Metabolic Syndrome Over 4 Years Before the Onset of Cardiovascular Disease
— Nested Case-Control Study —

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Background: We investigated the risk of cardiovascular disease (CVD) with duration of metabolic syndrome (MetS) for the past 4 years before the CVD event.

Methods and Results: We performed a nested case-control study within the Japan Epidemiology Collaboration on Occupational Health Study. A total of 139 registered cases of CVD and 561 self-reported cases of CVD were identified and matched individually on age, sex, and worksite with 695 and 2,803 controls, respectively. MetS was defined by the Joint Interim Statement definition. The odds ratio (95% confidence interval) for registered CVD was 4.7 (2.9, 7.5) for people with persistent MetS (positive for MetS for ≥ 3 assessments) and 1.9 (1.1, 3.3) for those with intermittent MetS (positive for MetS for 1–2 assessments), compared with people without MetS during the past 4 years before the event/index date (P for trend <0.001). The corresponding odds ratio for self-reported CVD was 2.7 (2.2, 3.5) and 1.8 (1.4, 2.3) (P for trend <0.001). The association with MetS duration was stronger for myocardial infarction than for other CVD subtypes. Similar results were obtained when using the Japanese MetS criteria.

Conclusions: The risk of CVD increases with increasing MetS duration. These findings contribute to risk stratification and encourage lifestyle modification for people with MetS to minimize their health risk.

Key Words: Cardiovascular disease; Metabolic syndrome; Nested case-control study

Metabolic syndrome (MetS) affects approximately one-quarter of the world’s adult population and is associated with increased risk of cardiovascular disease (CVD). A meta-analysis of 87 studies that used National Cholesterol Education Program (NCEP) definition or revised NCEP showed that MetS was associated with almost twice the relative risk of CVD. In these previous studies, MetS was assessed only at baseline, which may result in an underestimate of the associations between MetS and CVD, as MetS status may change over time.

Few studies have examined the effects of duration of MetS on cognition and diabetes. The Whitehall II study...
showed that persistent MetS (at least 2 of 3 screenings) over a 10-year follow-up, rather than MetS status at a given moment, is the factor that has adverse effects on cognitive performances in late midlife. A cohort study in Japan showed that a longer duration of MetS was associated with higher risk of diabetes. These findings emphasize the importance of considering the duration of MetS as an independent risk factor. To our knowledge, no previous study has examined the effect of the duration of prior MetS on CVD.

The present study’s aim was to examine the risk of CVD compared with duration of MetS of at least 4 years before the onset of CVD in a nested case-control study within the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study. We further investigated whether the magnitude of the association would differ among CVD subtypes. Given that different definitions of MetS exist, we also examined whether these associations would differ between the Joint Interim Statement (JIS) and Japanese Committee of the Criteria for Metabolic Syndrome (JCCMS) definitions.

**Methods**

**Study Design**

The J-ECOH Study is an ongoing multicenter epidemiologic study of workers from 12 companies covering various industries (electric machinery and apparatus manufacturing; steel, chemical, gas, and nonferrous metal manufacturing; automobile and instrument manufacturing; plastic product manufacturing; and healthcare). In Japan, workers are obliged to undergo a health examination at least annually under the Industrial Safety and Health Act; nearly all workers undergo a health examination each year. As of May 2016, 11 participating companies (12 worksites) provided health checkup data obtained between January 2008 and December 2015 or between April 2008 and March 2016. Prior to the collection of the data, the format of the J-ECOH Study was announced in each company by using posters that explained the purpose and procedure of the study. Participants did not give verbal or written informed consent to join the study but were allowed to refuse to participate. This procedure conforms to the Japanese Ethical Guidelines for Epidemiological Research, whereby the procedure for obtaining consent may be simplified for observational studies that use existing data.

The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan.

A nested case-control study design was used to investigate the association between duration of MetS and incident CVD in the J-ECOH Study. Before case-control sampling,
we excluded participants who self-reported stroke or any heart disease at the J-ECOH Study entry (n=1,773) (Figure).

**Ascertainment of CVD Cases and Control Selection**

Incident CVD cases were identified through 2 resources: a CVD registry (registered CVD) and annual health checkup data (self-reported CVD, without subsequent confirmation).

Within the J-ECOH Study, a CVD registry was set up in April 2012 to collect data on CVD events (including cerebral infarction, nontraumatic subarachnoid hemorrhage, nontraumatic intracerebral hemorrhage, and myocardial infarction [MI]) by occupational physicians at the participating companies. For most nonfatal cases, the occupational physician confirmed the diagnosis of each CVD event on the basis of medical certificate, which was written by a physician and submitted to the company by the worker. As the submission of a medical certificate is required when taking long-term sick leave, this registry mainly covers relatively severe cases. For fatal cases, occupational physicians judged the cause of death based on available information, including death certificate, and information obtained from the bereaved family or colleagues. Each case was coded using the 10th revision of the International Classification of Diseases (ICD). Event date was defined as the date of CVD diagnosis recorded in the registry.

We also used annual health checkup data to obtain information on less-severe CVD events that had occurred since 2012. If an event was both self-reported and recorded in the registry, we included it as a registered case not a self-reported one. History of stroke was collected by all participating companies, although detailed information on the subtype of stroke was not obtained. History of ischemic heart disease (IHD) was asked differently among the participating companies: MI and angina at 3 worksites, MI, angina, and IHD (unknown type) at 5 worksites, and IHD (subtype not collected) at 4 worksites. For self-reported CVD, the event date was defined as the date of health checkup when the CVD was first self-reported.

Controls were selected from the J-ECOH Study participants who did not develop CVD during the follow-up period. First, for each case, we created a pool of controls who were matched by worksite, sex, and date of birth (±2 years). Second, we allocated them an index date, which was the same as the event date of the matched case. Third, we excluded those who did not have data about MetS status at 4 years before the index date. For a given case, we randomly selected up to 5 controls from the pool of eligible controls. Once a control was sampled, we did not allow the control to be again chosen as the control of other cases.

**Periodic Health Checkup**

Participants underwent physical examinations, anthropometric measurements, and measurements of blood pressure (BP), blood glucose, and lipids during the health checkup. Body height and weight were measured using a scale while the participant wore light clothes and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the squared height in meters. BP was measured with an automated monitor while the participant was seated. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or receiving medical treatment for hypertension.19 Pulse pressure was calculated by subtracting the diastolic BP from the systolic BP. Plasma glucose was measured with either the enzymatic or glucose oxidase peroxidative electrode method. Glycated hemoglobin (HbA1c) was measured using a latex agglutination immunoassay, high-performance liquid chromatography, or the enzymatic method. Diabetes mellitus (DM) was defined as HbA1c ≥6.5%, fasting plasma glucose (FPG) ≥126 mg/dL, random plasma glucose ≥200 mg/dL, or currently under medical treatment for DM, according to the American Diabetes Association criteria for the diagnosis of DM.14 Triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol levels (HDL-C) were measured with enzymatic methods. Dyslipidemia was defined as TG ≥150 mg/dL, LDL-C ≥140 mg/dL, and HDL-C <40 mg/dL, or receiving medical treatment for dyslipidemia, based on the criteria of the Japan Atherosclerosis Society.15 All the laboratories involved in the health checkups of the participating companies have received satisfactory scores (rank A or a score >95 out of 100) from external quality-control agencies. Checkup participants also completed a questionnaire about their medical history, including CVD and health-related lifestyle. Because questions on lifestyle other than smoking were markedly different across the participating companies, the present study considered only smoking.

**Definition of MetS**

MetS was assessed at 1, 2, 3, and 4 years before the event/index date for cases and control, using the JIS® and JCCMS® criteria. Specifically, the JIS® defines MetS as having ≥3 of the following 5 risk factors: (1) waist circumference (WC) for men ≥90 cm and for women ≥80 cm; (2) TG ≥150 mg/dL or on treatment for TG; (3) HDL-C for men <40 mg/dL and for women <50 mg/dL or on treatment for HDL-C; (4) BP ≥130/85 mmHg or on treatment for hypertension; and (5) FPG ≥100 mg/dL or on treatment for DM. The JCCMS® defines MetS as central obesity (≥85 cm in men and ≥70 cm in women) plus ≥2 of the following: (1) BP of 130/85 mmHg or on treatment for hypertension; (2) FPG ≥110 mg/dL or on treatment for DM; and (3) TG ≥150 mg/dL or HDL-C <40 mg/dL in men and women.

Duration of MetS was based on the frequency of MetS among the last 4 assessments before the event/index date. We categorized the duration of MetS as “never” (negative for MetS at all 4 annual assessments), “intermittent” (positive for MetS for 1–2 assessments), and “persistent” (positive for MetS for ≥3 assessments). Missing data (<5%) about components of MetS were replaced with the last measured value.

**Statistical Analysis**

All analyses were performed separately for registered CVD and self-reported CVD. Characteristics of the study participants were described as means for continuous variables and percentages for categorical variables. Chi-square tests for categorical variables or t-tests for continuous variables were used to examine differences in characteristics between cases and controls. The Kappa coefficient was calculated to determine the agreement between the JIS® and JCCMS® definitions.

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the development of CVD associated with the duration of MetS. The analysis was conditioned on the matching variables and further adjusted for smoking status (current smoker, non-current smoker) at 4 years before the event/index date. Trend association was assessed by assigning to each group (never, intermittent, and persistent) ordinal numbers that
were treated as a continuous variable. We also examined the associations between the CVD and its subtype risk and MetS status assessed at different time points: 1, 2, 3, and 4 years before the event/index date.

We calculated the present study’s power to detect the difference in CVD risk between people with persistent MetS and those without MetS using the SAS PROC POWER procedure. Our study had a power of 99% to detect a relative risk of 2.0 with statistical significance (2-sided alpha level of 0.05) for the analysis on registered CVD, based on the given condition of the proportion of people with persistent MetS among controls (20%) and the numbers of cases and controls (113 cases and 576 controls). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A 2-sided P<0.05 was considered statistically significant.

**Results**

We identified 176 registered CVDs and 698 self-reported CVDs. After removing patients who did not attend the health checkup at 4 years before the event date (37 registered CVD and 136 self-reported CVD), 139 registered CVD cases (including 31 fatal cases) with 695 controls, and 561 self-reported CVD cases (excluded 1 case without a matched control) with 2,803 controls, remained in the present study. The 139 registered CVD cases included 49 cases of cerebral infarction (ICD-10: I63), 45 of hemorrhagic strokes (ICD-10: I60 and I61), and 45 of MI (ICD-10: I21). The 561 self-reported CVD cases included 249 cases of stroke, 96 of MI, 144 of angina, and 72 of unknown type of IHD.

### Table 1. Characteristics of Cases and Controls at 4 Years Before the Date of CVD Event, J-ECOH Study, Japan, 2008–2015

|                  | Registered CVD | Self-reported CVD |
|------------------|----------------|-------------------|
|                  | Cases          | Controls          | Cases          | Controls          |
| **n**            | 139            | 695              | 561            | 2,803             |
| **Age (years)**  | 49.9±7.3       | 49.8±7.3         | 49.8±8.5       | 48.5±8.6          |
| **Men (%)**      | 93.5           | 93.5             | 91.8           | 91.9              |
| **BMI (kg/m²)**  | 24.6±3.9       | 23.4±3.4*        | 24.5±3.6       | 23.5±3.2*         |
| **WC (cm)**      | 86.6±10.2      | 83.1±9.0*        | 85.6±9.3       | 83.2±8.6*         |
| **Current smoker (%)** | 56.8           | 36.8*            | 44.9           | 37.4*             |
| **TG (mg/dL)**   | 160.1±119.0    | 131.1±101.1*     | 151.8±108.3    | 127.2±96.1*       |
| **HDL-C (mg/dL)**| 52.7±14.6      | 58.8±15.4*       | 55.1±15.3      | 57.7±14.5*        |
| **LDL-C (mg/dL)**| 128.0±35.2     | 121.4±30.8       | 125.4±31.0     | 121.2±29.4        |
| **SBP (mmHg)**   | 132.2±16.4     | 123.6±16.0       | 126.3±15.9     | 122.5±15.4*       |
| **DBP (mmHg)**   | 83.7±11.7      | 77.9±11.1*       | 80.2±11.0      | 77.6±10.7*        |
| **Pulse pressure (mmHg)** | 48.6±9.8     | 45.7±9.3*        | 46.1±9.3      | 44.8±8.7*         |
| **FPG (mg/dL)**  | 114.3±33.7     | 101.3±19.6*      | 108.6±31.1     | 101.4±19.7*       |
| **HbA1c (%)**    | 6.1±1.1        | 5.6±0.7*         | 5.9±1.2       | 5.7±0.7*          |
| **JIS (%)**      | 41.7           | 19.3*            | 34.1           | 19.7*             |
| **JCCMS (%)**    | 39.9           | 16.1             | 26.1           | 15.8*             |
| **DM (%)**       | 24.1           | 9.1*             | 15.9           | 8.4*              |
| **DM treatment (%)** | 66.7           | 58.1*            | 59.1           | 53.7*             |
| **Hypertension (%)** | 45.3           | 25.3*            | 37.1           | 23.9*             |
| **Hypertension treatment (%)** | 46.0           | 54.0             | 61.5           | 54.8*             |
| **Dyslipidemia (%)** | 64.8           | 46.5*            | 60.8           | 47.3*             |
| **Dyslipidemia treatment (%)** | 8.9            | 14.9             | 23.8           | 14.5*             |

*P<0.05. aDenominator is the total number of people with diabetes; bdenominator is the total number of people with hypertension; cdenominator is the total number of people with dyslipidemia. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; JCCMS, Japanese Committee of the Criteria for Metabolic Syndrome (2005); J-ECOH Study, Japan Epidemiology Collaboration on Occupational Health Study; JIS, the Joint Interim Statement on metabolic syndrome definition (2009); LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.
The Kappa coefficient between the JIS and JCCMS definitions was 0.7 among all the participants. When MetS was defined using the JCCMS definition, similar results were obtained.

trend <0.001). The corresponding adjusted ORs (95% CI) for self-reported CVD was 2.7 (2.2, 3.5) and 1.8 (1.4, 2.3), respectively (P for trend <0.001). The CVD subgroup analysis showed that the association between duration of MetS and risk of CVD was stronger for MI than for other subtypes of CVD.

The Kappa coefficient between the JIS and JCCMS definitions was 0.7 among all the participants. When MetS was defined using the JCCMS definition, similar results were obtained.

### Table 2. Duration of MetS and Risk of CVD (Registered CVD), J-ECOH Study, Japan, 2008–2015

| CVD / MetS in past 4 years | JIS | JCCMS |
|---------------------------|-----|-------|
|                           | Cases | Controls | OR (95% CI)* | P for trend | Cases | Controls | OR (95% CI)* | P for trend |
| Total CVD                 |       |         |             |            |       |         |             |            |
| Never                     | 58    | 462     | 1           |            | 64    | 491     | 1           |            |
| Intermittent              | 26    | 119     | 1.9 (1.1, 3.3) | <0.001     | 27    | 101     | 2.3 (1.4, 4.0) |            |
| Persistent                | 55    | 114     | 4.7 (2.9, 7.5) | <0.001     | 46    | 93      | 4.1 (2.5, 6.6) | <0.001     |
| MI                        |       |         |             |            |       |         |             |            |
| Never                     | 14    | 152     | 1           |            | 18    | 151     | 1           |            |
| Intermittent              | 9     | 36      | 2.7 (1.0, 7.2) |            | 9     | 36      | 2.9 (1.1, 7.5) |            |
| Persistent                | 22    | 37      | 8.0 (3.3, 19.3) | <0.001     | 18    | 34      | 4.9 (2.1, 11.4) | <0.001     |
| Stroke                    |       |         |             |            |       |         |             |            |
| Never                     | 44    | 310     | 1           |            | 46    | 340     | 1           |            |
| Intermittent              | 17    | 83      | 1.6 (0.8, 3.1) |            | 18    | 65      | 2.1 (1.1, 4.1) |            |
| Persistent                | 33    | 77      | 3.6 (2.1, 6.4) | <0.001     | 28    | 59      | 3.7 (2.0, 6.8) | <0.001     |
| Cerebral infarction       |       |         |             |            |       |         |             |            |
| Never                     | 18    | 157     | 1           |            | 21    | 176     | 1           |            |
| Intermittent              | 9     | 47      | 1.9 (0.7, 4.8) |            | 11    | 38      | 3.0 (1.2, 7.7) |            |
| Persistent                | 22    | 41      | 5.7 (2.5, 13.0) | <0.001     | 17    | 29      | 5.0 (2.5, 14.4) | <0.001     |
| Hemorrhagic stroke        |       |         |             |            |       |         |             |            |
| Never                     | 26    | 153     | 1           |            | 25    | 164     | 1           |            |
| Intermittent              | 8     | 36      | 1.5 (0.6, 3.8) |            | 7     | 27      | 1.5 (0.6, 4.0) |            |
| Persistent                | 11    | 36      | 2.3 (1.0, 5.2) | 0.05       | 11    | 30      | 2.3 (1.0, 5.6) | 0.06       |

*aAdjusted for smoking. CI, confidence interval; MetS, metabolic syndrome; MI, myocardial infarction; OR, odds ratio. Other abbreviations as in Table 1.

### Table 3. Duration of MetS and Risk of CVD (Self-Reported CVD), J-ECOH Study, Japan, 2008–2015

| CVD / MetS in past 4 years | JIS | JCCMS |
|---------------------------|-----|-------|
|                           | Cases | Controls | OR (95% CI)* | P for trend | Cases | Controls | OR (95% CI)* | P for trend |
| Total CVD                 |       |         |             |            |       |         |             |            |
| Never                     | 261   | 1,812   | 1           |            | 323   | 1,968   | 1           |            |
| Intermittent              | 124   | 525     | 1.8 (1.4, 2.3) |            | 86    | 408     | 1.4 (1.1, 1.9) |            |
| Persistent                | 176   | 466     | 2.7 (2.2, 3.5) | <0.001     | 138   | 364     | 2.5 (2.0, 3.2) | <0.001     |
| Total IHD                 |       |         |             |            |       |         |             |            |
| Never                     | 129   | 950     | 1           |            | 167   | 1,065   | 1           |            |
| Intermittent              | 69    | 337     | 1.6 (1.2, 2.3) |            | 54    | 259     | 1.5 (1.1, 2.2) |            |
| Persistent                | 114   | 273     | 3.1 (2.3, 4.3) | <0.001     | 87    | 215     | 2.9 (2.1, 4.0) | <0.001     |
| MI                        |       |         |             |            |       |         |             |            |
| Never                     | 30    | 281     | 1           |            | 37    | 329     | 1           |            |
| Intermittent              | 20    | 105     | 1.8 (1.0, 3.4) |            | 22    | 80      | 2.7 (1.4, 5.2) |            |
| Persistent                | 46    | 94      | 4.2 (2.4, 7.4) | <0.001     | 37    | 62      | 6.3 (3.4, 11.7) | <0.001     |
| Angina                    |       |         |             |            |       |         |             |            |
| Never                     | 64    | 437     | 1           |            | 85    | 485     | 1           |            |
| Intermittent              | 37    | 158     | 1.8 (1.1, 2.9) |            | 20    | 120     | 1.2 (0.7, 2.1) |            |
| Persistent                | 43    | 125     | 2.4 (1.5, 3.9) | <0.001     | 36    | 105     | 2.4 (1.5, 3.9) | <0.001     |
| Stroke                    |       |         |             |            |       |         |             |            |
| Never                     | 132   | 862     | 1           |            | 156   | 903     | 1           |            |
| Intermittent              | 55    | 188     | 2.2 (1.5, 3.2) |            | 32    | 149     | 1.3 (0.9, 2.1) |            |
| Persistent                | 62    | 193     | 2.3 (1.6, 3.3) | <0.001     | 51    | 149     | 2.1 (1.4, 3.2) | <0.001     |

*aAdjusted for smoking. IHD, ischemic heart disease. Other abbreviations as in Tables 1, 2.
Discussion

Our study, based on a large-scale cohort study of a Japanese working population, provided evidence that a longer duration of MetS is associated with a higher risk of CVD. Furthermore, the magnitude of the association varied among CVD subtypes; the association was particularly strong for MI. No differences in the magnitude of the association between MetS duration and CVD risk were observed when using either the JIS or JCCMS definition.

Two large meta-analyses of prospective cohort studies showed that MetS at baseline is associated with a 2-fold increase in the risk of CVD.\(^2,3\) Using repeated assessment of MetS in the present study, the results for the registered CVD cases showed that people with persistent MetS had a 4–5-fold risk of CVD, and those with intermittent MetS had approximately twice the risk of CVD, compared with people without MetS throughout the study period. The results based on self-reported CVD data showed a similar association. The difference between the findings of our study and those of previous studies implies that the association between MetS and CVD risk may not be exactly captured if MetS is assessed at a single time point, because of changes in MetS status over time. For example, we observed that among people who had MetS at 4 years before the onset of CVD, 24%, 27%, and 27% of them became metabolically healthy 1, 2, and 3 years later, respectively (data not shown). Among those who did not have MetS at 4 years before the onset of CVD, 9%, 11%, and 13% of them had MetS 1, 2, and 3 years later, respectively. Our study provided evidence that the risk of CVD increased progressively with increasing duration of MetS.

Investigations into the association between MetS and the risk of CVD subtypes have been scarce. The present study showed that MetS was most strongly associated with MI, followed by cerebral infarction and hemorrhagic stroke. A community-based cohort study from Japan reported that the hazard ratios associated with MetS based on the NCEP definition were 2.1 for IHD, 2.0 for ischemic stroke, and 1.1 for hemorrhagic stroke.\(^17\) A prospective study from China showed that the hazard ratios for ischemic stroke and hemorrhagic stroke with MetS based on the revised NCEP definition were 1.7 and 1.4, respectively.\(^18\) Taken together, the studies show that MetS is associated with the risk of ischemic and hemorrhagic events, with a stronger association with ischemic events. However, the number of CVD events was limited in these studies, including ours. Further research is needed to elucidate the difference in the magnitude of association between MetS and CVD subtype.

In the present study, we observed similar associations between MetS and CVD for both the JIS and the JCCMS definition, regardless of MetS status at a single time point or the duration of MetS. There is conflicting evidence regarding the predictability of different definitions of MetS (JCCMS vs. international definitions) and whether central obesity should be a prerequisite for MetS.\(^19,20\) Given the difference in study design, study population, and definitions of MetS, it is difficult to compare our findings with those of previous studies. The JIS and JCCMS definitions differ in the cutoff points of MetS components, especially for WC.\(^7,8\) In the JIS definition, the cutoffs for WC are 90 cm for men and 80 cm for women, whereas the JCCMS definition adopts WC cutoff points of 85 cm for men and 90 cm for women and treats WC as a prerequisite component. These differences may influence the diagnosis of MetS, especially for women. In our study, the Kappa coefficient (0.3) suggested a poor agreement between the JIS and JCCMS definitions among women. However, because few women with CVD were enrolled in our study, we were unable to further assess the difference in CVD risk between the JIS and JCCMS definitions among women.

We observed that the magnitude of the association between both MetS at single time points and duration of MetS and CVD was stronger for registered CVD cases than for self-reported CVD. This could be caused by differences in the severity of CVD between registered CVD (more severe CVD) and self-reported CVD. MetS may be more strongly associated with severe CVD than with mild CVD events, as previous studies have shown that MetS appears to be associated with aggravation of acute ischemic stroke and MI.\(^20,21\) Another possible explanation is that the associations for self-reported CVD are underestimated because of imprecise self-reporting of the physician’s diagnosis.

Our study is novel because it is the first to examine the association between duration of MetS and CVD risk. Objective data for the MetS components were collected before the onset of CVD. However, this study has some limitations. First, workers who take long-term sick leave must submit a medical certificate to the occupational physician; therefore, diagnostic information for registered CVD cases, largely based on this certificate, is much more reliable than that of self-reported cases. We acknowledge that milder forms of CVD were not well covered by this registration system. However, our results did not significantly differ between analyses based on the 2 sources. Second, because of the lack of data on socioeconomic status, family history of CVD, and lifestyle habits other than smoking (e.g., diet, physical activity), we were unable to control for the potential effects of these factors. Third, the number of registered CVD cases for each subtype was not sufficiently large, and thus underpowered, to detect the association between the risk of each CVD subtype and MetS duration, especially for people with intermittent MetS. Last, given that the majority of study participants were employees of large companies, caution should be exercised in generalizing the present finding to workers in smaller companies, the self-employed, or the unemployed.

Conclusions

In conclusion, longer duration of MetS was associated with higher risk of CVD. The duration of MetS should be taken into account when assessing the effect of this syndrome on health. This finding also emphasizes the importance of improving metabolic profiles through lifestyle changes for people with MetS. Minimizing the duration an individual has MetS would help combat the rise in CVD risk with each year of the syndrome.

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Supplementary Files

Supplementary File 1

Table S1. Associations between CVD and MetS assessed at single time points, J-ECOH Study, Japan, 2008–2015
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