, 30]. This phenotype attracts clinical interests, particularly regarding its impact on subclinical CVD.

IMT is an established marker for subclinical CVD in the general population and is a good predictor of subsequent CVD. According to preceding studies, obesity and MetS are associated with increased IMT and carotid plaque formation[31-34]. However, the relationship between MHO phenotype and the prevalence of carotid plaque has remained unknown. Therefore, we investigated whether the MHO phenotype is associated with increased carotid plaque formation in the general population.

Approximately one-third of our subjects were obese. This percentage is similar to that in preceding studies involving a general population[35-37]. Among subjects with obesity, more than half of the subjects were categorized as having MHO; therefore, MHO is not a rare condition in the general population. IMT was significantly different between non-obese, MHO, and MUO groups (**Supplementary Fig. 1**). Similar to IMT, the prevalence of carotid plaque formation was also higher in subjects with obesity. Multivariable analysis presented that MHO and MUO were independently associated with higher prevalence of carotid plaque, suggesting that obesity induced subclinical CVD regardless of the presence of MetS and that obesity itself should be the prevention target for future CVD events.

In contrast, the importance of metabolic disorders in subjects with obesity based on the results of this study cannot be denied. We defined MHO as obese subjects without MetS. Therefore, 68% of subjects with MHO had at least one component that met the criteria of MetS. Given that each component included in the definition of MetS, such as high blood pressure, hyperglycemia, and dyslipidemia, can induce atherosclerosis, metabolic disorders of subjects categorized as having MHO might weaken the potential difference in IMT between subjects with MHO and MUO. In fact, subjects with MUO tended to have a higher prevalence of carotid plaque formation. Although the difference did not reach a statistically significant value, this may be attributed to the limited sample size. Further studies with larger sample size are warranted to clarify this point.

Subgroup analysis showed the effect of MHO in each subgroup according to age and sex. In particular, presence of MHO increased the prevalence of carotid plaque formation as compared with non-obese subjects, even in subgroups with younger age or female sex, who are supposed to be at low risk of CVD.

Therefore, the risk of MHO in the general population with relatively low CVD risk should not be underestimated.

The present study has several limitations. First, the presented data are from a single-center experience; therefore, the present findings may not be simply generalized. The statistical power might not be sufficient for any statistically nonsignificant data to be conclusive because of the limited sample size. Although multivariable regression analysis was performed, unmeasured confounders may have influenced the results. Second, MHO is a novel concept and its definition has not yet established. In this study, we defined MHO as obesity without MetS. However, there are various definitions of MHO given in preceding studies[38-40]. Although detailed analysis is not available due to the limited sample size, the effect of obesity on the percentage of carotid plaque formation can differ according to the number subjects with metabolic disorders. Therefore, further study is required to establish the optimal definition of MHO. Third, among non-obese subjects, MetS was observed in 55 subjects (6.4%). Because of the small sample size, the significance of this subset could not be analyzed. Fourth, the effect of medication was not assessed in detail, particularly the type of lipid-lowering medications used. Fifth, detailed information regarding alcohol drinking status, which can influence the results, is not available. Finally, we did not perform multivariable analysis for IMT. Therefore, we cannot conclude that IMT was independently higher in subjects with MHO and MUO than in non-obese subjects.

Conclusion

The prevalence of carotid plaque is higher in both subjects with MHO and MUO as compared with non-obese subjects in the general population. Regardless of the presence of MetS, we need to consider obesity as a high-risk factor for subsequent CVD.

Acknowledgments

Funding Source

Conflict of Interest

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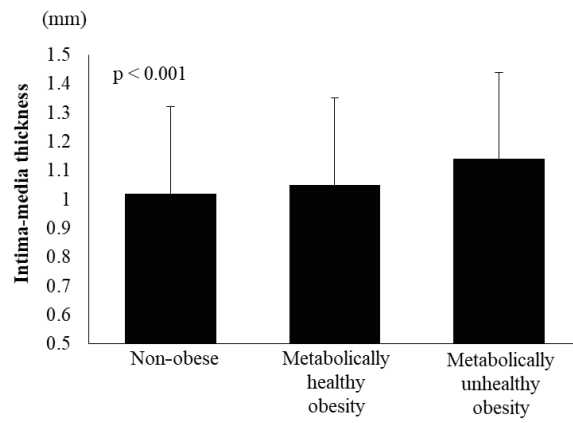
Supplementary Fig. 1. Intima-media thickness