Original Article

Coffee and Metabolic Phenotypes: A Cross-sectional Analysis of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

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Abbreviations

MetS	Metabolic syndrome
BMI	Body mass index
CVD	Cardiovascular disease
MHNW	Metabolically healthy normal weight
MUNW	Metabolically unhealthy normal weight
MHO	Metabolically healthy obesity
MUHO	Metabolically unhealthy obesity
METs	Metabolic equivalents
HDL	High-density lipoprotein

Abstract (235 words/250 words)

Background and Aims

To date, the relationship between coffee consumption and metabolic phenotypes has hardly been investigated and remains controversial. Therefore, the aim of this cross-sectional study is to examine the associations between coffee consumption and metabolic phenotypes in a Japanese population.

Methods and Results

We analyzed the data of 26363 subjects (aged 35-69 years) in the baseline survey of the Japan Multi-Institutional Collaborative Cohort Study. Coffee consumption was assessed using a questionnaire. Metabolic Syndrome (MetS) was defined according to the Joint Interim Statement Criteria of 2009, using body mass index (BMI) instead of waist circumference. Subjects stratified by the presence or absence of obesity (normal weight: BMI < 25 kg/m^2; obesity: BMI ≥ 25 kg/m^2) were classified by the number of MetS components (metabolically healthy: no components; metabolically unhealthy: one or more components) other than BMI.

In multiple logistic regression analyses adjusted for sex, age, and other potential confounders, high coffee consumption (≥3 cups/day) was associated with a lower prevalence of MetS and metabolically unhealthy phenotypes both in normal weight (OR 0.83, 95% CI 0.76-0.90) and obese subjects (OR 0.83, 95% CI 0.69-0.99). Filtered/instant coffee consumption was inversely associated with the prevalence of MetS and metabolically unhealthy phenotypes, whereas canned/bottled/packed coffee consumption was not.

Conclusion

The present results suggest that high coffee consumption, particularly filtered/instant coffee, is inversely associated with the prevalence of metabolically unhealthy phenotypes in both normal weight and obese Japanese adults.

Introduction

Metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors that include visceral obesity, elevated serum triglyceride levels, low serum levels of high-density lipoprotein (HDL) cholesterol, high blood pressure, and elevated blood glucose levels [1]. To date, a number of studies have been performed on the relationships between various lifestyle habits and MetS, such as diet, physical activity, and sleep duration [2-5]. A similar concept to MetS, metabolic phenotypes, which are classified according to the number of MetS components in subjects stratified by the presence or absence of obesity, have attracted attention [6]. Although there is currently no consensus on the definition of metabolic phenotypes, the risks of various diseases have been suggested to differ among these phenotypes [7-11]. Previous studies showed that the risk of the occurrence and mortality from cardiovascular disease (CVD) was higher in subjects with a metabolically unhealthy normal weight (MUNW) than in those with a metabolically healthy normal weight (MHNW) [7]. Moreover, metabolically healthy obese (MHO) subjects were suggested to have a higher risk of CVD, diabetes, and respiratory diseases than MHNW subjects, but a lower risk than metabolically unhealthy obese (MUHO) subjects [9]. Other than that, the risk of chronic kidney disease and site-specific cancers may be different among metabolic phenotypes [10, 11]. Moreover, weight gain generally may cause metabolic abnormalities; however, it is suggested that lower BMI rather leads to worsening of the condition in normal weight subjects with metabolic abnormalities [12, 13]. Therefore, it is said that MUNW and MUO may be different in the pathogenesis including genetic background [13]. Similar to

MetS, evidence is emerging to suggest relationships between various lifestyle factors, such as dietary patterns or physical activity, and metabolic phenotypes [14, 15]. These findings will contribute to the development of strategies that prevent and manage metabolically unhealthy phenotypes; however, the amount of evidence is limited.

Coffee is one of the most popular beverages in the world. In Japan, average coffee consumption per week by each person was 11.53 cups in 2020 [16]. The findings of meta-analyses [17, 18] support the inverse association between coffee consumption and MetS, particularly in general populations in a number of countries, including Japan [19-22], even though there is no evidence of causality in Mendelian randomization studies with genetic variants related to coffee consumption [23-26]. On the other hand, associations have been reported between coffee consumption and metabolic phenotypes [27, 28]; however, they remain controversial. Therefore, the aim of the present study was to investigate the relationships between coffee consumption and metabolic phenotypes in a Japanese population.

Methods

Study subjects

This cross-sectional study included female and male Japanese subjects aged 35 to 69 years who had participated in the baseline survey of the Japan Multi-Institutional Collaborative Cohort (J-MICC) study (Version 09.01.2021 data set). Subjects from 7 out of 14 research sites (Okazaki, Shizuoka, Takashima, Kyoto, Kagoshima, Tokushima, and Shizuoka-Sakuragaoka), who answered the same questionnaires and underwent the blood examination needed to diagnose MetS, were included. Among

33936 subjects, we excluded those with a self-reported history of ischemic heart disease (n = 879), stroke (n = 587), cancer (n = 1398), diabetes or the use of hypoglycemic agents (n = 2027), or missing information on these diseases (n = 1041). A total of 5374 subjects were excluded in this phase. We also excluded subjects with missing values for items on smoking and drinking habits, physical activity, coffee consumption, or education level in the questionnaire (n = 1828) or whose total energy intake was extremely high or low (≥4000 or <1000 kcal/day) (n = 371). Therefore, 26363 subjects were included in the analysis (Figure 1).

The J-MICC study is one of the largest cohort studies in Japan and was launched in 2005 to detect and confirm gene-environment interactions in lifestyle-related diseases. The details of this cohort were described in previous studies [29-31]. Written informed consent was obtained from each subject and the study protocol was approved by the Institutional Review Boards of the Aichi Cancer Center Research Institute (the affiliation of the present principal investigator Keitaro Matsuo) (IRB No. 2021-0-252), the Nagoya University Graduate School of Medicine (the affiliation of the former principal investigator Kenji Wakai) (IRB No. 2010-0939-8), Tokushima University Hospital (IRB No. 466-8) and each participating institution.

Questionnaire

Each study participant was asked to fill out a self-administered questionnaire on disease history, physical activity, education level, frequency of the intake of foods and beverages, and smoking and drinking habits. Trained staff verified the data obtained. A validated food-frequency questionnaire,

which was developed by the Nagoya City University Graduate School of Medical Sciences, included items on the intake frequency of 47 foods and beverages during the previous year [32-34]. The daily total energy intake was calculated using an original program developed by the Department of Public Health, Nagoya City University School of Medicine. There were two items on coffee consumption, which consisted of (i) filtered or instant coffee consumption and (ii) canned, bottled, or packed coffee consumption. The amount of consumption for each item was divided into seven categories: rarely, 2 cups or less/week, 3-4 cups/week, 5-6 cups/week, 1-2 cups/day, 3-4 cups/day, and 5 cups or more/day. In the present study, these seven categories were signified by 0, 1, 3.5, 5.5, 10.5, 24.5, and 35 cups/week, respectively, and the amount of total coffee consumption was calculated by adding the amount of the two items together, as described in a previous study [19]. The questionnaire on smoking and drinking habits had three categories each: non-, ex-, and current smokers and non-, ex-, and current drinkers (≥once a month). Physical activity was estimated with a self-administered questionnaire, similar to the short format of the International Physical Activity Questionnaire [35]. Total physical activity levels were estimated by multiplying the frequency (five categories from none to ≥5 times/week) and average duration (six categories from ≤30 min to ≥4 h) of light intensity exercises (e.g., walking, golf) at 3.4 metabolic equivalents (METs), moderate intensity exercises (e.g., jogging, swimming) at 7.0 METs, and vigorous intensity exercises (e.g., marathon running) at 10.0 METs. The MET hours/week of the three levels of exercises during leisure time was summed. Information on the educational background of subjects was obtained and education levels were classified into four

categories: ≤9 years, 10-15 years, ≥16 years, and others (i.e., subjects who have received some education, but are unsure how long they have been educated).

Anthropometric and biochemical measurements

Anthropometric and biochemical measurements were performed in each study center according to standardized protocols. Height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured with shoes off. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Systolic and diastolic blood pressure (mmHg) were measured while subjects were sitting at rest. Serum triglyceride, HDL cholesterol, and plasma glucose levels (mg/dL) were measured with overnight fasting venous blood.

Classification of MetS and Metabolic Phenotypes

The Joint Interim Statement Criteria of 2009 [36] were used as the criteria of MetS in the present study. Since waist circumference was not measured in all subjects, BMI was used. Previous studies reported a correlation between BMI and waist circumference and the BMI cut-off point as a replacement for waist circumference for the diagnosis of MetS for Asians (90 cm for men and 80 cm for women) is approximately 25 kg/m^2 [36, 37]. Subjects with three or more of the following five components were diagnosed as having MetS: (i) Obesity: BMI ≥25 kg/m^2; (ii) Elevated triglycerides: serum triglyceride level ≥150 mg/dL; (iii) Low HDL cholesterol: HDL cholesterol level <40 mg/dL in men or <50 mg/dL in women; (iv) High blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment for hypertension; and (v) Elevated blood glucose: fasting plasma glucose level

≥100 mg/dL. Metabolic phenotypes were classified as previously reported [38]. Subjects were stratified according to BMI and divided into those with a normal weight (BMI <25 kg/m^2) and those who were obese (BMI ≥25 kg/m^2). Normal weight subjects were classified as MHNW (no MetS components) or MUNW (≥1 MetS component). Obese subjects were classified as MHO (no components of MetS other than BMI) or metabolically unhealthy obesity (MUO: 1 MetS component other than BMI). Sensitivity analyses were also performed by changing the cut-off from one to two or three components in normal weight subjects and to two components other than BMI in obese subjects.

Statistical Analysis

Regarding subject characteristics, the Wilcoxon rank-sum test was applied to continuous variables and the chi-square test to categorical variables. The amount of coffee consumed was re-classified into 3 categories: <1.5 cup/day; ≥1.5 and <3 cups/day; ≥3 cups/day. Multivariable logistic regression analyses were performed to assess the associations between coffee consumption and MetS, metabolic phenotypes, and components of MetS. Model 1 was adjusted for age (continuous), sex (two categories), and the research site (seven categories); model 2 was additionally adjusted for total energy intake (quartiles), physical activity (quartiles), education level (four categories: ≤9 years; >10 and <15 years; ≥16 years; Others), and smoking (three categories: Current; Ex; Non) and drinking (three categories: Current; Ex; Non) habits. Model 3 was adjusted for model 2 plus BMI (quartiles). The first category of coffee consumption was used as a reference to estimate odds ratios (OR) and their profile likelihood 95% confidence intervals (CI). Tests for trends were performed by introducing ordinal categorical

variables with assigning consecutive numbers 1, 2, 3 to the levels of the variables in each statistical model and using a likelihood ratio test. The methodology for the mediation analysis was previously reported [39, 40]. In brief, mediation analyses were conducted to clarify the associations between coffee consumption (ordinal categorical variables: 1 to 3) and metabolically unhealthy phenotypes or MetS components into direct and indirect associations mediated by BMI (continuous). We estimated direct and indirect associations by combining two models: a linear regression model for the mediator (BMI) conditional on exposure (coffee consumption) and covariates (age, sex, research site, total energy intake, physical activity, education level, and smoking and drinking habits) and a logistic regression model for metabolically unhealthy phenotypes or MetS components conditional on exposure, the mediator, and covariates. The Wilcoxon rank-sum test, chi-squared test, and multivariable logistic regression analyses were performed using FREQ, LOGISTIC and other procedures of SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA.). Mediation analyses were performed using the Paramed command of Stata version 17 (Stata Corp LLC, TX, USA.). The level of significance was set at $P < 0.05$.

Results

Table 1 shows the characteristics of subjects stratified according to obesity. Among 26363 subjects, 20129 were in the normal weight group and 6234 were in the obesity group. Obese subjects were more likely to be male, current or ex-smokers, current drinkers, have more severe metabolic abnormalities (higher blood pressure, higher triglyceride levels, lower HDL cholesterol levels, and higher fasting plasma glucose levels), less physical activity, less coffee consumption, a lower education level, and consume more total energy. Moreover, the prevalence of obese subjects significantly differed among research sites.

Table 2 shows the associations between coffee consumption and the prevalence of MetS and its components. In models 1 and 2, greater coffee consumption was associated with reduced OR of MetS (≥3 cups/day, OR for model 2 0.79, 95% CI 0.72-0.87, *p* for trend < 0.001), elevated serum triglyceride levels, high blood pressure, and elevated blood glucose levels. Regarding obesity and low HDL cholesterol, an inverse correlation was only observed for moderate coffee consumption.

The results of stratified analyses according to BMI are shown in Tables 3 and 4. Greater coffee consumption was inversely associated with elevated triglyceride levels, high blood pressure, and elevated blood glucose levels in normal weight subjects and was also inversely associated with low HDL cholesterol in addition to these parameters in obese subjects (Table 3). Furthermore, greater coffee consumption was associated with a lower prevalence of metabolically unhealthy phenotypes (MUNW in normal weight subjects and MUO in obese subjects) both in normal weight and obese

subjects (≥3 cups/day, OR for model 2 0.83, 95% CI 0.76-0.90, *p* for trend <0.001, OR for model 2 0.83, 95% CI 0.69-0.99, *p* for trend 0.050, respectively) (Table 4). In sensitivity analyses, which were performed by changing the number of components used as the cut-off value for metabolically unhealthy phenotypes, OR for metabolically unhealthy phenotypes decreased as the number of components increased both in normal weight (≥3 cups/day, No. of components ≥3: OR for model 2 0.61, 95% CI 0.50-0.75, *p* for trend < 0.001) and obese subjects (≥3 cups/day, No. of components ≥2: OR for model 2 0.75, 95% CI 0.65-0.86, *p* for trend < 0.001) (Table 4). After adjustments for BMI, similar results were obtained (Table 3, 4). In mediation analyses, direct and total associations were observed between coffee consumption and a lower prevalence of metabolically unhealthy phenotypes other than MUO (No. of components ≥1) (Supplementary Table 1). MetS components other than low HDL cholesterol levels in normal weight subjects and other than high blood pressure and elevated blood glucose levels in obese subjects also showed direct and total associations with coffee consumption (Supplementary Table 2). Moreover, indirect associations were noted between coffee consumption and metabolically unhealthy phenotypes in the sensitivity analysis or between coffee consumption and MetS components in normal weight and obese subjects (Supplementary Tables 1, 2).

Table 5 shows differences in the associations between coffee consumption and MetS or metabolic phenotypes depending on the types of coffee. In the present study, the types of coffee were divided into two categories, (i) filtered or instant coffee and (ii) canned, bottled, or packed coffee. Filtered or instant coffee consumption was associated with a lower prevalence of MetS or metabolic

phenotypes both in normal weight and obese subjects other than MUO (No. of components ≥1), even if the cut-off value was changed. On the other hand, apart from an association between moderate consumption with MUO (No. of components ≥2), canned, bottled, or packed coffee consumption was not associated with MetS or metabolically unhealthy phenotypes.

Discussion

In the present study, high coffee consumption was inversely associated with MetS and metabolically unhealthy phenotypes both in normal weight and obese subjects. To the best of our knowledge, there have only been two studies on the associations between coffee consumption and metabolically unhealthy phenotypes, while a few studies reported an inverse association between coffee consumption and MetS [18-22]. A prospective study on an Iranian urban population (n = 1114) demonstrated that coffee/tea consumption was inversely associated with metabolically unhealthy phenotypes both in normal weight and obese subjects [27]. However, they did not separate coffee and tea as an exposure variable. A cross-sectional study in the U.S. using data from the National Health and Nutrition Examination Survey (n = 2201) showed no associations between coffee consumption and metabolically unhealthy phenotypes [28]. The difference in ethnicity between the U.S. and Japan could be considered as a possible reason for this discrepancy; however, the true reason is unclear. Although the associations between some dietary patterns, including coffee, and metabolically unhealthy phenotypes has been examined, no correlations were reported [15, 41, 42]. Despite these findings, the present study appears to be the first to show inverse associations between coffee consumption itself and metabolically unhealthy phenotypes.

In the present study, despite stratification by BMI, inverse associations were observed between coffee consumption and several MetS components in normal weight and obese subjects. Moreover, adjustments for BMI did not affect the results obtained (Tables 3 and 4). Therefore, inverse associations

between coffee consumption and the prevalence of MetS components other than obesity did not appear to be strongly mediated by a decrease in BMI. This is also supported by the results of mediation analyses showing that total associations between coffee consumption and metabolically unhealthy phenotypes were mostly attributed to direct, not indirect, associations mediated by BMI (Supplementary Table 1). In this analysis, an inverse indirect association in obese subjects, while a positive indirect association in normal weight subjects were also observed (Supplementary Table 1). However, the effects were rather small as judged by the ORs, and the statistically significant results may be because of large sample size.

Although the biological mechanisms by which coffee consumption affects MetS components appear to be complicated, a number of mechanisms have been suggested [43]. For example, different components of coffee, such as caffeine and chlorogenic acid (CGA), may play an important role in attenuating glucose absorption and improving insulin sensitivity [44, 45]. The antioxidant effects of CGA metabolites may reduce blood pressure by improving endothelial function and enhancing nitric oxide bioavailability in the arterial vasculature [46]. Moreover, CGA and caffeine have been shown to increase fatty acid β-oxidation [47]. Magnesium, which is abundant in coffee [48], has also been reported to exert protective effects against hypertension, lipid profile abnormalities, and insulin resistance by increasing blood antioxidant concentrations [49-51]. Furthermore, in a metabolomics study, coffee consumption was associated with decreased triglyceride levels and elevated cholesteryl ester levels, which are mainly formed on HDL, during the transportation process of excess cholesterol

to the liver [52, 53].

Regarding low HDL cholesterol, an inverse association with coffee consumption was only found in the obese group (Table 3). Moreover, in the results of the mediation analysis, the inverse association between coffee consumption and low HDL cholesterol appeared to be attributed to a direct association, which was not mediated by BMI, in obese subjects (Supplementary Table 2). Regarding differences in characteristics between normal weight and obese subjects, body fat distribution has been shown to differ [54]. MUO subjects are characterized by an excess visceral fat mass and an elevated liver fat content, while MUNW subjects are characterized by a reduced leg fat mass, which may serve as a healthy sink to store excess fat [13]. Therefore, the effects of coffee components on lipid metabolism in the liver may be more pronounced in MUO subjects with excess liver fat than in MUNW subjects.

In the present study, filtered or instant coffee consumption was associated with a lower prevalence of metabolically unhealthy phenotypes in both normal weight and obese subjects in the sensitivity analysis other than MUO (cut-off: No. of components ≥1), while canned, bottled, or packed coffee consumption did not (Table 5). Some compounds, such as caffeine, CGA, and trigonelline, which have been reported to exert protective effects against metabolic abnormalities, may be lost during the manufacturing process of ready-to-drink coffee, such as canned and bottled coffee [55]. This may be one of the reasons why the consumption of filtered or instant coffee, but not canned, bottled, or packed coffee, showed inverse associations with metabolically unhealthy phenotypes in the present study (Table 5). However, further studies are needed to clarify the protective effects of different

types of coffee on metabolic abnormalities.

There are several limitations that need to be addressed. Since this was a cross-sectional study, the time sequence between exposure and outcomes is unknown. Moreover, we could not completely rule out the effect of confounding by residual and unmeasured variables as the same as other observational studies, even though various potential confounders were adjusted. Although it is known that randomized controlled trial is the most powerful method to deal with confounding, it is hard to conduct randomized controlled trials of long-term coffee consumption. This is because it requires substantial time and financial resources and it is difficult to exclude the effect of coffee consumption before the trial, since coffee is widely consumed. Furthermore, due to the lack of data on waist circumference, we used BMI to diagnose MetS; however, a strong correlation between waist circumference and BMI was previously reported in various ethnic groups, including the Japanese population (Pearson's correlation coefficients were 0.921 for Japanese men and 0.922 for Japanese women) [37, 56, 57]. We also did not obtain information on additives including sugar and creamers. Another limitation is that we did not distinguish between caffeinated and decaffeinated coffee using the questionnaire; however, the consumption of decaffeinated coffee is not common in Japan, as previously reported [19]. Moreover, since information on coffee consumption was based on self-reporting, a certain degree of misclassification may exist; however, this misclassification was presumably non-differential with the effect tending towards null results. In addition, since the present study was conducted on a Japanese population, our results may not be directly applied to populations

of different ethnicities.

In conclusion, the present results obtained from data of a large Japanese population suggest that the consumption of coffee, particularly filtered or instant coffee, is associated with a low prevalence of metabolically unhealthy phenotypes in both normal weight and obese Japanese adults. Further studies to examine the temporal relationships between coffee consumption and metabolically unhealthy phenotypes, such as a prospective analysis, are awaited.

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Author contributions

All authors contributed to the study design, data collection, and preparation of the manuscript and approved of the final version of the manuscript. TW and KA performed statistical analyses independently and confirmed that the results obtained were consistent. TW drafted the first version of the manuscript. KA, TVN, MI, SK, and the other authors critically revised the manuscript.

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Tables

Table 1. Characteristics of subjects according to the obesity classification

	Normal weight (BMI <25) (n = 20129)	Obesity (BMI ≥25) (n = 6234)	*P*-value
Age (years) [a]	53.8 (9.8)	53.9 (9.4)	0.65
Sex [b]			<0.001
Female	11082 (55.1)	2459 (39.4)	
Male	9047 (44.9)	3775 (60.6)	
BMI (kg/m^2) [c]	21.8 (20.2, 23.2)	26.7 (25.7, 28.3)	<0.001
Systolic blood pressure (mmHg) [a]	122.9 (17.6)	131.5 (17.2)	<0.001
Diastolic blood pressure (mmHg) [a]	75.4 (10.7)	81.3 (10.8)	<0.001
Triglycerides (mg/dl) [c]	85.0 (62.0, 122.0)	121.0 (87.0, 174.0)	<0.001
HDL cholesterol (mg/dl) [a]	67.5 (17.1)	56.6 (14.2)	<0.001
Fasting plasma glucose (mg/dl) [a]	93.7 (12.6)	99.2 (16.8)	<0.001
Total energy intake (kcal/day) [c]	1671.1 (1499.8, 1899.9)	1739.2 (1531.0, 1978.7)	<0.001
Leisure time physical activity (MET-hours/week) [c]	5.6 (0.4, 17.9)	5.1 (0.0, 17.9)	<0.001
Coffee consumption (cups/day) [b]			<0.001
<1.5	8430 (41.9)	2750 (44.1)	
1.5~3	7435 (36.9)	2056 (33.0)	
≥3	4264 (21.2)	1428 (22.9)	
Education level (years) [b]			<0.001
≤9	2170 (10.8)	901 (14.5)	
10~15	13019 (64.7)	3773 (60.5)	
≥16	4877 (24.2)	1540 (24.7)	
Others	63 (0.3)	20 (0.3)	
Smoking habit [b]			<0.001
Current	3208 (15.9)	1119 (18.0)	
Ex	4425 (22.0)	1740 (27.9)	
Non	12496 (62.1)	3375 (54.1)	
Drinking habit [b]			<0.001
Current	11496 (57.1)	3755 (60.2)	
Ex	294 (1.5)	93 (1.5)	
Non	8339 (41.4)	2386 (38.3)	
Research site [b]			<0.001
Okazaki	4249 (21.1)	1157 (18.6)	
Shizuoka	3310 (16.4)	949 (15.2)	
Takashima	1363 (6.8)	373 (6.0)	
Kyoto	3934 (19.5)	958 (15.4)	
Kagoshima	3516 (17.5)	1736 (27.9)	
Tokushima	764 (3.8)	279 (4.5)	
Shizuoka - Sakuragaoka	2993 (14.9)	782 (12.5)	

a) Mean(SD)
b) Number (%)
c) Median (25%, 75%)
BMI: Body mass index; HDL: High-density lipoprotein cholesterol; MET: Metabolic equivalents
The Wilcoxon rank-sum test for continuous variables
The chi-squared test for categorical variables

Table 2. Associations between coffee consumption and the prevalence of metabolic syndrome and its components

	Coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	≥3	*P* for trend
Metabolic syndrome (No. of components ≥3)				
No. of cases/subjects	1902/11180	1238/9491	755/5692	
Model 1 OR (95% CI)	1.00	0.82 (0.76 - 0.89)	0.81 (0.74 - 0.89)	<0.001
Model 2 OR (95% CI)	1.00	0.81 (0.75 - 0.88)	0.79 (0.72 - 0.87)	<0.001
Obesity				
No. of cases/subjects	2750/11180	2056/9491	1428/5692	
Model 1 OR (95% CI)	1.00	0.91 (0.85 - 0.97)	1.01 (0.94 - 1.10)	0.811
Model 2 OR (95% CI)	1.00	0.93 (0.86 - 0.99)	1.04 (0.96 - 1.12)	0.735
Elevated triglycerides				
No. of cases/subjects	2341/11180	1700/9491	1097/5692	
Model 1 OR (95% CI)	1.00	0.85 (0.79 - 0.92)	0.86 (0.79 - 0.94)	<0.001
Model 2 OR (95% CI)	1.00	0.81 (0.76 - 0.87)	0.76 (0.70 - 0.83)	<0.001
Low HDL cholesterol				
No. of cases/subjects	994/11180	700/9491	493/5692	
Model 1 OR (95% CI)	1.00	0.86 (0.78 - 0.95)	1.06 (0.94 - 1.19)	0.828
Model 2 OR (95% CI)	1.00	0.85 (0.76 - 0.94)	0.94 (0.83 - 1.06)	0.099
High blood pressure				
No. of cases/subjects	5453/11180	4216/9491	2200/5692	
Model 1 OR (95% CI)	1.00	0.91 (0.86 - 0.97)	0.81 (0.75 - 0.87)	<0.001
Model 2 OR (95% CI)	1.00	0.92 (0.87 - 0.98)	0.85 (0.79 - 0.91)	<0.001
Elevated blood glucose				
No. of cases/subjects	3246/11180	2312/9491	1320/5692	
Model 1 OR (95% CI)	1.00	0.93 (0.87 - 0.99)	0.87 (0.80 - 0.94)	<0.001
Model 2 OR (95% CI)	1.00	0.93 (0.87 - 0.99)	0.89 (0.82 - 0.96)	0.002

Model 1: Adjusted for age, sex, and the research site.
Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.
BMI: Body mass index; HDL: High-density lipoprotein cholesterol

Table 3. Associations between coffee consumption and components of metabolic syndrome in groups stratified by body mass index

normal weight (BMI <25) (n = 20129)	Coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	≥3	*P* for trend
Elevated triglycerides				
No. of cases/subjects	1378/8430	1014/7435	610/4264	
Model 1 OR (95% CI)	1.00	0.83 (0.76 - 0.91)	0.84 (0.75 - 0.93)	<0.001
Model 2 OR (95% CI)	1.00	0.79 (0.72 - 0.86)	0.74 (0.66 - 0.82)	<0.001
Model 3 OR (95% CI)	1.00	0.78 (0.71 - 0.86)	0.72 (0.64 - 0.80)	<0.001
Low HDL cholesterol				
No. of cases/subjects	549/8430	420/7435	278/4264	
Model 1 OR (95% CI)	1.00	0.92 (0.80 - 1.05)	1.15 (0.99 - 1.35)	0.192
Model 2 OR (95% CI)	1.00	0.90 (0.79 - 1.03)	1.01 (0.86 - 1.19)	0.820
Model 3 OR (95% CI)	1.00	0.90 (0.78 - 1.03)	0.99 (0.84 - 1.16)	0.609
High blood pressure				
No. of cases/subjects	3631/8430	2903/7435	1391/4264	
Model 1 OR (95% CI)	1.00	0.92 (0.86 - 0.98)	0.79 (0.73 - 0.86)	<0.001
Model 2 OR (95% CI)	1.00	0.92 (0.86 - 0.99)	0.83 (0.76 - 0.90)	<0.001
Model 3 OR (95% CI)	1.00	0.92 (0.85 - 0.98)	0.81 (0.75 - 0.89)	<0.001
Elevated blood glucose				
No. of cases/subjects	2099/8430	1564/7435	812/4264	
Model 1 OR (95% CI)	1.00	0.95 (0.88 - 1.03)	0.85 (0.77 - 0.94)	0.002
Model 2 OR (95% CI)	1.00	0.96 (0.88 - 1.04)	0.88 (0.79 - 0.97)	0.010
Model 3 OR (95% CI)	1.00	0.95 (0.88 - 1.03)	0.87 (0.78 - 0.96)	0.005
obesity (BMI ≥25) (n = 7246)	Coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	≥3	*P* for trend
Elevated triglycerides				
No. of cases/subjects	963/2750	686/2056	487/1428	
Model 1 OR (95% CI)	1.00	0.93 (0.82 - 1.05)	0.89 (0.77 - 1.02)	0.086
Model 2 OR (95% CI)	1.00	0.88 (0.77 - 1.00)	0.79 (0.68 - 0.92)	0.001
Model 3 OR (95% CI)	1.00	0.90 (0.79 - 1.02)	0.80 (0.69 - 0.92)	0.002
Low HDL cholesterol				
No. of cases/subjects	445/2750	280/2056	215/1428	
Model 1 OR (95% CI)	1.00	0.82 (0.70 - 0.97)	0.92 (0.76 - 1.10)	0.191
Model 2 OR (95% CI)	1.00	0.80 (0.67 - 0.94)	0.82 (0.68 - 0.99)	0.018
Model 3 OR (95% CI)	1.00	0.81 (0.68 - 0.96)	0.83 (0.69 - 1.00)	0.026
High blood pressure				
No. of cases/subjects	1822/2750	1313/2056	809/1428	
Model 1 OR (95% CI)	1.00	0.95 (0.84 - 1.08)	0.82 (0.71 - 0.95)	0.008
Model 2 OR (95% CI)	1.00	0.97 (0.85 - 1.11)	0.87 (0.75 - 1.00)	0.060
Model 3 OR (95% CI)	1.00	1.01 (0.89 - 1.15)	0.88 (0.76 - 1.02)	0.127
Elevated blood glucose				
No. of cases/subjects	1147/2750	748/2056	508/1428	
Model 1 OR (95% CI)	1.00	0.89 (0.79 - 1.01)	0.87 (0.76 - 1.01)	0.036
Model 2 OR (95% CI)	1.00	0.88 (0.78 - 1.00)	0.87 (0.75 - 1.00)	0.029
Model 3 OR (95% CI)	1.00	0.90 (0.80 - 1.02)	0.88 (0.76 - 1.01)	0.051

Model 1: Adjusted for age, sex, and the research site.
Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.
Model 3: Adjusted for model 2 plus BMI.
HDL: High-density lipoprotein cholesterol

Table 4. Associations between coffee consumption and metabolic phenotypes

	Coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	≥3	*P* for trend
MUNW (No. of components ≥1)				
No. of cases/subjects	5049/8430	4093/7435	2189/4264	
Model 1 OR (95% CI)	1.00	0.92 (0.86 - 0.99)	0.85 (0.78 - 0.92)	<0.001
Model 2 OR (95% CI)	1.00	0.91 (0.84 - 0.97)	0.83 (0.76 - 0.90)	<0.001
Model 3 OR (95% CI)	1.00	0.90 (0.84 - 0.97)	0.81 (0.74 - 0.88)	<0.001
MUNW (No. of components ≥2)				
No. of cases/subjects	2078/8430	1471/7435	752/4264	
Model 1 OR (95% CI)	1.00	0.85 (0.79 - 0.92)	0.79 (0.72 - 0.88)	<0.001
Model 2 OR (95% CI)	1.00	0.84 (0.77 - 0.91)	0.78 (0.71 - 0.86)	<0.001
Model 3 OR (95% CI)	1.00	0.83 (0.77 - 0.90)	0.76 (0.68 - 0.84)	<0.001
MUNW (No. of components ≥3)				
No. of cases/subjects	480/8430	299/7435	134/4264	
Model 1 OR (95% CI)	1.00	0.78 (0.67 - 0.91)	0.66 (0.53 - 0.80)	<0.001
Model 2 OR (95% CI)	1.00	0.76 (0.65 - 0.89)	0.61 (0.50 - 0.75)	<0.001
Model 3 OR (95% CI)	1.00	0.75 (0.65 - 0.88)	0.59 (0.48 - 0.73)	<0.001
MUO (No. of components ≥1)				
No. of cases/subjects	2358/2750	1730/2056	1155/1428	
Model 1 OR (95% CI)	1.00	0.96 (0.81 - 1.13)	0.84 (0.70 - 1.00)	0.057
Model 2 OR (95% CI)	1.00	0.96 (0.81 - 1.13)	0.83 (0.69 - 0.99)	0.050
Model 3 OR (95% CI)	1.00	1.00 (0.85 - 1.19)	0.85 (0.71 - 1.02)	0.114
MUO (No. of components ≥2)				
No. of cases/subjects	1422/2750	939/2056	621/1428	
Model 1 OR (95% CI)	1.00	0.84 (0.74 - 0.94)	0.79 (0.69 - 0.91)	<0.001
Model 2 OR (95% CI)	1.00	0.82 (0.72 - 0.92)	0.75 (0.65 - 0.86)	<0.001
Model 3 OR (95% CI)	1.00	0.85 (0.75 - 0.96)	0.76 (0.66 - 0.88)	<0.001

Model 1: Adjusted for age, sex, and the research site.
Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.
Model 3: Adjusted for model 2 plus BMI.

Table 5. Associations between the consumption of filtered or instant coffee and canned, bottled, or packed coffee and metabolic syndrome and its metabolic phenotypes

	Filtered or instant coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	≥3	*P* for trend
Metabolic syndrome (No. of components ≥3)				
No. of cases/subjects	2161/12586	1204/9650	530/4127	
Model 2 OR (95% CI)	1.00	0.78 (0.72 - 0.84)	0.83 (0.74 - 0.92)	<0.001
MUNW (No. of components ≥1)				
No. of cases/subjects	5632/9434	4120/7573	1579/3122	
Model 2 OR (95% CI)	1.00	0.89 (0.83 - 0.95)	0.82 (0.75 - 0.90)	<0.001
MUNW (No. of components ≥2)				
No. of cases/subjects	2307/9434	1479/7573	515/3122	
Model 2 OR (95% CI)	1.00	0.83 (0.77 - 0.90)	0.74 (0.66 - 0.83)	<0.001
MUNW (No. of components ≥3)				
No. of cases/subjects	534/9434	283/7573	96/3122	
Model 2 OR (95% CI)	1.00	0.71 (0.61 - 0.83)	0.62 (0.49 - 0.78)	<0.001
MUO (No. of components ≥1)				
No. of cases/subjects	2700/3152	1735/2077	808/1005	
Model 2 OR (95% CI)	1.00	0.92 (0.78 - 1.08)	0.83 (0.68 - 1.01)	0.054
MUO (No. of components ≥2)				
No. of cases/subjects	1627/3152	921/2077	434/1005	
Model 2 OR (95% CI)	1.00	0.78 (0.70 - 0.88)	0.79 (0.68 - 0.92)	<0.001
	Canned, bottled, or packed coffee consumption (cups/day)			
	<1.5	≥1.5 and <3	3	*P* for trend
Metabolic syndrome (No. of components ≥3)				
No. of cases/subjects	3397/23344	393/2421	105/598	
Model 2 OR (95% CI)	1.00	0.94 (0.83 - 1.06)	1.03 (0.82 - 1.28)	0.624
MUNW (No. of components ≥1)				
No. of cases/subjects	10126/17974	966/1731	239/424	
Model 2 OR (95% CI)	1.00	1.00 (0.89 - 1.12)	1.11 (0.90 - 1.37)	0.489
MUNW (No. of components ≥2)				
No. of cases/subjects	3832/17974	381/1731	88/424	
Model 2 OR (95% CI)	1.00	1.07 (0.94 - 1.22)	1.08 (0.83 - 1.38)	0.281
MUNW (No. of components ≥3)				
No. of cases/subjects	820/17974	78/1731	15/424	
Model 2 OR (95% CI)	1.00	0.98 (0.76 - 1.25)	0.79 (0.44 - 1.30)	0.468
MUO (No. of components ≥1)				
No. of cases/subjects	4528/5370	574/690	141/174	
Model 2 OR (95% CI)	1.00	0.95 (0.75 - 1.20)	0.81 (0.55 - 1.24)	0.332
MUO (No. of components ≥2)				
No. of cases/subjects	2577/5370	315/690	90/174	
Model 2 OR (95% CI)	1.00	0.83 (0.70 - 0.99)	1.06 (0.77 - 1.45)	0.278

Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.

Figure legend

Figure 1. A flowchart of the selection of study subjects

Supplementary Table 1. Direct and indirect associations mediated by BMI between coffee consumption and metabolic phenotypes

Coffee consumption (exposure)→BMI(M)→MUNW (No. of components ≥1) (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.90	0.86-0.94	<0.001
Indirect association	1.02	1.01-1.02	<0.001
Total association	0.91	0.87-0.95	<0.001

Coffee consumption (exposure)→BMI(M)→MUNW (No. of components ≥2) (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.86	0.82-0.90	<0.001
Indirect association	1.02	1.01-1.03	<0.001
Total association	0.88	0.83-0.92	<0.001

Coffee consumption (exposure)→BMI(M)→MUNW (No. of components ≥3) (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.76	0.69-0.85	<0.001
Indirect association	1.02	1.01-1.04	<0.001
Total association	0.78	0.70-0.87	<0.001

Coffee consumption (exposure)→BMI(M)→MUO (No. of components ≥1) (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.91	0.79-1.05	0.217
Indirect association	0.97	0.95-0.99	0.004
Total association	0.89	0.76-1.03	0.114

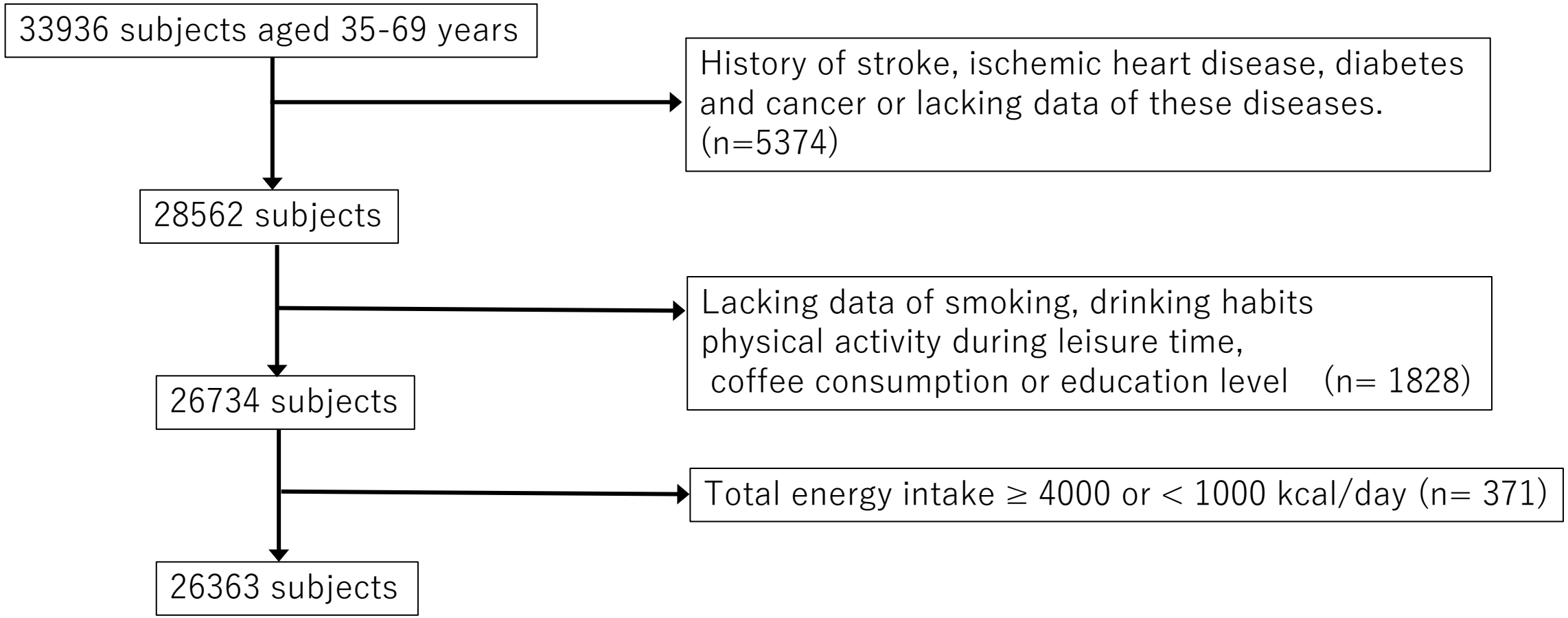
Coffee consumption (exposure)→BMI(M)→MUO (No. of components ≥2) (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.89	0.83-0.96	0.003
Indirect association	0.98	0.97-0.99	0.004
Total association	0.88	0.81-0.95	0.001

Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.
BMI: Body mass index

Supplementary Table 2. Direct and indirect associations mediated by BMI between coffee consumption and MetS components

normal weight			
Coffee consumption (exposure)→BMI(M)→Elevated triglycerides (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.83	0.79-0.88	<0.001
Indirect association	1.02	1.01-1.03	<0.001
Total association	0.85	0.80-0.90	<0.001
Coffee consumption (exposure)→BMI(M)→Low HDL cholesterol (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.97	0.89-1.06	0.540
Indirect association	1.02	1.01-1.02	0.001
Total association	0.99	0.91-1.08	0.793
Coffee consumption (exposure)→BMI(M)→High blood pressure (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.90	0.86-0.94	<0.001
Indirect association	1.01	1.01-1.02	<0.001
Total association	0.91	0.87-0.95	<0.001
Coffee consumption (exposure)→BMI(M)→Elevated blood glucose (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.93	0.89-0.98	0.005
Indirect association	1.01	1.00-1.02	0.001
Total association	0.94	0.90-0.99	0.016
obesity			
Coffee consumption (exposure)→BMI(M)→Elevated triglycerides (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.89	0.83-0.96	0.003
Indirect association	0.99	0.98-1.00	0.008
Total association	0.88	0.82-0.95	0.001
Coffee consumption (exposure)→BMI(M)→Low HDL cholesterol (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.90	0.82-0.99	0.037
Indirect association	0.99	0.99-1.00	0.030
Total association	0.90	0.82-0.99	0.026
Coffee consumption (exposure)→BMI(M)→High blood pressure (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.97	0.89-1.05	0.424
Indirect association	0.98	0.96-0.99	0.004
Total association	0.94	0.87-1.03	0.205
Coffee consumption (exposure)→BMI(M)→Elevated blood glucose (outcome)			
Model 2	OR	95% CI	P value
Direct association	0.94	0.88-1.01	0.101
Indirect association	0.99	0.98-1.00	0.007
Total association	0.93	0.86-1.00	0.053

Model 2: Adjusted for age, sex, the research site, total energy intake, physical activity, education level, and smoking and drinking habits.
BMI: Body mass index


33936 subjects aged 35-69 years
History of stroke, ischemic heart disease, diabetes and cancer or lacking data of these diseases. (n=5374)
28562 subjects
Lacking data of smoking, drinking habits physical activity during leisure time, coffee consumption or education level (n= 1828)
26734 subjects
Total energy intake ≥ 4000 or < 1000 kcal/day (n= 371)
26363 subjects