Association among age, gender, menopausal status and small dense low-density lipoprotein cholesterol: a cross-sectional study

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ABSTRACT

Objectives Small dense low-density lipoprotein cholesterol (sdLDL-C) might be a better cardiovascular disease (CVD) indicator than low-density lipoprotein cholesterol (LDL-C); however, details regarding its epidemiology remain elusive. The present study aimed at evaluating the association between the demographic factors, such as age, gender and menopausal status, and sdLDL-C levels and sdLDL-C/LDL-C ratio in the Japanese population.

Design This was a cross-sectional study.

Setting 13 rural districts in Japan, 2010–2017.

Participants This study included 5208 participants (2397 men and 2811 women), who underwent the health mass screening that was conducted in accordance with the medical care system for the elderly and obtained informed consent for this study.

Results In total, 517 premenopausal women (mean age ±SD, 45.1±4.2 years), 2294 postmenopausal women (66.5±8.8 years) and 2397 men (64.1±11.2 years) were analysed. In men, the sdLDL-C levels and sdLDL-C/LDL-C ratio increased during younger adulthood, peaked (36.4 mg/dL, 0.35) at 50–54 years, and then decreased. In women, relatively regular increasing trends of sdLDL-C level and sdLDL-C/LDL-C ratio until approximately 65 years (32.7 mg/dL, 0.28), followed by a downward or pleated trend. Given the beta value of age, body mass index, fasting glucose and smoking and drinking status by multiple linear regression analysis, standardised sdLDL-C levels and sdLDL-C/LDL-C ratio in 50-year-old men, premenopausal women and postmenopausal women were 26.6, 22.7 and 27.4 mg/dL and 0.24, 0.15 and 0.23, respectively. The differences between premenopausal and postmenopausal women were significant (p<0.001).

Conclusions SdLDL-C and sdLDL-C/LDL-C ratio showed different distributions by age, gender and menopausal status. A subgroup-specific approach would be necessary to implement sdLDL-C for CVD prevention strategies, fully considering age-related trends, gender differences and menopausal status.

INTRODUCTION

Although hypercholesterolaemia is one of the leading causes of cardiovascular disease (CVD), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (nonHDL-C) have not been good enough to predict risk stratification and the novel target is needed. Small dense low-density lipoprotein cholesterol (sdLDL-C) easily penetrates into the arterial wall, has a high susceptibility to oxidation and may exacerbate and perpetuate atherosclerosis. To the best of our knowledge, the present study is the first to demonstrate the association between age, gender and menopausal status on the small dense low-density lipoprotein cholesterol (sdLDL-C) and sdLDL-C/LDL-C ratio. This study is based on a large representative sample from Japanese general population. Serum lipid markers were measured by the standardised programme proposed by the Clinical and Laboratory Standards Institute. It is unclear whether our results of sdLDL-C would be valid for other populations. This study did not control for several confounding factors, such as diet, life activity, socioeconomic status and genetic factors.
LDL-C ratio over a wide age range and distinguished the effects of menopause and gender on sdLDL-C and sdLDL-C fraction from those of ageing. 10,11 Diet composition, which is affected by ageing, is associated with blood cholesterol and the absorption, synthesis and metabolism per se of fat and lipoproteins change with age. 12 13 Another study showed Asian age-related trends of traditional lipid profiles displayed roughly an increasing trend, followed by a decreasing one at the middle-aged stage. 14 15 Meanwhile, sdLDL-C has been regulated by more complex mechanisms than regulating traditional lipids and might be plateaued or increased even at the middle aged by changed metabolic functions with ageing influencing sdLDL-C synthesis. 3 7 12 16 17 Furthermore, the detailed multiple mechanisms of metabolising sdLDLs are unknown in the real-world, population-based setting and the age-related trend of sdLDL-C might be different from the sdLDL-C/LDL-C ratio. In other words, the ability to generate sdLDL-C from LDL-C might be different among each generation, gender and menopausal status. Therefore, we evaluated the association between the demographic factors, such as age, gender and menopausal status, and sdLDL-C and sdLDL-C/LDL-C ratio in Japanese general population.

METHODS
Population
The present cross-sectional study was conducted as part of the Jichi Medical School-II Cohort Study, a population-based cohort study of the risk factors of atherosclerosis and CVD in the Japanese general population. A total of 6436 individuals participated in this study. Details of the methods of enrolment have been reported previously. 18 19 In brief, from April 2010 through December 2017, this study evaluated Japanese individuals who were residents of 13 rural districts in Japan, Shimotsuke, Kakara, Sue, Omori, Kamichi, Wara, Takasu, Onabi, Nakatsu, Yame, Miwa, Ueno and Saji areas. Local government offices in each community issued invitations to eligible residents for the mass CVD screening, and personal invitations were also sent to all potential participants by mail. All the participants in the present study provided written informed consent prior to inclusion.

We excluded individuals as follows: (1) taking lipid-lowering agents or antihyperglycaemia agents (n=1073); (2) the use of hormone replacement therapy (n=96); and (3) the data such as age, gender status, menopausal status and sdLDL-C were not available (n=73).

Measurements
A central committee, composed of the chief medical officers of all 13 participating districts, developed a detailed manual for data collection. Body weight was recorded with the subjects clothed. Height was measured with stockinged feet. Body mass index (BMI) was calculated as weight (kg)/height (m²). Blood samples were taken after overnight fasting. TC was measured via a cholesterol dehydrogenase-ultraviolet method. Triglycerides (TG) was measured using an enzymatic method. LDL-C and high-density lipoprotein cholesterol (HDL-C) were measured by direct methods using a commercial kit (Cholestest from Sekisui Medical, Tokyo, Japan). sdLDL-C level was directly and selectively measured using a commercial kit (sdLDL-EX from Denka Seiken, Tokyo, Japan). An external laboratory (SRL, Tokyo, Japan) measured the serum lipid markers. The markers were measured by the standardised programme proposed by the Clinical and Laboratory Standards Institute. The nonHDL-C was calculated by subtracting HDL-C from TC. Information about medical history, lifestyle and menopausal status were obtained with a self-reported questionnaire. Smoking status was classified as smoking, former smoking, or never smoking.

Statistical analysis
Baseline characteristics were summarised as mean±SD for normally distributed continuous variables and numbers and percentages for categorical variables. SdLDL-C and TG were highly skewed; these data were expressed as the median and IQR and transformed into natural logarithms before statistical analysis. The participants were divided into three groups (men, premenopausal women and postmenopausal women) according to gender and menopausal status.

The one-way analysis of variance was used for comparison among three groups, and differences were tested via post hoc pairwise comparison (Bonferroni). To explore the age-related trend in sdLDL-C and sdLDL-C/LDL-C ratio with age, geometric means or means and 95% CIs for each variable in 5-year age ranges were derived and plotted against age range in each of the three groups.

Among the three groups, correlations between age and each parameter were assessed using multiple linear regression analysis. Considering the beta value of age, BMI, fasting glucose and smoking and drinking status, we calculated the estimated sdLDL-C and sdLDL-C/LDL-C ratio. The agreement between the estimated sdLDL-C and sdLDL-C/LDL-C ratio and measured ones was assessed by Pearson’s correlation coefficient. To evaluate the effect of menopausal status on sdLDL-C and sdLDL-C/LDL-C ratio, using the beta value of each variable from the analysis in the premenopausal and postmenopausal group, data were standardised to a nominal 50 years of menopausal age, never smoking and zero alcohol for participants with normal weight (BMI 18.5–22.0). All statistical analyses were performed using SPSS V.22 (IBM), and statistical significance was defined as p<0.05.

Patient and public involvement
Participants of this study or members of the public were not directly and personally involved with study design, data provision, analysis and publication of the study.
## RESULTS

### Baseline characteristics

After exclusions, 517 premenopausal women (mean age ±SD, 45.1±4.2 years), 2294 postmenopausal women (66.5±8.8 years) and 2397 men (64.1±11.2 years) were analysed. Demographic data for the three groups are shown in table 1. Compared with men, premenopausal women had higher HDL-C and postmenopausal women had higher TC, LDL-C, HDL-C and nonHDL-C. Compared with premenopausal women, postmenopausal women had higher fasting glucose, TC, LDL-C, TG, nonHDL-C, TC/LDL-C, sdLDL-C and sdLDL-C/LDL-C. TC and LDL-C did not differ between men and premenopausal women.

### sdLDL-C trends in 5-year age groups

To assess the age-related trend in sdLDL-C levels, a 5-year age stratification was applied, and geometric mean sdLDL-C levels for each age groups were calculated and plotted against gender.

For men, the level of sdLDL-C increased from 34.1 mg/dL in those <39 years to a maximum of 37.7 mg/dL in those of 50–54 years, followed by decreasing from 36.4 mg/dL in those of 55–59 years to 27.4 mg/dL in those of 80 ≤ years (figure 1). For women, a relatively regular increasing trend of the sdLDL-C level was found up to 60–64 year olds. After 65 years, a downward trend was fitted. The maximum of the sdLDL-C level of women was 32.7 mg/dL. Moreover, sdLDL-C levels in men were higher than those in women for all age groups younger than 70–74year olds but exceeded those in women after the age of 75–79 years.

### sdLDL-C/LDL-C ratio trends in 5-year age groups

SdLDL-C/LDL-C ratio in men increased from 0.30 in 40–44 year olds to a maximum of 0.35 in 50–54year olds, plateaued in those of 55–59 years, and then decreased from 0.34 in those of 60–64 years to 0.28 in those of 80 ≤ years (figure 2). For women, these values increased from 0.20 in those <39 years to a maximum of 0.28 in those of 65–69 years and plateaued after 70≤years (with mean levels of 0.27). SdLDL-C/LDL-C ratio in men was higher than those in women for all age groups and the crossover of sdLDL-C/LDL-C ratio for the genders did not occur.

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### Table 1 Baseline characteristics

|                | Group 1 (G1) | Group 2 (G2) | Group 3 (G3) | P value | P value | P value |
|----------------|-------------|--------------|--------------|---------|---------|---------|
|                | Men (n=2397)| Premenopausal women (n=517) | Postmenopausal women (n=2294) | G1 versus G2 | G1 versus G3 | G2 versus G3 |
| Age, years     | 64.1±11.2  | 45.1±4.2     | 66.5±8.8     | <0.001  | <0.001  | <0.001  |
| BMI, kg/m²     | 23.3±3.0   | 22.3±3.6     | 22.5±3.3     | <0.001  | <0.001  | 0.631   |

| Smoking        |            |              |              |         |         |         |
|----------------|------------|--------------|--------------|---------|---------|---------|
| Current        | 600 (25.1%)| 40 (7.7%)    | 67 (2.9%)    | <0.001  | <0.001  | 0.007   |
| Ex             | 1204 (50.3%)| 73 (14.1%)  | 97 (4.2%)    | <0.001  | <0.001  | <0.001  |
| Drinker        | 1869 (78.2%)| 316 (61.1%) | 866 (37.8%)  | <0.001  | <0.001  | <0.001  |
| Glucose, mg/dL | 100.7±17.8 | 90.9±9.4     | 96.3±12.3    | <0.001  | <0.001  | <0.001  |
| TC, mg/dL      | 198.7±32.9 | 199.2±31.2   | 215.4±31.6   | 1.000   | <0.001  | <0.001  |
| LDL-C, mg/dL   | 115.2±29.6 | 114.2±28.5   | 126.7±28.7   | 1.000   | <0.001  | <0.001  |
| TGs, mg/dL     | 100 (71 to 146) | 68 (50 to 94) | 89 (67 to 123) | <0.001  | <0.001  | <0.001  |
| HDL-C, mg/dL   | 56.3±13.8  | 67.8±14.7    | 62.8±14.9    | <0.001  | <0.001  | <0.001  |
| Non HDL-C, mg/dL | 142.4±32.6 | 131.4±31.2  | 152.5±31.3   | <0.001  | <0.001  | <0.001  |
| TC/HDL-C       | 3.7±1.0    | 3.1±0.8      | 3.6±0.9      | <0.001  | <0.001  | <0.001  |
| SdLDL-C, mg/dL | 34.1 (24.8 to 46.5) | 23.0 (16.8 to 30.5) | 31.2 (23.5 to 41.8) | <0.001  | <0.001  | <0.001  |
| SdLDL-C/LDL-C  | 0.32±0.14  | 0.22±0.08    | 0.29±0.12    | <0.001  | <0.001  | <0.001  |

Data are expressed as mean±SD, %, and median (25th percentile, 75th percentile). P values were assessed in one-way analysis of variance and post hoc pairwise comparison (Bonferroni).

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non HDL-C, non high-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.
Trends in other lipoproteins (LDL-C, TC, TG, HDL-C and TC/HDL-C ratio) in 5-year age groups

LDL-C level in men decreased almost linearly, while LDL-C level in women rapidly increased from 100.3 mg/dL in those aged <39 years to a maximum of 132.8 mg/dL in 60–64 year olds and decreased from 128.2 mg/dL in those aged 65–69 to 119.5 mg/dL in those ≥80 years (figure 3). The level of TC, nonHDL-C and TC/HDL-C ratio revealed a pattern similar to the trend of LDL-C levels (see online supplemental figures 1-3). The TG levels in men decreased almost linearly, while the level in women increased linearly (see online supplemental figure 4). HDL-C in both men and women decreased almost linearly (see online supplemental figure 5).

sdLDL-C and sdLDL-C/LDL-C ratio in the standardised analysis among the three groups

To standardise sdLDL-C and sdLDL-C/LDL-C ratio among the three groups and validate the above-mentioned turning points, the participants were restratified by age ranges corresponding to increasing, plateau and decreasing phases for each marker by gender and multiple linear regression analysis was then applied.

As shown in table 2, among men, age was positively and negatively associated with log-transformed small dense low-density lipoprotein cholesterol (LNsdLDL-C) levels in those ≤54 years and ≥55 years. Among premenopausal women, postmenopausal women ≤64 years and postmenopausal women 65≥years, age was positively, positively and negatively associated with LNsdLDL-C levels. But the association between LNsdLDL-C and age was not significantly associated with men ≤54 years.

| Variable                  | β   | SE   | P value |
|---------------------------|-----|------|---------|
| Men ≤54, n=475; mean±SD, 46.7±4.9 years, Pearson’s r=0.320 (p<0.001) |     |      |         |
| Age                       | 0.006 | 0.004 | 0.169  |
| BMI                       | 0.033 | 0.006 | <0.001 |
| Fasting glucose           | 0.004 | 0.002 | 0.003  |
| Smoker                    |     |      |         |
| Current                   | 0.018 | 0.054 | 0.747  |
| Ex                        | 0.050 | 0.053 | 0.342  |
| Drinker                   | 0.144 | 0.059 | 0.015  |
| Men ≥55, n=1922; 68.4±7.6 years, Pearson’s r=0.316 (p<0.001) |     |      |         |
| Age                       | −0.010 | 0.001 | <0.001 |
| BMI                       | 0.032 | 0.003 | <0.001 |
| Fasting glucose           | 0.002 | 0.001 | <0.001 |
| Smoker                    |     |      |         |
| Current                   | 0.025 | 0.030 | 0.402  |
| Ex                        | 0.032 | 0.024 | 0.192  |
| Drinker                   | 0.076 | 0.024 | 0.001  |
| Women (premenopausal), n=517; 45.1±4.2 years, Pearson’s r=0.330 (p<0.001) |     |      |         |
| Age                       | 0.014 | 0.005 | 0.002  |
| BMI                       | 0.024 | 0.006 | <0.001 |
| Fasting glucose           | 0.008 | 0.002 | <0.001 |
| Smoker                    |     |      |         |
| Current                   | 0.021 | 0.072 | 0.775  |
| Ex                        | −0.005 | 0.056 | 0.934  |
| Drinker                   | 0.033 | 0.039 | 0.398  |
| Women ≤64 years (postmenopausal), n=978; 58.3±4.5 years, Pearson’s r=0.261 (p<0.001) |     |      |         |
| Age                       | 0.014 | 0.003 | <0.001 |
| BMI                       | 0.019 | 0.004 | <0.001 |
| Fasting glucose           | 0.004 | 0.001 | <0.001 |
| Smoker                    |     |      |         |
| Current                   | 0.052 | 0.067 | 0.437  |
| Ex                        | 0.036 | 0.051 | 0.479  |
| Drinker                   | 0.007 | 0.026 | 0.792  |
| Women 65≥years (postmenopausal), n=1316; 72.6±5.7 year olds, Pearson’s r=0.228 (p<0.001) |     |      |         |
| Age                       | −0.004 | 0.002 | 0.045  |
| BMI                       | 0.022 | 0.004 | <0.001 |
| Fasting glucose           | 0.003 | 0.001 | 0.001  |
| Smoker                    |     |      |         |
| Current                   | −0.086 | 0.078 | 0.267  |
| Ex                        | 0.204 | 0.076 | 0.007  |

Continued
As shown in Table 3, age in men ≤54 years, 55–59 years and 60+ years, was positively, positively and negatively associated with sdLDL-C/LDL-C ratio. In women, age in premenopausal women, postmenopausal women ≤69 years was positively associated with sdLDL-C/LDL-C ratio, whereas age in postmenopausal women 70+ years was not significantly associated sdLDL-C/LDL-C ratio. The association between sdLDL-C/LDL-C and age was not significantly associated with men 55–59 years, premenopausal women and postmenopausal women 70+ years.

Considering the beta value of each variable, 50-year-old standardised sdLDL-C levels in men, premenopausal women and postmenopausal women were 26.6 mg/dL (95% CI 26.4 to 26.9 mg/dL), 22.7 mg/dL (95% CI 22.5 to 22.9 mg/dL) and 27.4 mg/dL (95% CI 27.3 to 27.5 mg/dL), respectively. Standardised sdLDL-C/LDL-C ratio in men, premenopausal women and postmenopausal women were 0.24 (95% CI 0.24 to 0.24), 0.15 (95% CI 0.15 to 0.16) and 0.23 (95% CI 0.22 to 0.23), respectively. These differences between premenopausal women and postmenopausal women were significant (Bonferroni analysis, p<0.001).

**DISCUSSION**

To the best of our knowledge, the present study is the first to demonstrate the association between age, gender, menopausal status and sdLDL-C and sdLDL-C/LDL-C ratio. The age-related sdLDL-C trend showed roughly an increasing phase, followed by a decreasing phase in men and a plateaued phase in middle-aged women. The age-related sdLDL-C trend in men, but not in women, was similar to traditional lipid cholesterol profiles. The reason for this gender difference might be related to the mechanism of hypertriglyceridaemia in postmenopausal women, which induced small LDL particles. There were age or gender-related differences in sdLDL-C/LDL-C ratio, reflecting the ability to generate sdLDL-C from LDL-C. This ability in men was higher than that in women for all age groups or standardised groups, which is identical to the fact that atherosclerosis is more common in men than in women, considering sdLDL-C is a highly atherogenic factor.

Our study showed three important results. First, age showed partial correlation trends with sdLDL-C levels and sdLDL-C/LDL-C ratio and non-linear trends between age and sdLDL-C and sdLDL-C/LDL-C ratio were found in both men and women. Therefore, using the sdLDL-C and sdLDL-C/LDL-C ratio, the definition of CVD risk

### Table 2

| Variable | β    | SE    | P value |
|----------|------|-------|---------|
| Drinker  | −0.007 | 0.024 | 0.760   |

β is a coefficient indicating a one-unit increase in an independent variable in multivariable linear logic regression analyses. BMI, body mass index.

### Table 3

| Variable | β    | SE    | P value |
|----------|------|-------|---------|
| Age      | 0.003 | 0.001 | 0.020   |
| BMI      | 0.005 | 0.002 | 0.012   |
| Fasting glucose | 0.001 | 0.000 | 0.010   |
| Smoker Current | 0.029 | 0.016 | 0.081   |
| Ex       | 0.011 | 0.016 | 0.501   |
| Drinker  | 0.049 | 0.018 | 0.007   |
| Men 55–59 years, n=245; 57.2±1.4 years, Pearson’s r=0.222 (p<0.001) | 0.004 | 0.007 | 0.589   |
| BMI      | 0.003 | 0.003 | 0.385   |
| Fasting glucose | 0.001 | 0.001 | 0.285   |
| Smoker Current | 0.049 | 0.032 | 0.125   |
| Ex       | 0.062 | 0.030 | 0.042   |
| Drinker  | 0.055 | 0.027 | 0.041   |
| Men 60+ years, n=1677; 70.0±6.8 years, Pearson’s r=0.272 (p<0.001) | −0.002 | 0.000 | <0.001   |
| BMI      | 0.005 | 0.001 | <0.001   |
| Fasting glucose | 0.001 | 0.000 | <0.001   |
| Smoker Current | 0.029 | 0.009 | 0.001   |
| Ex       | 0.009 | 0.007 | 0.235   |
| Drinker  | 0.055 | 0.007 | <0.001   |
| Women (premenopausal), n=517; 45.1±4.2 years, Pearson’s r=0.313 (p<0.001) | 0.001 | 0.001 | 0.147   |
| BMI      | 0.003 | 0.001 | 0.002   |
| Fasting glucose | 0.001 | 0.000 | <0.001   |
| Smoker Current | 0.010 | 0.012 | 0.413   |
| Ex       | 0.000 | 0.010 | 0.988   |
| Drinker  | 0.015 | 0.007 | 0.027   |
| Women (postmenopausal), n=1434; 61.0±5.5 years, Pearson’s r=0.264 (p<0.001) | 0.002 | 0.000 | <0.001   |
| BMI      | 0.004 | 0.001 | <0.001   |
| Fasting glucose | 0.001 | 0.000 | <0.001   |
| Smoker Current | 0.001 | 0.012 | 0.914   |
| Ex       | 0.013 | 0.010 | 0.201   |
| Drinker  | 0.003 | 0.005 | 0.555   |

Continued
assessment and the adaption of the lipid-lowering therapy should fully consider age-related trends and gender differences.

Second, menopausal status was an additional determinant of increasing sdLDL-C and sdLDL-C/LDL-C ratio. Many factors such as excess adiposity, free fatty acids, apolipoproteins and action of lipoprotein lipase activity and cholesterol ester transfer protein affected multiple and complex mechanisms regulating sdLDL.\(^1\)\(^2\)\(^3\) In postmenopausal women, the decrease of plasma oestrogen levels plays a significant role in reducing the clearance of LDL particles via LDL receptor and increasing TG and levels of traditional lipid factors. It is also unknown whether these factors might affect sdLDL-C levels and sdLDL-C/LDL-C ratio because sdLDLs are regulated through complex mechanisms. Third, we did not control for the effects of diet, life activity, socioeconomic status and genetic factors, which might be associated with changes in lipid metabolism.\(^28\)\(^-\)\(^30\) Fourth, there might be several biases. Selection bias might come from potential non-representativeness of the study population, which was rural dwelling. There might be information bias and data misclassification due to error in measurement of the lipid parameters. Fifth, as shown in the online supplemental figures 6 and 7, the results regarding the association between demographic factors and sdLDL-C and sdLDL-C/LDL-C ratio remained the same in 6282 participants including patients taking lipid-lowering therapy. SdLDL-C/LDL-C ratio in men including patients taking lipid-lowering therapy was higher than in men excluding these patients (0.45 vs 0.35). Our assessment was limited in terms of this difference, because data regarding type and dose of medications for dyslipidaemia were not available. We need to validate the association in patients taking lipid-lowering therapy in another cohort. Finally, our study could not evaluate the association between the demographic factors and other lipid markers, such as Lp(a) and oxidised LDL-C. Lp(a) was a significant risk factor for cardiovascular disorders and to be in the spotlight due to a novel therapy using anti-sense oligonucleotides. These lipid markers should be discussed in further study.\(^31\)

### CONCLUSION

SdLDL-C and sdLDL-C/LDL-C ratio are differently distributed by age, gender and menopausal status. Our findings suggest that a subgroup-specific approach is required to develop efficient CVD prevention strategies using the sdLDL-C and sdLDL-C/LDL-C ratio.

| Variable | \(\beta\) | SE | \(P\) value |
|----------|--------|----|----------|
| Women 70±years (postmenopausal), n=860; 75.6±4.6 year olds, Pearson’s \(r=0.167\) (\(p<0.001\)) | | |
| Age | 0.000 | 0.001 | 0.704 |
| BMI | 0.004 | 0.001 | <0.001 |
| Fasting glucose | 0.001 | 0.000 | <0.001 |
| Smoker | | |
| Current | -0.049 | 0.025 | 0.052 |
| Ex | 0.034 | 0.021 | 0.0102 |

\(\beta\) is a coefficient indicating a one-unit increase in an independent variable in multivariable linear logic regression analyses. BMI, body mass index.
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Competing interests None declared.

Patient consent for publication All the participants included in the present study provided written informed consent for publication.

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All the participants included in the present study provided written informed consent prior to inclusion, and this study was approved by the Institutional Review Board of Jichi Medical School (Tochigi, Japan, IRB No. G09-39 [G17-64 revised]).

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