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Association between anthropometric indices of obesity and risk of cardiovascular disease in Japanese men

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Abstract

Objectives: We aimed to compare the association of body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR) with risk of cardiovascular disease (CVD) among middle-aged working Japanese men.

*Japan Epidemiology Collaboration on Occupational Health Study Group are included in the Appendix.

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Methods: A nested case-control study was performed among middle-aged male employees who underwent periodic health checkup. A total of 241 CVD cases were identified and matched individually on age, gender, and worksite with 1205 controls. Data on BMI, WC, WHtR, smoking, hypertension, diabetes, and dyslipidemia collected at 4 years before the event/index date were retrieved. Associations between BMI, WC, WHtR, and CVD risk were assessed by using conditional logistic regression models.
Results: The strength of the association of BMI, WC, and WHtR with CVD risk was similar. The smoking-adjusted odds ratio (95% confidence interval) for CVD was 1.60 (1.38-1.85), 1.53 (1.33-1.78), and 1.56 (1.35-1.81) for a 1 SD unit increase in BMI, WC, and WHtR respectively. After further adjustment for hypertension, diabetes, and dyslipidemia, these associations were attenuated but remained statistically significant.
Conclusions: Measures of general (BMI) and abdominal (WC and WHtR) obesity were similarly associated with CVD in middle-aged Japanese men.

KEYWORDS
body mass index, cardiovascular disease, waist circumference, waist-to-height ratio

1 | INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death worldwide.[1] Obesity is a strong predictor of CVD risk.[2] To assess risk for CVD, a variety of anthropometric indices have been used as a proxy for general obesity (ie, body mass index [BMI]) or abdominal obesity (ie, waist circumference [WC] and waist-to-height ratio [WHtR]).[2] There is controversy, however, as to whether these measures of obesity are similarly related to CVD risk. A systematic review of 22 prospective studies showed that WHtR and WC were significant predictors of cardio-metabolic outcomes more often than BMI.[3] In contrast, a meta-analysis using individual records from 58 prospective studies indicated that there was no significant difference in the strength of the association with CVD risk between BMI and abdominal obesity measures (WC and waist-to-hip ratio).[4] These reviews included few studies in the Japanese population, which is characterized by a low prevalence of obesity.

In Japan, risk of CVD has been linked to either general obesity (BMI)[5-7] or abdominal obesity (WC and WHtR).[8] Only one cohort study among the general population compared the association of BMI and WC with CVD risk, suggesting that abdominal obesity is a better predictor for CVD than general obesity in women.[8] However, no obesity measure was appreciably associated with CVD risk in men.[8] Given that CVD remains the leading cause of deaths in Japan,[9] clarifying the impact of obesity on CVD in Japanese is important.

Previous studies on the strength of associations between general obesity, abdominal obesity, and CVD are mainly based on cohort studies with a median follow-up of ≥10 years.[3,4,8] The long length of follow-up can avoid reverse causality bias and link obesity to the initiation and development of CVD. On the other hand, it can introduce bias due to loss to follow-up and cannot account for the change of obesity status over the long follow-up period. More importantly, it cannot answer the association between obesity and the development of a clinical CVD from a latent precursor (a few years prior to the onset of CVD). To the best of our knowledge, no previous study has compared the risk of CVD associated with general obesity and abdominal obesity assessed a few years before the onset of CVD.

Thus, using a nested case-control study design which can be used to investigate the risk of diseases associated with exposures assessed at a particular time point, we compared the association of CVD with BMI, WC, and WHtR collected at 4 years (data collected between 1 year and 3 years were not used for minimizing reverse causality bias) before the CVD event among middle-aged working Japanese men.

2 | METHODS

2.1 | Study design

This is a case-control study nested in the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study, an ongoing multi-company study of workers in Japan. Details on the J-ECOH Study and the CVD registration has been described elsewhere.[10,11] As the present study aimed to examine whether BMI, WC, and WHtR collected at 4 years before the CVD event were similarly associated with the development of CVD, we retrieved obesity data and other annual health checkup data collected from more than 100 000 workers between January 2008 and December 2013 or between

April 2008 and March 2014 in 11 participating companies (12 worksites) and their CVD data collected between April 2012 and March 2018. The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan (NCGM-G-001140-15).

2.2 | Ascertainment of CVD cases and control selection

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

From April 2012 to March 2018, 249 males and 20 females with incident CVD were registered. Emerging evidence suggests that sex hormones and sex-specific patterns of adiposity and fat distribution can lead to sex differences in the association between obesity and CVD.[12] In the present study, the number of female CVD cases was too small (n = 20) to analyses the association between obesity and CVD among women. Thus, we excluded women from the current analyses. Among these 249 male cases, we excluded eight patients without matched controls. Finally, 241 CVD cases (51 fatal cases), including 81 with MI (ICD-10: I21), and 160 with stroke (ICD-10: I60, I61, and I63), remained in the present study.

Controls were selected from study participants who did not self-report stroke or MI at J-ECOH Study entry and did not develop CVD during the follow-up period. Those who self-reported a history of CVD at annual health checkups during the study period were also excluded. For each case, we created a pool of controls who were matched by worksite, gender, and date of birth (±2 years). We then allocated an index date, which was the same as the event date of its matched case. We excluded people who did not attend health checkup at 4 years before the index date. Finally, for a given case, we randomly selected up to five 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. A total of 1,205 matched controls were included in the present study.

2.3 | Exposure

Measurements of body height, body weight, and waist circumference obtained 4 years prior to the event/index date were used for both cases and controls. The body height and weight were measured using a scale while the participant wore light clothes and no shoes. BMI was calculated as the weight in kilograms divided by the squared height in meters. WC was measured at the umbilical level in the standing position. WHtR was calculated as WC (cm) divided by height (cm).

2.4 | Covariates

The covariates included smoking, hypertension, diabetes, and dyslipidemia. We retrieved data collected at 4 years before the event/index date. Data collection methods have been described in detail in previous papers.[10,11,13] Smoking status was divided in to the following five groups: never smokers, past smokers, current low-intensity smokers (1-10 cigarettes/day), medium-intensity smokers (11-20 cigarettes/day), or high-intensity smokers (≥21 cigarettes/day). Hypertension was defined as systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or use of treatment for hypertension.[14] Diabetes was defined as a fasting plasma glucose level of at least 126 mg/dL, or a random plasma glucose level of at least 200 mg/dL, an HbA1c level of at least 6.5%, or medical treatment of diabetes.[15] Dyslipidemia was defined as an low-density lipoprotein-cholesterol level of at least 140 mg/dL, high-density lipoprotein-cholesterol level of less than 40 mg/dL, triglyceride level of at least 150 mg/dL, or use of medications for dyslipidemia.[16]

2.5 | Statistical analysis

In the present study, about 20% of study participants had one or more missing values. To improve efficiency and reduce bias, we handled missing data with multiple imputation using matching variables and full-conditional specification.[17] Fifty imputed data sets were produced, and analyses were combined using Rubin's rules.

The characteristics of the study participants were expressed as means (standard deviation) for continuous variables and as percentages for categorical variables. To examine differences in characteristics between cases and controls, we performed conditional logistic regression for categorical variables. For continuous variables, paired t-test was performed. There were five controls for each case. We first calculated the mean of matched controls, and then compared it with their case using paired *t* test.

Conditional logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) for the development of CVD associated with a one standard deviation (SD) unit change in BMI, WC, and WHtR respectively. We adjusted for smoking status in model 1. In model 2, we further adjusted for hypertension (yes or no), diabetes (yes or no), and dyslipidemia (yes or no). In addition, ORs were estimated at tertiles of BMI, WC, and WHtR respectively. BMI, WC, and WHtR were categorized into tertiles among controls, separately. The lowest tertile was used as the reference group. Trend association was assessed with ordinal scores 0-2 assigned to the three groups of BMI, WC and WHtR.

We also performed a sensitivity analysis using individuals with complete data. A two-sided $P < .05$ was considered statistically significant. Multiple imputation was performed in StataMP 15 (StataCorp). All other statistical analyses were performed using SAS version 9.4 (SAS Institute).

3 | RESULTS

The characteristics of cases and controls at 4 years prior to the CVD event/index date are summarized in Table 1. The mean (standard deviation) age of cases was 50.5 (6.2) years, and 80% of the individuals were ages less than 60 years. The mean values of BMI, WC, and WHtR were higher among cases than those among controls. Cases had higher prevalence of hypertension, diabetes, and dyslipidemia as well as smoking than controls.

As shown in Table 2, BMI, WC, and WHtR demonstrated generally similar strength of association with CVD risk. In model 1, the ORs (95% CIs) for CVD were 1.60 (1.38-1.85), 1.53 (1.33-1.78), 1.56 (1.35-1.81) for 1 SD increase in BMI, WC, and WHtR respectively. After additionally adjusting for hypertension, diabetes, and dyslipidemia (model 2), these associations were attenuated but remained statistically significant. The ORs (95% CIs) for CVD in the highest versus lowest tertile of BMI, WC, and WHtR were 2.94 (1.99-4.33), 2.61 (1.75-3.89), and 2.61 (1.76-3.87) respectively (model 1). Similar findings were observed in the sensitivity analysis using complete data (Table S1).

In Table 3, the three obesity measures (BMI, WC, and WHtR) were similarly and positively associated with all CVD subtypes. The ORs (95% CIs) for MI were 1.70 (1.34-2.17), 1.73 (1.35-2.23), 1.75 (1.35-2.27) for 1 SD increase in BMI, WC, and WHtR respectively. For stroke, the corresponding ORs (95% CIs) were 1.54 (1.28-1.85) for BMI, 1.44 (1.20-1.73) for WC, 1.47 (1.23-1.77) for WHtR. These associations were attenuated after additional adjustment for hypertension, diabetes, and dyslipidemia (model 2).

TABLE 1 Characteristics of cases and controls at 4 years before the date of CVD event, J-ECOH Study, Japan[a]

	Cases	Controls	*P*-value*
N	241	1,205	
Age (y)	50.5 (7.2)	50.4 (7.3)	<.001
Smoking status, %			
Never smokers	26.3	35.3	<.001
Past smokers	15.6	27.9	
Current low-intensity smokers[b]	8.4	6.9	
Medium-intensity smokers[b]	33.0	21.5	
High-intensity smokers[b]	16.8	8.5	
BMI (kg/m^2)	25.3 (3.8)	23.7 (3.1)	<.001
WC (cm)	87.9 (9.5)	84.0 (8.4)	<.001
WHtR	0.52 (0.05)	0.49 (0.05)	<.001
Hypertension, %	48.8	26.6	<.001
Hypertension treatment[c], %	52.5	59.6	<.001
Diabetes, %	27.1	10.9	<.001
Diabetes treatment[d], %	51.9	57.7	<.001
Dyslipidemia, %	68.5	60.2	<.001
Lipid-lowering treatment[e], %	11.2	14.6	.84

Note: Data were expressed as mean (standard deviation) or as percentages.
Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol levels; J-ECOH Study, the Japan Epidemiology Collaboration on Occupational Health Study; LDL-C, low-density lipoprotein-cholesterol; TG, Triglyceride; WC, waist circumference; WHtR, waist-to-height ratio.

[a]Dataset without multiple imputation was used for Table 1.

[b]Current low-intensity smokers, 1-10 cigarettes/d; medium-intensity smokers, 11-20 cigarettes/d; high-intensity smokers, ≥21 cigarettes/d.

[c]The denominator is the total number of people with hypertension (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current medical care for hypertension).

[d]The denominator is the total number of people with diabetes (FPG ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, or current medical care for diabetes).

[e]The denominator is the total number of people with dyslipidemia (LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, TG ≥ 150 mg/dL, or use of medications for dyslipidemia).

*Paired *t* test for continuous variables and conditional logistic regression for categorical variables.

4 | DISCUSSION

In this nested case-control study among middle-aged Japanese working men, we found that both general (BMI) and abdominal (WC and WHtR) obesity showed a significant and positive association with CVD, and that they demonstrated generally similar strength of association with CVD.

TABLE 2 Associations among BMI, WC, and WHtR and the risk of CVD, J-ECOH Study, Japan

	OR (95% CI)					
	1st tertile	2nd tertile	3rd tertile	*P* for trend	OR (95% CI) per SD increment	*P*
BMI (kg/m^2)	<22.2	22.2 to <24.5	≥24.5			
Model 1	1.00	1.43 (0.93–2.18)	2.94 (1.99–4.33)	<.001	1.60 (1.38–1.85)	<.001
Model 2	1.00	1.06 (0.67–1.65)	1.75 (1.14–2.68)	.01	1.29 (1.10–1.52)	.002
WC (cm)	<80	80 to <86.5	≥86.5			
Model 1	1.00	1.03 (0.66–1.62)	2.61 (1.75–3.89)	<.001	1.53 (1.33–1.78)	<.001
Model 2	1.00	0.70 (0.44–1.13)	1.46 (0.94–2.26)	.09	1.24 (1.05–1.46)	.01
WHtR	<0.47	0.47 to <0.51	≥0.51			
Model 1	1.00	1.12 (0.73–1.73)	2.61 (1.76–3.87)	<.001	1.56 (1.35–1.81)	<.001
Model 2	1.00	0.77 (0.48–1.22)	1.41 (0.91–2.18)	.10	1.25 (1.05–1.48)	.01

Notes: Model 1 adjusted for smoking status (never smokers, past smokers, current low-intensity smokers (1-10 cigarettes/d), medium-intensity smokers (11-20 cigarettes/d), or high-intensity smokers (≥21 cigarettes/d))

Model 2 additionally adjusted for hypertension (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current medical care for hypertension), diabetes (FPG ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, or current medical care for diabetes), dyslipidemia (LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, TG ≥ 150 mg/dL, or use of medications for dyslipidemia).

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol levels; J-ECOH Study, the Japan Epidemiology Collaboration on Occupational Health Study; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; OR, odds ratio; SD, standard deviation; TG, Triglyceride; WC, waist circumference; WHtR, waist-to-height ratio.

Our finding is in line with that of a meta-analysis mainly based on cohort studies,[4] suggesting that general obesity and abdominal obesity show similar associations with CVD. The current finding is also compatible with that of our previous report showing that BMI, WC, and WHtR showed similar associations with the clustering of cardio-metabolic risk factors in the cross-sectional analysis of the J-ECOH Study data.[10] In contrast, Browning et al[3] reviewed 22 prospective studies on cardiometabolic outcomes and concluded that WHtR and WC are more strongly associated with CVD than BMI. That systematic review, however, included only seven publications with CVD as an outcome and did not perform a meta-analysis. Our study and previous meta-analysis[4] provided evidence that the strength of association for each measure (WC, WHtR, and BMI) was similar, suggesting that general and abdominal obesity can be equally used in the assessment of the risk of CVD.

In the analysis by CVD subtypes, we found that the three obesity measures (BMI, WC and WHtR) were equally strongly associated with stroke and MI. The strength of the association with stroke observed in the present study is similar to that in the above-mentioned meta-analysis.[4] Specifically, in age group of 40-59 years in the meta-analysis, the age-, gender-, and smoking-adjusted ORs (95% CIs) of stroke for 1 SD increase in BMI and WC were 1.34 (1.21-1.48) and 1.45 (1.30-1.60) respectively. In the present study (mean age, 54 years), the corresponding ORs (95% CIs) were 1.54 (1.28-1.85) and 1.44 (1.20-1.73) (Table 3, Model 1). With regard to MI, we observed a somewhat stronger association (BMI, OR = 1.70, 95% CI, 1.34-2.17; WC, OR = 1.73, 95% CI, 1.35-2.23), compared to that for coronary heart disease (BMI, OR = 1.41, 95% CI, 1.30-1.53; WC, OR = 1.50, 95% CI, 1.37-1.63) in the above-mentioned meta-analysis. This may be due to the difference in study design, outcome (MI vs coronary heart disease), or to chance, given the fewer MI events in our study. The findings based on stratified analyses in our study and previous meta-analysis[4] provide further evidence that general obesity and abdominal obesity are similarly associated with CVD regardless of its subtypes.

The mechanisms underlying the association between obesity and CVD remain incompletely understood. Hypertension, diabetes, and dyslipidemia are established conditions linking obesity to CVD.[18,19] Yet, we found that after adjustment for these risk factors, the associations of BMI, WC and WHtR with CVD risk still remained statistically significant, a finding consistent with previous reports.[20,21] These results may suggest a pathway other than those through traditional CVD risk factors, such as obesity-induced prothrombotic state and inflammation, which may additionally contribute to the development of CVD.[18,19]

Strengths of the current study include its prospective design as a nested case-control study within a well-defined cohort; objective measures of obesity based on measured height, weight, and WC; and assessment of confounding (smoking) and mediating (hypertension, diabetes, and dyslipidemia) variables at 4 years prior to the CVD event for cases and the index date for controls. There are several limitations that warrant mention. First, due to the lack of data on socioeconomic status, family history of CVD, and lifestyles other than smoking (eg, alcohol drinking, diet, physical activity), we were unable to control for potential effects of these factors. Further, residual confounding may

TABLE 3 Associations among BMI, WC, and WHtR and the risk of MI and Stroke, J-ECOH Study, Japan

	OR (95% CI)					
	1st tertile	2nd tertile	3rd tertile	*P* for trend	OR (95% CI) per SD increment	*P*
MI						
BMI (kg/m^2)	<22.2	22.2 to <24.5	≥24.5			
Model 1	1.00	2.16 (1.00–4.66)	3.58 (1.75–7.33)	<.001	1.70 (1.34–2.17)	<.001
Model 2	1.00	1.36 (0.59–3.15)	1.92 (0.87–4.28)	.09	1.33 (1.01–1.76)	.04
WC (cm)	<80	80 to <86.5	≥86.5			
Model 1	1.00	2.27 (0.93–5.54)	5.43 (2.29–12.9)	<.001	1.73 (1.35–2.23)	<.001
Model 2	1.00	1.53 (0.60–3.90)	2.69 (1.05–6.89)	.02	1.37 (1.02–1.82)	.04
WHtR	<0.47	0.47 to <0.51	≥0.51			
Model 1	1.00	1.71 (0.78–3.77)	3.64 (1.68–7.87)	<.001	1.75 (1.35–2.27)	<.001
Model 2	1.00	1.03 (0.43–2.43)	1.52 (0.63–3.66)	.24	1.36 (0.99–1.84)	.05
Stroke						
BMI (kg/m^2)	<22.2	22.2 to <24.5	≥24.5			
Model 1	1.00	1.43 (0.93–2.18)	2.71 (1.70–4.33)	<.001	1.54 (1.28–1.85)	<.001
Model 2	1.00	0.92 (0.54–1.58)	1.75 (1.05–2.92)	.01	1.29 (1.05–1.58)	.02
WC (cm)	<80	80 to <86.5	≥86.5			
Model 1	1.00	0.77 (0.45–1.31)	2.05 (1.30–3.22)	<.001	1.44 (1.20–1.73)	<.001
Model 2	1.00	0.52 (0.29–0.91)	1.23 (1.75–2.04)	.15	1.20 (0.97–1.47)	.09
WHtR	<0.47	0.47 to <0.51	≥0.51			
Model 1	1.00	0.93 (0.55–1.57)	2.30 (1.46–3.45)	<.001	1.47 (1.23–1.77)	<0.001
Model 2	1.00	0.77 (0.48–1.22)	1.41 (0.91–2.18)	.07	1.22 (0.99–1.50)	0.05

Notes: Model 1 adjusted for smoking status (never smokers, past smokers, current low-intensity smokers (1-10 cigarettes/d), medium-intensity smokers (11-20 cigarettes/d), or high-intensity smokers (≥21 cigarettes/d)).

Model 2 additionally adjusted for hypertension (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current medical care for hypertension), diabetes (FPG ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, or current medical care for diabetes), dyslipidemia (LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, TG ≥ 150 mg/dL, or use of medications for dyslipidemia).

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol levels; J-ECOH Study, the Japan Epidemiology Collaboration on Occupational Health Study; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; OR, odds ratio; SD, standard deviation; TG, Triglyceride; WC, waist circumference; WHtR, waist-to-height ratio.

also exist due to the incomplete assessment of covariates such as smoking (the lack of data on smoking duration). Second, the number of CVD cases for each subtype was not sufficiently large to detect a modest association with statistical significance. Third, the small number of female CVD cases (n = 20) precludes us to compare the strength of association for general obesity and abdominal obesity in women. In addition, our study is a Japanese occupational cohort. Thus, our findings may not be generalizable to female workers, the general population, or other racial/ethnic groups.

5 | CONCLUSIONS

General (BMI) and abdominal (WC and WHtR) obesity demonstrated generally similar strength of association with CVD and its subtypes among middle-aged Japanese men.

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DISCLOSURE

Approval of the research protocol: The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and

Medicine, Japan. 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. *Informed consent:* Participants did not provide their verbal or written informed consent to join the study but were allowed to refuse their participation. This procedure conforms to the Japanese Ethical Guidelines for Epidemiological Research, where the procedure for obtaining consent may be simplified for observational studies that use existing data. *Registry and the registration no. of the study/trial:* N/A. *Animal studies:* N/A. *Conflict of interest:* Authors declare no conflict of interests for this article.

AUTHOR CONTRIBUTIONS

SD and T Mizoue were involved in the design of the study as the principal investigators; TI, A Nishihara, NS, TO, AH, TN, SY, TH,HO, AU, MY, T Miyamoto, TK, ME, T Murakami, MS, KT, SN, I Kabe, and SD collected health check-up data; MK and A Nanri cleaned CVD data; T Mizoue, MK, and KK created database; MX, HH, T Mizoue, SA, I Kashino, MY, KK and NK drafted the plan for the data analysis; HH and MX conducted data analysis; MX drafted manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

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