

ORIGINAL ARTICLE

Association of seasonal variation in the prevalence of metabolic syndrome with insulin resistance

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The aim of this study was to examine the hypothesis that seasonal variation in the prevalence of metabolic syndrome (MetS) is associated with increased insulin resistance. Among 840 Japanese male workers who were evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR) in June (summer) 2010, we prospectively studied a total of 758 subjects (40–65 years of age) who underwent an assessment in December (winter) 2010. MetS was defined according to the criteria proposed by the International Diabetes Federation (IDF) and the Japanese Society of Internal Medicine (JSIM). The median level of HOMA-IR in the study subjects was 0.84 (interquartile range: 0.60–1.19). The prevalence rates of IDF- and JSIM-MetS significantly increased from 12.4 and 9.6% in the summer to 16.6 and 13.3% in the winter, respectively (each $P < 0.05$). Our data suggest that these increases are mainly due to increases in blood pressure (BP) and glucose during the winter assessment. The prevalence rates of IDF-MetS in the first, second, third and fourth quartiles of HOMA-IR were 1.1, 5.8, 14.3 and 29.1% in the summer and 3.1, 10.6, 21.9, and 31.3% in the winter, respectively. Similar results were obtained when using the JSIM criteria. In the third quartile, the frequency of elevated BP increased from 42.4% in the summer to 61.2% in the winter ($P < 0.05$), and these values were mainly correlated with significant variations in IDF- and JSIM-MetS prevalence rates. This study demonstrates that seasonal variation in MetS prevalence is associated with mildly to moderately increased insulin resistance in middle-aged Japanese men.

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INTRODUCTION

Metabolic syndrome (MetS) is a possible cause of type 2 diabetes and atherosclerotic cardiovascular disease worldwide.^{1,2} MetS consists of atherogenic dyslipidemia, elevation in blood pressure (BP), and increased glucose concentration as well as a general prothrombotic and proinflammatory condition.³ MetS can be clinically diagnosed using several simple measurements including waist circumference (WC), triglyceride (TG) levels, high-density lipoprotein (HDL) cholesterol levels, BP and fasting glucose levels.^{4,5} Evidence suggests that these metabolic parameters can show seasonal variations, and these variations usually tend to be on the higher end during the fall and winter than in the spring and summer.^{6–10} Seasonal variations in these metabolic parameters could be partially driven by gene variation, lifestyle factors such as diet, physical activity and sleep duration, climate conditions such as air temperature and light exposure, and mood changes such as depressive symptoms.^{11–18} These findings indicate that seasonal variations in metabolic parameters may affect the assessment of MetS. A recent study demonstrated the seasonal variation of MetS prevalence in Japanese

men, but the underlying mechanisms involved with seasonal variation and the associated clinical implications remain unknown.¹⁹ Ample evidence suggests that increased insulin resistance is a pathophysiological basis for MetS. However, little is known about the relationship between seasonal variations in metabolic parameters and increased insulin resistance. Therefore, we hypothesized that seasonal variation in MetS prevalence is associated with increased insulin resistance. To test this hypothesis, we assessed Japanese workers using periodic health assessments.

METHODS

Study subjects

Among 969 male workers (40–65 years of age) who underwent a health checkup in June (summer) 2010, 840 subjects (86.7%) provided written informed consent to participate in this study and thus were evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR). After excluding subjects who did not undergo a health checkup in December (winter) 2010 ($n = 76$) and subjects who self-reported the use of antidiabetic drugs ($n = 6$), which could interfere with accurate evaluations

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using HOMA-IR, a total of 758 subjects (researchers, technical experts or clerks) were included in the study. At each checkup, demographic data and health information were collected using self-administered questionnaires. Smoking habits and alcohol intake were dichotomized as current smoker and/or drinker or not current smoker and/or drinker. All participants were subjected to a physical examination assessing height, weight, WC and BP. WC was taken as the circumference at the umbilicus using a flexible anthropometric tape, and resting BP was measured from a sitting position by trained technicians using a standard mercury sphygmomanometer. Venous blood samples were collected from each subject after fasting for 9 h or overnight. Using automated measurement devices, serum levels of TG (enzymatic method; Determiner C-TG, Kyowa Medex, Tokyo, Japan) and HDL cholesterol (direct method; Determiner L HDL-C, Kyowa Medex), and plasma glucose levels (hexokinase method; Quick auto II GLU-HK, Shino-test, Kanagawa, Japan) were measured.

This study was conducted in accordance with the principles expressed in the Declaration of Helsinki and was ethically approved by the institutional committee of the Nuclear Science Research Institute of the Tokai Research and Development Center at the Japan Atomic Energy Agency.

Definition of MetS

In this study, MetS was defined according to the criteria proposed by six major world organizations including the International Diabetes Federation (IDF) and the joint committee of eight Japanese medical societies including the Japanese Society of Internal Medicine (JSIM).^{4,5,20,21} The IDF criteria are as follows: subjects with three or more of the following components are considered to have IDF-MetS: (1) elevated WC defined as WC ≥ 85 cm according to the JSIM criteria; (2) elevated TG defined as TG ≥ 150 mg per 100 ml or self-reported consumption of lipid-lowering medications; (3) reduced HDL cholesterol defined as HDL cholesterol < 40 mg per 100 ml; (4) elevated BP defined as BP $\geq 130/85$ mmHg or self-reported consumption of antihypertensive drugs; (5) elevated glucose defined as having a fasting glucose level of ≥ 100 mg per 100 ml. The sole criterion for JSIM diagnosis is abdominal obesity defined as a WC of ≥ 85 cm. In addition, subjects with two or more of the following criteria are considered to have JSIM-MetS: (1) dyslipidemia defined as TG ≥ 150 mg per 100 ml, HDL cholesterol < 40 mg per 100 ml or self-reported consumption of lipid-lowering medications; (2) elevated BP defined as BP $\geq 130/85$ mmHg or self-reported consumption of antihypertensive drugs; (3) elevated glucose defined as having a fasting glucose level of ≥ 110 mg per 100 ml. In this study, subjects who met the criteria in the summer, winter and both seasons were defined as having summer-, winter- and summer-winter-MetS, respectively.

Evaluation of HOMA-IR

Fasting blood samples were transported to the same laboratory for analysis. Using an automated measurement device, the fasting insulin levels in the plasma of all subjects were measured by chemiluminescent immunoassay (ARCHITECT Insulin, Abbott Japan, Tokyo, Japan) in the summer 2010 checkup. In this assay, the interassay coefficients of variation were $< 7\%$, and the lower limit of detection was $1.0 \mu\text{IU ml}^{-1}$. HOMA-IR was calculated using the following equation: (fasting insulin ($\mu\text{IU ml}^{-1}$) \times fasting glucose (mg per 100 ml))/405. HOMA-IR has been well correlated with estimates derived from the euglycemic clamp test.^{22,23}

Statistical analysis

Continuous data are expressed as the median with the associated interquartile range (IQR) because the values do not display a normal distribution. All of the continuous data were log transformed to approximately normalize the distribution for the subsequent analyses. Categorical data are presented as absolute values and percentages. Comparisons of continuous variables were performed by using analysis of covariance with age as a covariate. Comparisons of categorical variables were evaluated using chi-squared tests. Analysis of variance (ANOVA) was used for multiple comparisons, and ANOVA tests were followed by the Tukey-Kramer *post hoc* test. *P*-values < 0.05 were considered to be statistically significant. Statistical analysis was performed using the JMP

Statistical Discovery Software for Windows version 8 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of study subjects

The characteristics of the study subjects ($n = 758$, median age 49 years (IQR: 44–55)) during the summer assessment are shown in Table 1. Some study participants were receiving medications for hyperlipidemia ($n = 55$, 7.3%) and hypertension ($n = 87$, 11.5%). Current smokers and drinkers comprised 23.2% ($n = 176$) and 46.0% ($n = 349$) of the study population, respectively. Of the clinical and demographic parameters shown in Table 1, systolic and diastolic BP showed significant seasonal variation. Systolic and diastolic BP levels increased from 126 mm Hg (IQR: 120–132 mm Hg) and 74 mm Hg (IQR: 70–80 mm Hg) in the summer to 130 mm Hg (IQR: 122–136 mm Hg) and 76 mm Hg (IQR: 72–82 mm Hg) in the winter, respectively (each $P < 0.05$).

Seasonal variations in MetS prevalence and components

All subjects were assessed for variables of MetS components during the summer and winter checkups. The seasonal variations in MetS prevalence and the associated metabolic parameters are listed in Table 2. The prevalence rates of IDF- and JSIM-MetS in this study

Table 1 Characteristics of study subjects

Characteristic	<i>n</i> = 758
Body mass index, kg m ⁻²	23.5 (21.7–25.3)
Total cholesterol, mg per 100 ml	215 (194–236)
LDL cholesterol, ^a mg per 100 ml	130 (112–150)
Waist circumference, cm	83.1 (78.4–88.0)
Triglyceride, mg per 100 ml	100 (73–145)
HDL cholesterol, mg per 100 ml	63 (54–75)
Systolic blood pressure, mm Hg	126 (120–132)
Diastolic blood pressure, mm Hg	74 (70–80)
Fasting glucose, mg per 100 ml	89 (84–94)
Lipid-lowering medication, <i>n</i> (%)	55 (7.3)
Antihypertensive medication, <i>n</i> (%)	87 (11.5)
Current smoking, <i>n</i> (%)	76 (23.2)
Current drinking, <i>n</i> (%)	349 (46.0)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are expressed as median with interquartile range (IQR), or number (%).^aLDL cholesterol levels were evaluated by a direct measurement.

Table 2 Seasonal variations in MetS prevalence and components

	Summer	Winter	<i>P</i> -value
IDF-MetS prevalence, %	12.4	16.6	< 0.05
JSIM-MetS prevalence, %	9.6	13.3	< 0.05
Elevated waist circumference, %	39.3	41.3	0.43
Elevated triglyceride, %	27.8	28.6	0.73
Reduced HDL cholesterol, %	3.0	2.0	0.19
Elevated blood pressure, %	42.6	54.4	< 0.05
Elevated glucose, %			
Fasting glucose ≥ 100 mg per 100 ml	11.0	14.6	< 0.05
Fasting glucose ≥ 110 mg per 100 ml	4.4	5.8	0.20
Dyslipidemia, %	28.4	29.4	0.65

Abbreviations: HDL, high-density lipoprotein; IDF, International Diabetes Federation; JSIM, Japanese Society of Internal Medicine; MetS, metabolic syndrome. All data are expressed as percentage.

significantly increased from 12.4% ($n=94$) and 9.6% ($n=73$) in the summer to 16.6% ($n=126$) and 13.3% ($n=101$) in the winter, respectively (each $P<0.05$). Although the frequencies of elevated WC, elevated TG, reduced HDL cholesterol, and elevated glucose defined as fasting glucose ≥ 110 mg per 100 ml and dyslipidemia were comparable between the two seasons ($P=0.43$, $P=0.73$, $P=0.19$, $P=0.20$, and $P=0.65$, respectively), the frequencies of elevated BP and elevated glucose defined as fasting glucose ≥ 100 mg per 100 ml significantly increased from 42.6% ($n=323$) and 11.0% ($n=83$) in the summer to 54.4% ($n=412$) and 14.6% ($n=111$) in the winter, respectively (each $P<0.05$). Notably, the frequency of elevated BP had a large impact on the seasonal variation of MetS prevalence in our study subjects.

HOMA-IR levels in subjects with summer-, winter- and summer-winter-MetS

The median levels of fasting insulin and HOMA-IR in the study subjects were $3.7 \mu\text{IU ml}^{-1}$ (IQR: $2.7\text{--}5.2 \mu\text{IU ml}^{-1}$) and 0.84 (IQR: $0.60\text{--}1.19$), respectively. Based on the IDF criteria, the median levels of HOMA-IR in subjects with summer- ($n=27$, 1.17 (IQR: $0.92\text{--}1.66$)), winter- ($n=59$, 1.01 (IQR: $0.80\text{--}1.32$)), and summer-winter-MetS ($n=67$, 1.31 (IQR: $0.95\text{--}1.73$)) were significantly higher than the median levels of HOMA-IR in subjects without MetS ($n=605$, 0.76 (IQR: $0.54\text{--}1.07$)) (each $P<0.05$) (Figure 1a). Furthermore, the levels of HOMA-IR were comparable in subjects with summer- and summer-winter-MetS ($P=0.98$), whereas the levels of HOMA-IR were significantly lower in subjects with winter-MetS when compared with subjects with summer-winter-MetS ($P<0.05$). When using the JSIM criteria, the median levels of HOMA-IR were comparable in subjects with summer-, winter- and summer-winter-MetS, and these levels were significantly higher than the HOMA-IR levels of subjects without MetS (Figure 1b).

Association of HOMA-IR with seasonal variation in MetS prevalence

To examine our initial hypothesis, we compared the influence of HOMA-IR levels on seasonal variations of MetS prevalence among four subgroups. Although the prevalence rates of IDF- and JSIM-MetS in both seasons increased in patients in higher quartiles of HOMA-IR level and the prevalence data were higher in all quartiles during the winter when compared with the respective quartiles during the summer, the differences were not statistically significant except for the third quartile (Figures 2a and 2b): the rates of IDF- and JSIM-MetS in the third quartile increased from 14.3 and 11.2% in the summer to 21.9 and 17.9% in the winter, respectively (each $P<0.05$). In the third quartile, seasonal frequencies of elevated WC, elevated TG, reduced HDL cholesterol, elevated glucose or dyslipidemia exhibited little change (data not shown), whereas the frequency of elevated BP increased from 42.4% ($n=83$) in the summer to 61.2% ($n=120$) in the winter ($P<0.05$), which was related to the significant variation in both the IDF- and JSIM-MetS prevalence (Figure 3). Otherwise, there were no significant seasonal variations in glucose levels in any of the quartiles based on the HOMA-IR level (data not shown).

DISCUSSION

The ultimate aim of MetS screening is to identify subjects who are at a high risk of developing type 2 diabetes and cardiovascular disease.²⁴ Although MetS consists of various pathological conditions, MetS can be diagnosed clinically using several simple measurements including WC, TG levels, HDL cholesterol levels, BP and fasting glucose levels.

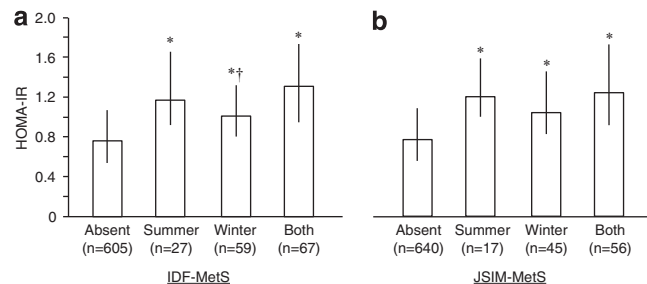


Figure 1 Homeostasis model assessment of insulin resistance (HOMA-IR) levels according to seasonal IDF-MetS (a) and JSIM-MetS (b). All data are expressed as the median with the associated interquartile range. * $P<0.05$ when compared with subjects without MetS, † $P<0.05$ when compared with subjects with summer-winter-MetS by analysis of variance followed by the Tukey-Kramer *post hoc* test. IDF, International Diabetes Federation; JSIM, Japanese Society of Internal Medicine; MetS, metabolic syndrome.

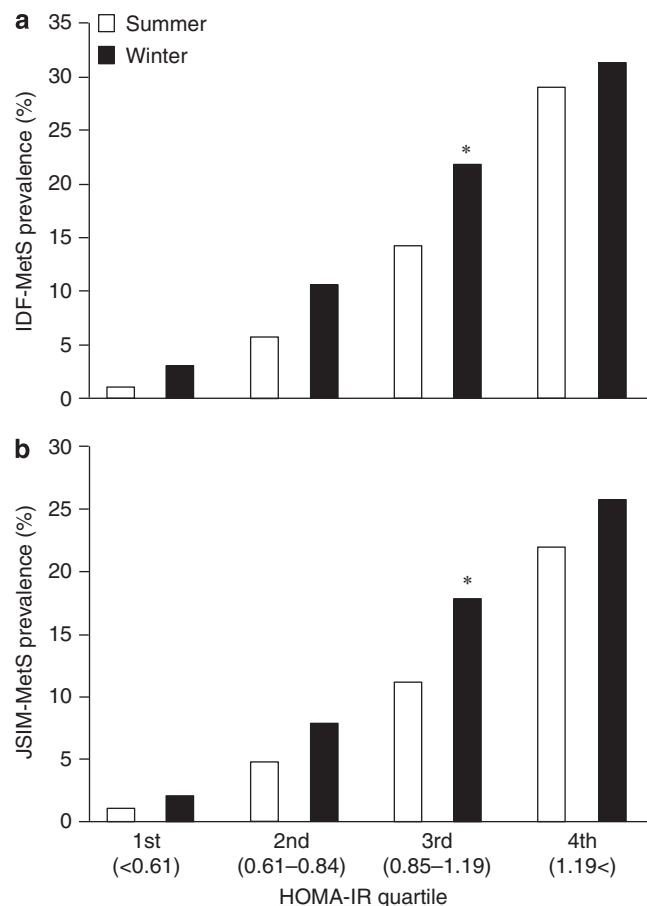


Figure 2 Seasonal prevalence rates of IDF-MetS (a) and JSIM-MetS (b) according to homeostasis model assessment of insulin resistance (HOMA-IR) levels. * $P<0.05$ when compared with summer-MetS as determined by the chi-squared test. IDF, International Diabetes Federation; JSIM, Japanese Society of Internal Medicine; MetS, metabolic syndrome.

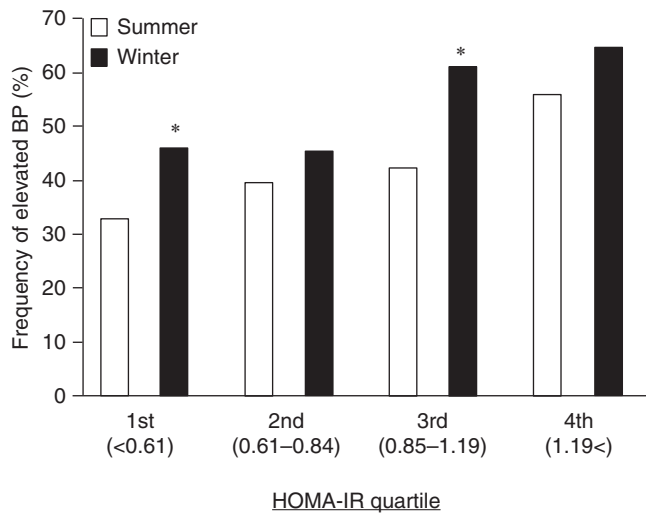


Figure 3 Seasonal frequency of elevated blood pressure (BP) according to homeostasis model assessment of insulin resistance (HOMA-IR) levels. * $P < 0.05$ when compared with summer-MetS as determined by the chi-squared test. MetS, metabolic syndrome.

However, despite accumulating evidence of seasonal variations in these metabolic parameters, seasonal variations are not included in the criteria used to diagnose MetS. These seasonal variations are usually higher in the fall and winter than in the spring and summer, and the incidence of cardiovascular disease is proportionately higher in the winter when compared with the other seasons.^{25,26} A recent report has suggested that seasonal variations in metabolic parameters may serve as a partial explanation for the higher incidence of cardiovascular disease during the winter.²⁷ These findings indicate that seasonal variations in various metabolic parameters may be risk factors for cardiovascular disease. We recently demonstrated the seasonal variation of MetS prevalence in Japanese male workers.¹⁹ However, our study could not determine the underlying mechanism and clinical implication of this variation. Increased insulin resistance is one of the pathophysiological bases for MetS, and the HOMA-IR model is widely used to estimate insulin resistance in clinical practice.²⁸ In the present study, we examined the association between seasonal variation in MetS prevalence and insulin resistance evaluated by HOMA-IR.

There are several important findings in the present study. First, seasonal variation in MetS prevalence exists in middle-aged Japanese male workers. This study showed that almost 4% of subjects met the criteria for MetS seasonal variation, and MetS diagnosis occurred more often in the winter than in the summer. Current estimates suggest that ~25% of the world adult population have MetS. Therefore, the choice of the season in which health checkups are conducted may result in overlooking many subjects who should be diagnosed with MetS, which can delay the initiation of therapeutic interventions, such as lifestyle management (for example, weight reduction, smoking cessation, increased physical activity and diet modification). Our data suggest that seasonal variation should be carefully considered in the clinical diagnosis and management of MetS and that MetS screening can be more useful when performed during the winter season. The second important result of the current study is that seasonal variation in MetS prevalence is associated with a mild-to-moderate increase in insulin resistance. This study showed that the prevalence rate of MetS in the third quartile of patients

stratified based on HOMA-IR levels was significantly higher in the winter. The frequency of elevated BP in the third quartile was 18.8% higher in the winter, which correlated with the variation observed in the prevalence data in this study. On the other hand, the decreased variation of the prevalence data in the fourth quartile appeared to be dependent on the severity of the MetS components. These results indicate that increased insulin resistance may be one of the potential mechanisms for seasonal variation of MetS prevalence, and seasonally elevated BP certainly appears to be involved with seasonal variation in MetS. Although the mechanism of seasonal variability in BP is not fully understood, cold temperatures increase the activation of the sympathetic nervous system and the secretion of catecholamines. A large cross-sectional study reported that systolic BP decreases as the air temperature increases with an 8.0 mm Hg difference between the lowest and highest air temperature quintiles.²⁹ Increased insulin resistance is associated with the activation of not only the sympathetic nervous system but also the renin-angiotensin systems, which could partially contribute to the seasonal variations in BP. Elevated BP has been well characterized as the most common component of MetS and the most attributable risk factor for cardiovascular disease mortality.³⁰⁻³² The INTERSALT study reported that 2.2 mmHg or greater decrease in systolic BP is associated with a 4% lower risk of coronary death and a 6% lower risk of stroke-related death in middle-aged adults.³³ We propose that the strict management of both elevated BP levels and seasonal BP variability has an important role in the prevention of cardiovascular disease. Finally, subjects diagnosed with summer-, winter- and summer-winter-MetS had significantly higher HOMA-IR levels when compared with subjects without MetS. Additionally, HOMA-IR levels were lower in subjects with winter-MetS than in subjects with summer- and summer-winter-MetS. The UK Prospective Diabetes Study reported that the incidence of type 2 diabetes was higher during the winter than during other seasons.³⁴ These findings indicate that seasonal variation may exist with respect to insulin resistance and that HOMA-IR levels according to MetS prevalence may display more significant seasonal variation in subjects with winter-MetS than in subjects with summer- and summer-winter-MetS. Moreover, a recent prospective study showed that even minimal increases in HOMA-IR levels predicted subsequent cardiovascular events in non-diabetic Japanese men.³⁵ The results of this study strongly suggest that we should not overlook subjects diagnosed with MetS, regardless of the season.

Study limitations

First, our study was limited to a single year; therefore, extended observation will be necessary to confirm that the trend remains true. Second, similar studies should be performed using different populations of subjects because the study subjects of the current study may not be representative of all Japanese men. In addition, the results should be confirmed for Japanese female workers because the prevalence rate of MetS in Japanese women is significantly lower when compared with the prevalence rate of MetS in Japanese men. Third, we could not investigate differences in diet, physical activity, climate conditions and mood among the study subjects. To some extent, differences in these factors between the summer and the winter may have influenced the study results. Finally, this study could not demonstrate whether seasonal variation in MetS prevalence actually has a role in type 2 diabetes and cardiovascular disease. We hope that additional studies will be performed in the near future to further our understanding of the clinical role of seasonal variation in MetS prevalence.

CONCLUSIONS

We demonstrated that seasonal variation of MetS prevalence was associated with mildly to moderately increased insulin resistance in middle-aged Japanese male workers. This result suggests that increased insulin resistance may be a potential mechanism for the observed seasonal variation in MetS prevalence. Based on the results of this study, seasonal variation in MetS should be taken into account for the clinical diagnosis and management of MetS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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