Midlife and late-life diabetes and sarcopenia in a general older Japanese population: The Hisayama Study

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ABSTRACT
Aims/Introduction: To investigate the association between midlife or late-life diabetes and the development of sarcopenia in an older Japanese population.

Materials and Methods: A total of 824 Japanese residents aged 65 to 84 years without sarcopenia were followed up from 2012 to 2017. Sarcopenia was determined following the Asian Working Group for Sarcopenia definition. The time of diabetes diagnosis was classified as midlife or late-life diabetes by the age at first diagnosis of diabetes (< 65 or ≥ 65 years) based on annual health checkups data over the past 24 years. The duration of diabetes was categorized into three groups of < 10, 10–15, and > 15 years. The odds ratios of incident sarcopenia according to the diabetic status were estimated using a logistic regression analysis.

Results: During follow-up, 47 subjects developed sarcopenia. The multivariable-adjusted odds ratio for incident sarcopenia was significantly greater in subjects with diabetes at baseline than in those without it (odds ratio 2.51, 95% confidence interval 1.26–5.00). Subjects with midlife diabetes had a significantly greater risk of incident sarcopenia, whereas no significant association between late-life diabetes and incident sarcopenia was observed. With a longer duration of diabetes, the risk of incident sarcopenia increased significantly (P for trend = 0.002).

Conclusions: The present study suggests that midlife diabetes and a longer duration of diabetes are significant risk factors for incident sarcopenia in the older population. Preventing diabetes in midlife may reduce the risk of the development of sarcopenia in later life.

INTRODUCTION
Sarcopenia, determined as a combined low muscle mass and low muscle function1,2, is widely recognized to be associated with the development of falls, functional decline, and mortality3–5. As the aging of the worldwide population has accelerated, the prevention of sarcopenia in older people has become increasingly important to extend healthy life expectancy.

Although malnutrition and a sedentary lifestyle are the major determinants of sarcopenia6,7, further exploration of possible risk factors is required to extend intervention options.

Diabetes is a major public health problem worldwide. Several prospective studies have demonstrated that diabetes increased the risk of physical disability8 and accelerated both muscle volume and loss of strength over time among older people9–11. Therefore, diabetes may be considered to be a risk factor for incident sarcopenia. Moreover, one cross-sectional study has shown that a longer duration of diabetes was associated with...
poorer muscle quality in older adults in the USA12, which raises the possibility that the impact of diabetes diagnosed in midlife (i.e., midlife diabetes) may be different from that of diabetes diagnosed in late-life (i.e., late-life diabetes). However, only one cross-sectional study has investigated the association of diabetic status with sarcopenia in older populations13, and there has been no prospective study examining the association of the diabetic status, including midlife and late-life diabetes, with incident sarcopenia.

The present study investigated the association of diabetic status with incident sarcopenia, focusing particularly on the difference in the influence of midlife and late-life diabetes, as well as the duration of diabetes. The findings from the present study are expected to provide clear evidence of the divergent associations of midlife and late-life diabetes with the risk of sarcopenia in the older population.

MATERIALS AND METHODS

Study population

The Hisayama Study is an ongoing cohort study designed to study cardiovascular disease and its risk factors in the town of Hisayama, a suburb of Kyushu Island in Japan. Details of the survey were reported previously14. Briefly, full community surveys have been repeated annually since 1961 for residents aged 40 years or older14. Moreover, comprehensive screening surveys of activities of daily living (ADL) and cognitive function have been conducted for older residents every 6–7 years since 198515. A flow chart of the sample selection for the present study is shown in Figure 1. A total of 1,906 residents (participation rate: 93.8%) aged 65 years or older took part in the screening survey in 2012. Of those, 44 subjects who did not consent to enroll in this study, 300 subjects aged 85 years or older, 71 subjects with sarcopenia at the baseline examination, 297 subjects who lacked sufficient data to determine the presence of sarcopenia, 14 subjects with missing plasma glucose measurement in 2012, 110 subjects without data on diabetes status in midlife (aged 40–64 years) based on the data of annual health checkups over the past 24 years (1988–2011), and 27 subjects with missing data of other risk factors were excluded from the baseline examination. The remaining 1,043 subjects (448 men and 595 women) were reexamined for sarcopenia in 2017. After excluding 63 subjects who died before the survey in 2017, 32 subjects who did not attend the survey in 2017, and 124 subjects who lacked sufficient data to determine the diagnosis of sarcopenia in 2017, a total of 824 subjects (345 men and 479 women) were finally enrolled in the present study (follow up rate: 79.0%).

Written informed consent was obtained from all participants. This study was done under the approval of Kyushu University Institutional Review Board for Clinical Research.

Definition of diabetes

In the 2012 survey, among 824 eligible subjects, 716 (86.9%) subjects had a 75 g oral glucose tolerance test after fasting for at least 12 h, and the remaining 108 subjects underwent a single measurement of fasting or postprandial plasma glucose concentrations. Plasma glucose concentrations were measured using the hexokinase method in 2012. Glycated hemoglobin (HbA1c) levels were measured by high-performance liquid chromatography in 2012. Diabetes was defined as a fasting plasma glucose (FPG) concentration of ≥ 7.0 mmol/L, a postprandial or 2 h postload glucose concentration of ≥ 11.1 mmol/L, or the current use of any antidiabetic agents (oral hypoglycemic agents or insulin)10. The type of diabetes (type 1 or type 2) was determined based on clinical information.

In addition, the time of diabetes diagnosis was classified as midlife or late-life by the age at first diagnosis of diabetes based on the data of annual health checkups over the past 24 years (between 1988 and 2011). Plasma glucose concentrations were measured using the glucose-oxidase method from 1988 to 1999, and the hexokinase method from 2000 to 2011. In each survey, diabetes was defined according to the definition used in the 2012 survey mentioned above. The time of diabetes diagnosis was classified as follows: (a) late-life diabetes was determined as diabetes first diagnosed at age 65 years or older; and (b) midlife diabetes was determined as diabetes first diagnosed at an age less than 65 years. The duration of diabetes was determined as the number of years from the first diagnosis of diabetes to 2012. Subjects with diabetes were categorized into one of three categories (< 10, 10 to 15, and > 15 years) according to the duration of diabetes. In a sensitivity analysis, we investigated the association of the age at first diagnosis of diabetes with incident sarcopenia. Subjects with diabetes were categorized into one of three categories (40–59, 60–69, and ≥ 70 years) according to the age at first diagnosis of diabetes.

Definition of sarcopenia

Following the Asian Working Group for sarcopenia (AWGS) definition, sarcopenia was determined as low muscle mass plus low muscle function (either low handgrip strength or low gait speed)2. The detailed diagnostic procedure for sarcopenia was described in our previous study5.

Muscle mass was measured by bioelectrical impedance analysis using an MC-190 body composition analyzer (Tanita Co., Tokyo). Skeletal muscle mass index (SMI, kg/m2) was calculated by appendicular skeletal muscle mass divided by height in meters squared17. Low muscle mass was determined using the following cut-off values: SMI of < 7.0 kg/m2 for men and < 5.7 kg/m2 for women2.

Handgrip strength was measured using a digital strength dynamometer (GRIP-D, T.K.K.5401; Takei Scientific Instruments, Niigata, Japan) under the direction of trained medical staff. Participants were instructed to exert the maximum force of grip, alternating for each hand. Using the maximum value of four trials, low handgrip strength was determined by the following cutoff values: < 26 kg for men and < 18 kg for women2.

Gait speed was measured in the middle 5 meters of the course, and low gait speed was determined using the faster of
the two trials. Maximum gait speed was measured in both the 2012 and 2017 surveys, while the usual gait speed was measured in the 2017 survey but not in the 2012 survey. Therefore, in the main analyses, low gait speed was assessed using the maximum gait speed. The cut-off values for maximum gait speed corresponding to those for usual gait speed in the AWGS definition (0.80 m/s for both men and women) were calculated in our previous study5. Low gait speed was determined using the following cut-off values: maximum gait speed < 1.25 m/s for men and < 1.15 m/s for women5.

As sensitivity analyses, we performed an analysis with usual gait speed for the diagnosis of sarcopenia in the 2017 survey (i.e., low gait speed was defined as a usual gait speed of ≤ 0.80 m/s for both men and women). Moreover, we performed an analysis with the AWGS 2019 definition18, which revised the cut-off value of grip strength for men to < 28 kg and the cut-off value of usual gait speed to < 1.00 m/s for both men and women. In the present study, the cut-off values for maximum gait speed corresponding to those for usual gait speed were calculated by using sex-specific linear regression equations for usual gait speed and maximum gait speed, which were reported in our previous study5: maximum gait speed < 1.46 m/s for men and < 1.36 m/s for women.

**Other risk factor measurements**
A self-administered questionnaire concerning educational status, smoking habits, alcohol intake, regular exercise habits, medical treatments (antihypertensive and antidiabetic agents), history of cardiovascular disease or cancer, and history of fracture at all body sites was filled in by each participant and was confirmed by trained staff. Smoking habits and alcohol intake were categorized as current use or not. Regular exercise habits were defined as performing sports ≥ 3 times a week in leisure time. ADL disability was determined as a Barthel Index of ≤ 9519,20.

Height and weight were measured with participants in light clothing without shoes and used for calculating the body mass index (BMI). Sitting blood pressure was taken using an automated sphygmomanometer (BP-203 RVIIIIB; Omron Healthcare, Kyoto, Japan) three times after ≥ 5 minutes of rest. The mean of the three measurements was used in the analysis. Hypertension was defined as blood pressure levels of ≥ 140/90 mmHg or current treatment with antihypertensive agents. Serum creatinine concentrations were measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation21.

Dementia was determined with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised through a screening survey using the Mini-Mental State Examination and comprehensive investigations by psychiatrists as described previously35,22. Total energy intake was determined with Semi-Quantitative Food Frequency Questionnaire23.

**Statistical analysis**
The age- and sex-adjusted means (standard error) for continuous variables were estimated by using analysis of covariance. The frequencies of risk factors were adjusted for age and sex using the direct method and tested using logistic regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) for incident sarcopenia according to the diabetic status at baseline (i.e., the presence of diabetes, time of diabetes diagnosis,
RESULTS
Of the 824 subjects (mean age 71.9 ± 4.9 years), 272 subjects had diabetes at baseline (271 subjects with type 2 diabetes and 1 subject with type 1 diabetes), and 47 subjects (5.7%) developed sarcopenia at the follow-up survey in 2017. Table 1 shows the baseline characteristics of the study participants according to diabetes status. Subjects with late-life diabetes were older than those without diabetes, whereas subjects with midlife diabetes were younger than those without diabetes. The proportion of men was significantly higher in subjects with midlife diabetes than those without diabetes. The mean values of BMI, FPG, and HbA1c and the frequencies of obesity and hypertension were significantly higher in the subjects with late-life or midlife diabetes compared with those without diabetes.

Table 2 shows the association between diabetes status and the risk of the development of sarcopenia. The age- and sex-adjusted OR for sarcopenia was greater in subjects with diabetes at baseline than those without diabetes at baseline, although the difference did not reach statistical significance. After adjusting for BMI, diabetes was associated with a significantly higher risk of incident sarcopenia. This relationship was not substantially altered by adjusting for other potential confounding factors. Next, we assessed the association between the time of diabetes diagnosis and the risk of the development of sarcopenia, and found that the age- and sex-adjusted OR of incident sarcopenia was significantly greater in subjects with midlife diabetes than in subjects without diabetes (OR 2.57, 95% CI 1.28–5.17). On the other hand, no clear associations were observed between late-life diabetes and the risk of incident sarcopenia. This association was not changed after adjusting for the above confounding factors. In the sensitivity analysis with the AWGS definition using usual gait speed and the AWGS 2019 definition for the diagnosis of sarcopenia, similar findings to the main results were observed (Tables S1 and S2).

Moreover, we examined the association of the duration of diabetes with the risk of incident sarcopenia (Figure 2). In a multivariable-adjusted analysis, the risk of incident sarcopenia increased significantly with increasing duration of diabetes (P for trend < 0.01). Subjects with a diabetes duration of >15 years had a significantly higher risk of incident sarcopenia than those without diabetes (OR 4.67, 95% CI 1.77–12.28). In the sensitivity analysis for the age at first diagnosis of diabetes (Figure 3), subjects with diabetes diagnosed at age 40–59 years had a significantly higher risk of incident sarcopenia than those without diabetes, whereas there was no clear association between those with diabetes diagnosed at 60–69 or ≥70 years of age and incident sarcopenia.

Finally, we investigated the association between late-life or midlife diabetes and the incidence of components of sarcopenia – namely, low muscle mass, low muscle strength, and low handgrip strength (Table 3). The results showed that subjects with midlife diabetes were at a significantly greater risk of the development of low muscle mass (OR 2.11, 95% CI 1.11–4.01) and low handgrip strength (OR 2.82, 95% CI 1.65–4.83) than those without diabetes after adjusting for the above-confounding factors (both P < 0.05), whereas there was no clear association between midlife diabetes and low gait speed (P = 0.53). No significant associations with the development of any of the sarcopenia components were observed for late-life diabetes in the multivariable-adjusted analyses (all P values > 0.15).

DISCUSSION
The present study demonstrated in an older Japanese population that the subjects having diabetes, particularly midlife diabetes, had a significantly greater risk of incident sarcopenia. A longer duration of diabetes was more deleteriously linked with a greater risk of incident sarcopenia. Regarding components of sarcopenia, midlife diabetes was significantly associated with the development of low muscle mass or low handgrip strength. The findings of our study highlight the clinical significance of early prevention of diabetes in midlife to lower the risk of incident late-life sarcopenia.

One cross-sectional study in a general older Chinese population assessed the association of diabetes with sarcopenia. That study reported that diabetes was significantly associated with an increased risk of having sarcopenia. Our study extended the findings of this previous study by showing that diabetes was prospectively associated with an increased risk of incident sarcopenia over 5 years after adjusting for potential confounding factors. Intriguingly, our study demonstrated a difference in the
influence of midlife and late-life diabetes on the incident sarcopenia — that is, midlife diabetes, but not late-life diabetes, was significantly associated with a greater risk of incident sarcopenia. Moreover, the risk of incident sarcopenia was significantly increased as the duration of diabetes became longer. These findings are consistent with a previous study which demonstrated that a longer duration of diabetes was negatively associated with muscle quality. The finding that subjects with midlife diabetes had a significantly greater risk of incident sarcopenia may be mainly due to the longer duration of diabetes.
in subjects with midlife diabetes. Taken together, our findings strongly suggest that midlife diabetes, especially with long-term exposure, is one risk factor for incident sarcopenia.

Several previous reports have demonstrated that diabetes accelerated muscle volume and strength loss over time among older people. In the previous reports from the Health, Aging and Body Composition Study, diabetes was associated with accelerated leg muscle strength loss and with excessive skeletal muscle mass loss. Likewise, a prospective study of the general Chinese population reported that diabetes was associated with a higher loss of appendicular lean mass. The current study revealed that midlife diabetes had a significantly greater risk of the incidence of low muscle mass and low handgrip strength, which was consistent with previous findings, whereas no clear association was observed between midlife diabetes and low gait speed. The different associations of diabetes with each component of sarcopenia may be attributable to the limited statistical power since the number of subjects with low gait speed was small. Moreover, low gait speed has recently been considered an adverse outcome resulting from sarcopenia, rather than a component of sarcopenia. Therefore, further evidence from large, long-term cohort studies is needed to confirm these results.

The underlying mechanisms that may support the association between diabetes and risk of incident sarcopenia have not been clarified, but there are several possible explanations for our findings. First, increased insulin resistance in diabetes may reduce the synthesis of whole-body proteins, which could potentially affect the components of sarcopenia. In support of this idea, some previous prospective studies reported negative correlations between insulin resistance and total lean mass, handgrip strength, or gait speed. Second, polyneuropathy, a common long-term diabetes complication, results in motor dysfunction as well as sensory and autonomic dysfunction. An electromyography study indicated that incomplete reinnervation following the axonal loss was involved in the muscle strength loss in diabetic patients. Several studies have demonstrated a relationship between diabetic neuropathy and muscle weakness. Third, increased levels of systemic inflammatory cytokines among subjects with diabetes may adversely affect muscle mass, strength, and physical performance among older adults. Recent evidence has shown that chronic low-grade inflammation adversely affects muscle protein synthesis and breakdown through several signaling pathways. Although these multiple factors may be involved in the association between diabetes and incident sarcopenia, further basic and interventional studies will be expected to confirm the mechanism.

The present study has some strengths, which include its longitudinal population-based design with an accurate determination of diabetes, and its evaluation of midlife or late-life diabetes by using the data of annual medical checkups over 24 years rather than self-reported histories. However, several potential limitations should be noted. First, some degree of misclassification of sarcopenia status because only two assessments of sarcopenia were conducted. Second, low gait speed was determined using the maximum gait speed rather than the usual gait speed when determining the diagnosis of sarcopenia in this study, because usual gait speed was not measured in 2012. Nevertheless, when we performed an additional analysis with the usual gait speed to define sarcopenia in 2017, the...
findings were not altered substantially. Therefore, the influence of this limitation on the conclusion of this study may have been modest. Third, 640 subjects were excluded from this analysis, which likely led to a selection bias, due to the lack of available data for determining the diabetes status or sarcopenia in the 2012 or 2017 surveys. This limitation may have tended to weaken the association between diabetic status and sarcopenia because the excluded subjects were older and had a lower BMI, and thus were more likely to have sarcopenia, than those included in this study at the 2012 survey (age 75.9 years vs. 71.9 years, and BMI 22.8 kg/m² vs. 23.5 kg/m² for the included vs. excluded subjects). Fourth, the information on lifestyle changes, such as exercise habits and diet, after the onset of diabetes, was not taken into consideration in the present study. Finally, the small number of subjects with late-life diabetes might have limited the statistical power, resulting in an underestimation of the association between late-life diabetes and sarcopenia.

In conclusion, midlife diabetes and a longer duration of diabetes were associated with the risk of incident sarcopenia in an older Japanese population. Our results suggest the possibility that the decreasing duration of diabetes by prevention of diabetes in midlife reduces the risk of incident sarcopenia in later life in the general Japanese population.

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DISCLOSURE
No potential conflicts of interest relevant to this article were reported.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Age- and sex-adjusted and multivariable-adjusted odds ratios for the development of sarcopenia defined using usual gait speed in the 2017 survey according to diabetes status (2012–2017).

Table S2 | Age- and sex-adjusted and multivariable-adjusted odds ratios for the development of sarcopenia defined by the AWGS 2019 definition according to diabetes status (2012–2017).