Smoking Cessation without Educational Instruction could Promote the Development of Metabolic Syndrome

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Aim: Smoking cessation is particularly important for maintaining health; however, the subsequent risk of an increased body weight is of major concern. The present study investigated the influence of smoking cessation on the incidence of metabolic syndrome and its components in the Japanese general population.

Methods: This study enrolled individuals without metabolic syndrome or a history of smoking via our annual health checkup program (n = 5,702, 55.2 ± 11.5 years). Participants were divided into three groups mentioned below and followed up with the endpoint being the development of metabolic syndrome: (1) subjects who had never smoked and did not smoke during the observation period (non-smoker); (2) those who continued smoking during the observation period (continuous smoker); and (3) those who ceased smoking during the observation period (smoking cessation).

Results: During the observation period (median 1,089 days), 520 subjects developed metabolic syndrome, and Kaplan–Meier analysis showed a higher incidence of metabolic syndrome in the smoking cessation group than in the other groups. Smoking cessation was confirmed as an independent predictor of the new onset of metabolic syndrome by multivariate Cox proportional hazard analysis after adjustment. Subjects only from the smoking cessation group showed a significant deterioration in metabolic factors during the study in correlation with an increased waist circumference after smoking cessation.

Conclusions: Smoking cessation without instruction could be followed by the development of metabolic syndrome, and the incidence of metabolic syndrome might reduce the benefit obtained from smoking cessation. Therefore, further educational outreach is needed to prevent the progression of metabolic syndrome during the course of smoking cessation.

Key words: Smoking, Cessation, Metabolic syndrome, Body weight, Waist circumference
and lipid metabolism disorder, leading to the development of metabolic syndrome\(^\text{11}\). Thus, smoking cessation may increase body weight and the risk of metabolic syndrome, and thus counteract the beneficial effects of not smoking.

Despite several studies on body weight gain after smoking cessation, there are limited data on the subsequent development of metabolic syndrome\(^\text{5, 6, 12, 13}\) particularly on how ethnicity might affect the impact of an increasing body weight as a risk factor for cardiovascular disease. For instance, obesity is not a significant risk factor for myocardial infarction in the Japanese population\(^\text{14}\), while the incidence of diabetes is higher in Japan than in Western countries among individuals with similar body weight gain\(^\text{15, 16}\). This study thus investigated the effects of smoking cessation on the incidence of metabolic syndrome and its components in the Japanese general population.

### Study Subjects and Procedures

Individuals who visited the Department of Health Checkup, Enshu Hospital two times or more from July 2008 to June 2013 \(n=9,018\) were screened for eligibility for this study. Subjects with metabolic syndrome at the first visit \(n=1,273\) and those with incomplete data \(n=39\) were first excluded. Then, those participants who did not smoke at the first visit, but had a history of smoking \(n=1,918\), and those who started smoking during the observation period \(n=86\) were excluded. The remaining 5,702 participants (males: 49.7%, average age: 55.2 ± 11.5 years) were finally enrolled in this study and followed up with the endpoint being the onset of metabolic syndrome. We divided subjects into the following three groups: (1) subjects who had never smoked and did not smoke during the observation period (non-smoker); (2) those who continued smoking during the observation period (continuous smoker); and (3) those who ceased smoking during the observation period (smoking cessation). Information about the smoking status was obtained by questionnaire. Data obtained at the first health checkup during the study period were considered as baseline data in the non-smoker and continuous smoker groups and data obtained at the last health checkup as a smoker (data collected immediately prior to smoking cessation) were considered as baseline data in the smoking cessation group. Group differences in the incidence of metabolic syndrome

### Methods

#### Study Design

This was a retrospective observational study of participants in our annual health checkup program at the Department of Health Checkup, Enshu Hospital. The study protocol was approved by the Ethics Committee of Enshu Hospital and written informed consent was obtained from all subjects prior to the start of the study.

### Table 1. Demographics of study participants at baseline; comparison by smoking status

|                      | Non-smoker group \((n=3,968)\) | Continuous smoker group \((n=1,336)\) | Smoking cessation group \((n=398)\) |
|----------------------|-------------------------------|----------------------------------------|------------------------------------|
| Age (years)          | 55.6 ± 11.3                   | 50.9 ± 11.1*                           | 55.9 ± 11.3§                        |
| Male, n (%)          | 1,262 (31.8%)                 | 1,205 (90.2%)                          | 368 (92.5%)                         |
| Body mass index (kg/m²) | 22.0 ± 2.9                  | 22.3 ± 2.9*                            | 22.0 ± 2.9                          |
| Waist circumference (cm) | 81.8 ± 8.0               | 82.7 ± 8.2*                            | 82.2 ± 7.9                          |
| Systolic blood pressure (mmHg) | 123.8 ± 16.1            | 118.8 ± 14.5*                          | 119.9 ± 15.4*                       |
| Diastolic blood pressure (mmHg) | 75.4 ± 9.6               | 74.2 ± 9.6*                            | 74.4 ± 9.8                          |
| Pulse rate (bpm)     | 63.8 ± 9.5                   | 61.1 ± 8.7*                            | 60.0 ± 8.0*                         |
| Fasting plasma glucose (mg/dL) | 94.2 ± 14.1             | 94.4 ± 15.8                            | 93.8 ± 13.7                         |
| LDL-cholesterol (mg/dL) | 121.1 ± 27.0               | 116.0 ± 28.9*                          | 115.9 ± 27.1*                       |
| HDL-cholesterol (mg/dL) | 62.6 ± 13.8                | 56.1 ± 13.2*                           | 57.3 ± 12.5*                        |
| Triglyceride (mg/dL)  | 92.5 ± 51.0                  | 120.0 ± 85.6*                          | 105.7 ± 69.7§                       |
| Serum creatinine (mg/dL) | 0.70 ± 0.21               | 0.80 ± 0.27*                           | 0.80 ± 0.14*                        |
| Uric acid (mg/dL)    | 4.9 ± 1.2                    | 5.8 ± 1.3*                             | 5.7 ± 1.2*                         |
| Comorbidities:       |                               |                                       |                                    |
| Hypertension, n (%)  | 979 (24.7%)                  | 196 (14.7%)*                            | 80 (20.1%)§                         |
| Diabetes mellitus, n (%) | 170 (4.3%)              | 57 (4.3%)                              | 15 (3.8%)                           |
| Dyslipidemia, n (%)  | 1,428 (36.0%)                | 502 (37.6%)                            | 122 (30.7%)§                        |

\(* p<0.05\) vs. non-smoker group. \(\ddagger p<0.05\) vs. continuing smoker group by ANOVA-Scheffe or chi-square test

LDL-cholesterol, low-density lipoprotein-cholesterol; HDL-cholesterol, high-density lipoprotein-cholesterol
after the collection of baseline data during the observation period were analyzed using the Kaplan–Meier method. Changes in each component of the metabolic syndrome during the observation period were compared among the groups.

Metabolic syndrome was defined based on the Japanese diagnostic criteria (waist circumference $\geq 85$ cm for males and $\geq 90$ cm for females and 2 or more of the following three criteria: (1) triglyceride $\geq 150$ mg/dL and/or high-density lipoprotein (HDL) cholesterol $< 40$ mg/dL; (2) systolic pressure $\geq 130$ mmHg and/or diastolic pressure $\geq 85$ mmHg; and (3) fasting plasma glucose $\geq 110$ mg/dL)\(^{17}\). Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol $\geq 140$ mg/dL, triglyceride $\geq 150$ mg/dL, HDL-cholesterol $< 40$ mg/dL, and/or use of anti-lipid drugs\(^{18}\). Hypertension was defined as systolic pressure $\geq 140$ mmHg, diastolic pressure $\geq 90$ mmHg, and/or use of anti-hypertensive drug. Diabetes mellitus was defined as fasting plasma glucose $\geq 126$ mg/dL and/or use of anti-diabetic medication\(^{19, 20}\).

**Statistical Analysis**

All the data are expressed as the mean $\pm$ SD and were analyzed using IBM SPSS statistics 24 software (Chicago, IL). The paired Student’s $t$ test was used for the comparison of data obtained at baseline and at the end of the observation period. Differences in continuous variables among the three groups were tested using analysis of variance (ANOVA) followed by Scheffe’s post-hoc analysis. The chi-squared test was used for comparison of categorized data among three groups, which was followed by 2-way contingency table analysis. Cumulative incidence rates of metabolic syndrome were calculated using the Kaplan–Meier method. Differences in the cumulative incidence rates were evaluated by the log-rank test and adjusted by multivariate Cox proportional hazard regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set as $< 5\%$.

**Results**

The number of visits per participant after baseline assessment during the observation period was as follows: 2 visits ($n = 1,722$), 3 visits ($n = 1,167$), 4 visits ($n = 1,032$), 5 visits ($n = 1,671$), and 6 visits ($n = 110$). A total of 398 subjects ceased smoking during the observation period. Table 1 lists the subject demographics across the three groups at baseline. The smoking cessation group was older and had lower triglyceride levels than the continuous smoker group, while BMI, fasting plasma glucose, and HDL cholesterol were similar in both these groups.

During the median follow up of 1,089 days, 520 subjects were newly diagnosed as having metabolic syndrome (33.3/1,000 person-years; Fig. 1). The incidence was higher in males (48.0/1,000 person-years) than in females (18.7/1,000 person-years), and Kaplan–Meier analysis indicated a higher incidence of metabolic syn-
significantly correlated with those in systolic blood pressure ($r=0.119$), diastolic blood pressure ($r=0.171$), triglyceride ($r=0.200$), and HDL-cholesterol ($r=-0.109$).

### Discussion

This study demonstrated that smoking cessation may be followed by the new onset of metabolic syndrome in the general population without metabolic syndrome at baseline. Since deterioration in metabolic factors was closely associated with the increase in waist circumference after smoking cessation in our study cohort, health professionals and educational programs need to provide appropriate instruction against these unfavorable changes for individuals who are going to stop smoking.

The increase in body weight after smoking cessation observed in this study has already been reported in Western countries and Japan. However, body weight gain itself does not always mean the development of metabolic syndrome and, to the best of our knowledge, this is the first study demonstrating a higher risk of metabolic syndrome in subjects who ceased smoking as compared to those who continued smoking. A previous study demonstrating an increased risk...
An increase in waist circumference indicates the accumulation of visceral fat, which is the fundamental cause of metabolic syndrome, leading to insulin resistance, elevation of blood pressure, and activation of the sympathetic nerve system. Indeed, changes in blood pressure, triglyceride, fasting plasma glucose levels were correlated with changes in waist circumference in the smoking cessation group in this study. It should be noted that waist circumference was not different at baseline in the continuous smoker and smoking cessation groups. Smoking cessation could therefore play a major role in increasing waist circumference. The observation that subjects who stopped smoking experienced an increase in both body weight and HDL-cholesterol in this study appears somewhat contrary to the overall results; however, similar findings have been previously reported. HDL-cholesterol might have increased due to an increase in physical activity, such as exercise. Alternatively, an increased HDL-cholesterol associated with smoking cessation might be attributable to an improvement from an individual’s deconditioning due to smoking.

A cross-sectional analysis, including non-smokers, continuous smokers, and past smokers, at the first visit indicated that the prevalence of metabolic syndrome was 9.8%, 14.2%, and 19.9%, respectively. Moreover, the incidence of metabolic syndrome in past smokers at baseline was higher than in non-smokers or continuous smokers (data not shown). These results are compatible with the present study results. A meta-analysis of prospective studies demonstrated that active smoking is associated with the development of metabolic syndrome and that smoking cessation seems to reduce the risk of metabolic syndrome. It is noteworthy this meta-analysis included studies with varying lengths of metabolic syndrome in male subjects who stopped smoking was an observational study where non-smokers, but not continuous smokers, were considered as a reference. Thus, this study further expands the concept that smoking cessation might increase the risk of developing metabolic syndrome in the general population.

The results of Kaplan–Meier analysis suggested that smoking cessation increases the risk of metabolic syndrome and multivariate analysis confirmed smoking cessation as an independent predictor of developing metabolic syndrome. The incidence of metabolic syndrome in non-smokers seemed to increase after 1,500 days of observation. However, Kaplan–Meier analysis of data obtained during an extended follow-up period (until March 2014) showed a clear separation of the cumulative incidence curves in continuous smokers and non-smokers (data not shown). Thus, the incidence of metabolic syndrome remained higher in continuous smokers than in non-smokers, confirming previous findings of a higher risk of metabolic syndrome in active smokers than in non-smokers. This study does not clarify the mechanisms underlying the close relationship between smoking cessation and the development of metabolic syndrome; however, an increased waist circumference is likely to play a major role as a risk factor for metabolic syndrome. Notably, changes in body weight and waist circumference were correlated with each other in the smoking cessation group, although the continuous smoking group showed an increased body weight and a reduced waist circumference. Thus, an increase in body weight is not necessarily followed by an increase in waist circumference, and an increase in body weight may not be the only crucial determinant of developing metabolic syndrome.

### Table 2. Cox-Hazard analysis for the incidence of metabolic syndrome

| Smoking status: | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                 | HR (95%CI)          | P value              |
|                 |                     | HR (95%CI)           | P value |
| Non-smoker group| 1 (reference)       | –                    |
| Continuous smoker group | 1.609 (1.328–1.950) | < 0.001 |
| Smoking cessation group | 2.584 (1.956–3.412) | < 0.001 |
| Age (years)     | 1.026 (1.018–1.034) | < 0.001 |
| Sex (male)      | 2.589 (2.142–3.128) | < 0.001 |
| Waist circumference (cm) | 1.122 (1.112–1.132) | < 0.001 |
| Triglyceride (mg/dL) | 1.003 (1.003–1.004) | < 0.001 |
| HDL-cholesterol (mg/dL) | 0.957 (0.950–0.964) | < 0.001 |
| Systolic blood pressure (mmHg) | 1.030 (1.025–1.035) | < 0.001 |
| Fasting plasma glucose (mg/dL) | 1.014 (1.012–1.017) | < 0.001 |
|                 | 1.194 (0.946–1.508) | 0.135 |
|                 | 1.727 (1.276–2.338) | < 0.001 |
|                 | 1.030 (1.021–1.039) | < 0.001 |
|                 | 1.976 (1.581–2.468) | < 0.001 |
|                 | 1.113 (1.102–1.124) | < 0.001 |
|                 | 1.002 (1.001–1.003) | < 0.001 |
|                 | 0.982 (0.973–0.990) | < 0.001 |
|                 | 1.023 (1.018–1.023) | < 0.001 |
|                 | 1.012 (1.009–1.016) | < 0.001 |

HDL-cholesterol, high-density lipoprotein cholesterol

An increase in waist circumference indicates the accumulation of visceral fat, which is the fundamental cause of metabolic syndrome, leading to insulin resistance, elevation of blood pressure, and activation of the sympathetic nerve system. Indeed, changes in blood pressure, triglyceride, fasting plasma glucose levels were correlated with changes in waist circumference in the smoking cessation group in this study. It should be noted that waist circumference was not different at baseline in the continuous smoker and smoking cessation groups. Smoking cessation could therefore play a major role in increasing waist circumference. The observation that subjects who stopped smoking experienced an increase in both body weight and HDL-cholesterol in this study appears somewhat contrary to the overall results; however, similar findings have been previously reported. HDL-cholesterol might have increased due to an increase in physical activity, such as exercise. Alternatively, an increased HDL-cholesterol associated with smoking cessation might be attributable to an improvement from an individual’s deconditioning due to smoking.
of follow-up, from 1 to 28 years, suggesting that the impact of smoking cessation on the incidence of metabolic syndrome could differ markedly among studies with different observational periods. Indeed, the risk of incident metabolic syndrome within 3 years of smoking cessation was higher than that for sustained smoking in one study\(^30\) and smoking cessation was higher than that for sustained metabolic syndrome within 3 years of observation. Moreover, information on lifestyle, such as physical activity and diet, was not available, and such changes were possible especially among the smoking cessation group who obviously had concerns for their health. The present study results therefore should be interpreted with caution considering the above-mentioned conditions. Long, prospective, observational studies are necessary to further define the relationship between the progression of metabolic syndrome and cardiovascular events after smoking cessation.

### Conclusions

Smoking cessation without educational instruction could be followed by the development of metabolic syndrome. Although smoking is one of the major risk factors for cardiovascular disease and smoking cessation is essential for health maintenance, the incidence of metabolic syndrome may reduce or overcome the benefit obtained from smoking cessation. Sufficient instruction should be provided to the public about the risk of smoking and metabolic syndrome, and further educational outreach is needed to prevent the progression of metabolic syndrome during the course of smoking cessation.

### Disclosure

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