

Walking Speed is the Sole Determinant of mild Cognitive Impairment in Japanese Patients with Type 2 Diabetes Mellitus

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Original investigation

Keywords: Type 2 diabetes mellitus, walking speed, sarcopenia

Posted Date: April 6th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-20599/v1>

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Abstract

Background To elucidate the clinical characteristics of type 2 diabetes mellitus patients with mild cognitive impairment (MCI) and to examine whether diagnosis of sarcopenia and/or its criterion are explanatory factors for MCI

Methods Patients with type 2 diabetes mellitus were categorized into the MCI group for MoCA-J (the Japanese version of the Montreal cognitive assessment) score <26 , and into the non-MCI group for MoCA-J ≥ 26 . Sarcopenia was defined by a low skeletal mass index along with low muscle strength (handgrip strength) or low physical performance (walking speed <1.0 m/s). Univariate and multivariate-adjusted odds ratio models were used to determine the independent contributors for MoCA-J <26 .

Results Among 438 participants, 221 (50.5%) and 217 (49.5%) comprised the non-MCI and MCI groups, respectively. In the MCI group, age (61 ± 12 vs. 71 ± 10 years, $p < 0.01$) and duration of diabetes (14 ± 9 vs. 17 ± 9 years, $p < 0.01$) were higher than those in the non-MCI group. Patients in the MCI group exhibited lower hand grip strength, walking speed, and skeletal mass index, but higher prevalence of sarcopenia. Only walking speed (rather than muscle loss or muscle weakness) was found to be an independent determinant of MCI after adjusting for multiple factors, such as age, gender, BMI, duration of diabetes, hypertension, dyslipidemia, smoking, drinking, eGFR, HbA1c, and history of coronary heart diseases and stroke. In subgroup analysis, a group consisting of male patients aged ≥ 65 years, with BMI <25 , showed a significant OR for walking speed.

Conclusions This is the first study to show that slow walking speed is a determinant for the presence of MCI in patients with type 2 diabetes. It was suggested that walking speed is an important factor in the prediction and prevention of MCI development in patients with diabetes mellitus.

Background

Dementia refers to a condition in which cognitive function, which has reached a normal level, is sustainably reduced due to acquired brain damage, thereby interfering with daily life and social life (ICD11 [1], DSM-5 [2]). There are several conditions that resemble cognitive decline or prodromal symptoms of dementia but cannot be diagnosed as dementia. One such condition, mild cognitive impairment (MCI), was proposed by Flicker et al. [3] and established by Petersen et al. [4]. It has been previously reported that more than 50% of individuals with MCI later develop dementia (5). Modifiable risk factors for mild dementia include (middle-aged) hypertension, diabetes, (middle-aged) obesity, dyslipidemia, smoking, physical activity, and depression [5, 6].

Diabetes is a risk factor for MCI and dementia (Alzheimer's dementia, vascular dementia, and mixed dementia) [7–9]. In the Japanese population, the risk of developing Alzheimer's disease and vascular dementia is approximately twice as high in diabetic patients as it is in healthy individuals [10]. The risk factors for MCI in diabetic patients may include hypertension, obesity, presence of dyslipidemia, effects of exogenous and endogenous insulin associated with the treatment of diabetes, degree of chronic

hyperglycemia, duration of diabetes, and presence of hypoglycemia [7, 8, 11]. Sarcopenia is a risk factor for dementia in elderly population without [12, 13] or with [14] diabetes mellitus. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength that is associated with the risk of physical dysfunction, poor quality of life, and death [15, 16]. Elderly patients with diabetes exhibit a combination of impaired insulin secretion and increased insulin resistance, which might be due to a combination of adiposity and sarcopenia [14]. There are three criteria for sarcopenia diagnosis: low muscle mass, low muscle strength, and low physical performance [15, 17]. However, it remains unclear how the diagnosis of sarcopenia and/or its three criteria are associated with the presence of MCI in diabetic patients.

The main objectives of this study included assessing the clinical characteristics of type 2 diabetes patients with MCI and elucidating whether the diagnosis of sarcopenia and/or its criterion could act as explanatory factors for MCI in type 2 diabetes patients.

Methods

Study design and subjects

This is an observational retrospective cohort study. The study protocol was approved by the Fukushima Medical University Ethics Committee (Number 29118). Written informed consent was obtained from the patients recruited between January 2018 and December 2019 in the Department of Diabetes, Endocrinology and Metabolism, School of Medicine, Fukushima Medical University Hospital. This study was conducted according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted by MHLW of Japan (<http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf> and <http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf>). Among 701 patients who gave written informed consent, 207 patients who were either non-diabetic or had type 1 diabetes mellitus were excluded from the study (Supplement 1). The remaining 494 patients with type 2 diabetes mellitus were enrolled in the study and their paper and/or electrical medical records were obtained. Various patient parameters, such as age, gender, history of diabetes, family and social history, medical checkup history, complications, medications, laboratory data, and all dates, were recorded. After excluding for missing data, 438 patients were finally included for data analysis.

Measurements

Trained staff measured the height, body weight, blood pressure, and waist circumference of each subject. Questionnaires were provided to record the data on smoking status (current smoker or not), drinking habits (everyday, sometimes, rarely, or never), regular exercise (exercise to sweat lightly for over 30 min on each occasion, two times weekly, walking > 1 h/day, and fast walking), anti-hypertensive drug use, anti-hyperglycemic drug use, and lipid-lowering drug use. A participant was diagnosed with diabetes mellitus when fasting plasma glucose level was ≥ 126 mg/dL or the HbA1c level was $\geq 6.5\%$ (48 mmol/mol), or if the participant regularly used anti-hyperglycemic drugs. A participant was diagnosed with hypertension if

the systolic blood pressure was ≥ 140 mmHg or if the diastolic blood pressure was ≥ 90 mmHg, or if she/he regularly used antihypertensive drugs. A participant was diagnosed with dyslipidemia if high-density lipoprotein (HDL) cholesterol levels were < 40 mg/dL (1.0 mmol/L), low-density lipoprotein (LDL) cholesterol levels were ≥ 140 mg/dL (3.6 mmol/L), or triglyceride levels were ≥ 150 mg/dL (1.7 mmol/L), or if they regularly used lipid-lowering drugs.

MoCA-J (the Japanese version of the Montreal cognitive assessment), hand grip strength, walking speed, skeletal muscle mass, and fat mass of the participants were assessed. In addition, routine anthropometry was performed by trained staff for each participant. Waist circumference was measured at the level of the umbilicus (cm) in the standing position. Hand grip strength (kg) was measured using an isokinetic dynamometer (Smedley hand dynamometer) on both hands, and values of the non-dominant arm were used. The compositions of fat and muscle in whole body, trunk, arms, and legs were assessed using a body composition analyzer (InBody 770, InBody Japan Inc.) based on the segmental multi-frequency bioelectrical impedance analysis (SMF-BIA) [18, 19]. The time required for walking 10 m was measured as described previously, with slight modifications [20, 21]. Fasting blood samples were collected after an overnight fasting for ≥ 10 hours and were assayed within 1 h using automatic clinical chemical analyzers. We excluded the participants from whom fasting blood samples could not be obtained.

Assessment of MCI

The Montreal Cognitive Assessment (MoCA), created in 1996 by Nasreddine, is a widely used screening assessment for detecting MCI [22]. The reliability and validity of the Japanese version of the MoCA (MoCA-J) had previously been tested in the Japanese population, and a cut-off point of 25/26 out of full 30 scores demonstrated a sensitivity of 93.0% and a specificity of 87.0% while screening for MCI [23]. Therefore, participants with MoCA-J score < 26 were categorized into the MCI group and the participants with MoCA-J score ≥ 26 into the non-MCI group.

Assessment of sarcopenia

The definition and diagnosis of sarcopenia were based on Asian Working Group for Sarcopenia (AWGS): 2019 Consensus Update on Sarcopenia Diagnosis and Treatment [17]. In brief, “low muscle strength” was defined as handgrip strength < 28 kg for men and < 18 kg for women; criterion for “low physical performance” was walking speed < 1.0 m/s as evaluated by the time required for walking 10 m; “low appendicular skeletal muscle mass (ASM)” was defined as bioimpedance < 7.0 kg/m² in men and < 5.7 kg/m² in women. Sarcopenia was defined by low ASM and low muscle strength or low physical performance.

Statistical analyses

Continuous and parametric values were expressed as mean \pm standard deviation. Two-tailed unpaired Student's t-test was used for analysis of parametric data. Categorical variables were shown as percentage and were analyzed using the chi-square test. Univariate (Model 1) and multivariate-adjusted models were used to determine the independent contributors to MoCA-J < 26 in Model 2 (sex, age, and

BMI), Model 3 (sex, age, BMI, duration of diabetes, hypertension, dyslipidemia, smoking, drinking, eGFR, and HbA1c), and Model 4 (sex, age, BMI, duration of diabetes, hypertension, dyslipidemia, coronary heart diseases, stroke, smoking, drinking, eGFR, and HbA1c). The odds ratios (ORs) between participant characteristics and MoCA-J < 26 were calculated using logistic regression analysis. Values of P < 0.05 were considered as statistically significant. Statistical analyses were conducted using SPSS version 25 (SPSS, Inc., Chicago, Illinois, USA).

Results

General characteristics

Baseline characteristics of the patients are shown in Table 1. Among 438 participants with type 2 diabetes mellitus, 217 (49.5%) participants exhibited MoCA-J < 26 (MCI group) and 221 (50.5%) participants exhibited MoCA-J \geq 26 (non-MCI group). Patients of the MCI group were older, but the proportion of the male participants in this group was comparable to that in the non-MCI group. Systolic blood pressure between patients of both groups was comparable, but the diastolic blood pressure was lower in the MCI group. Body weight, BMI, waist circumference, as well as total fat mass were lower in the MCI group. Hand grip strength, walking speed, and skeletal mass index were all lower and the prevalence of sarcopenia was higher in the MCI group compared to the non-MCI group (13% vs. 4%). Patients of the MCI group had suffered from diabetes mellitus for a longer duration, but there were no significant differences between the two groups with respect to prevalence of hypertension and dyslipidemia and prior history of coronary heart disease and stroke. Life habits, such as regular walking, smoking history, and drinking history, were also comparable between the two groups. There were no significant differences in the levels of plasma glucose and glycated hemoglobin between the two groups; however, the levels of albumin, LDL-cholesterol, and eGFR were lower in the MCI group. There were no significant differences with respect to the use of anti-diabetic medicine between the two groups.

Unadjusted odds ratio

The unadjusted odds ratio (OR) for MCI (MoCA-J < 26) is shown in Table 2. Diastolic blood pressure, body weight, BMI, fat mass, hand grip strength, walking speed, skeletal mass index, and levels of LDL-cholesterol and eGFR were inversely correlated and the risk of sarcopenia was directly correlated with MoCA-J < 26. Age and the duration of diabetes were positively associated with MoCA-J < 26, but the prevalence of hypertension and dyslipidemia, prior coronary heart disease and stroke, life habits, as well as the use of anti-diabetic medications were comparable between the two groups. There were no associations of the levels of plasma glucose and glycated hemoglobin, but the lower levels of albumin, LDL-cholesterol, and eGFR were associated with MoCA-J < 26.

Multivariate-adjusted odds ratio

Multivariate-adjusted OR for MCI (MoCA-J < 26) is shown in Table 3 and Fig. 1. Overall, the non-adjusted OR of hand grip strength, walking speed, and skeletal mass index were negatively associated and that of

sarcopenia was positively associated with MoCA-J < 26 (Model 1). However, after adjusting for sex, age, BMI (Model 2); Model 2 + duration of diabetes, hypertension, dyslipidemia, smoking, drinking, eGFR, and HbA1c (Model 3); and Model 3 + history of coronary heart diseases and stroke (Model 4), only walking speed was significantly associated with MoCA-J < 26.

Subgroup analysis (Table 3, lower panel) revealed that a group with age ≥ 65 years, male patients, and BMI < 25 showed a significant OR of walking speed for MoCA-J < 26. As shown in Supplement 2, there was a difference in the MoCA-J values between patients aged < 65 years and those aged ≥ 65 years (26.6 ± 2.5 vs. 24.1 ± 3.3 , $p < 0.01$); however, no differences were observed between men and women and between patients with BMI < 25 and those with BMI ≥ 25 .

Discussion

This study evaluated the clinical characteristics of the MCI group and the relationship between sarcopenia and/or its diagnostic criteria and MCI in Japanese patients with type 2 diabetic. We reported two major findings. First, we assessed the clinical characteristics of the diabetic patients in the MCI group. In patients of the MCI group, weight, BMI, abdominal circumference, and fat and muscle mass were lower compared to those of patients in the non-MCI group. Hand grip strength, walking speed, and skeletal mass index, which are associated with sarcopenia, were lower and the prevalence of sarcopenia was higher in the MCI group. Duration of diabetes was longer in the MCI group, but there was no significant difference between the two groups with respect to hypertension, dyslipidemia, and a history of coronary artery disease and stroke. There were no significant differences between the groups with respect to regular exercise habits, smoking history, and drinking history. Second, after correction for multivariate analysis, the OR for only the walking speed was found to be significant and the OR for other sarcopenia criteria and diagnosis of sarcopenia was not significant. The present study is the first to show that slow walking speed is the sole independent determinant of MCI in type 2 diabetes patients. In diabetic patients, it is necessary to verify whether the assessment of walking speed is effective for screening, early detection [24], and therapeutic intervention of MCI.

Characteristics of patients in the MCI group

Among the 438 diabetic patients, 49.5% patients belonged to the MCI group and 50.5% to the non-MCI group. Age of patients in the MCI group was higher; however, there was no significant difference in the gender ratios of the two groups. Systolic blood pressure was comparable between both groups, but the diastolic blood pressure was lower in the MCI group. Body weight, BMI, abdominal circumference, as well as fat and muscle mass were lower in the MCI group. Hand grip strength, walking speed, and skeletal muscle index, which are the criteria for sarcopenia, were all lower, and the prevalence of sarcopenia was higher in the MCI group. Duration of diabetes was longer for patients in the MCI group, but there was no significant difference between the two groups with respect to hypertension, dyslipidemia, and a history of coronary artery disease and stroke. There was no significant difference in the habits of regular exercise, smoking, and drinking of the two groups.

The patients in the MCI group exhibited lower BMI, grip strength, muscle mass, fat mass, and walking speed, which were all consistent with the characteristics of sarcopenia (23). Advanced age is a risk factor of MCI in subjects with or without diabetes [6, 25]. Elderly diabetes patients are likely to reflect a longer average duration of diabetes and a longer exposure to chronic hyperglycemia and glycemic excursions (7, 8, 11). We observed longer durations of diabetes in patients of the MCI group, but no significant difference between the average A1c levels of both groups. Previous reports have shown a weak association between average A1c levels and MCI risk (24, 25). Another report showed that blood glucose fluctuations were more strongly associated with MCI risk than A1c level (26). It has also been reported that risk of dementia is increased in patients with newly diagnosed diabetes [12], but not in diabetic patients who are being treated (11). In addition, findings from cross-sectional analyses on the association of HbA_{1c} with cognitive function and cognitive decline in people with type 2 diabetes have been inconsistent (11). Our results regarding HbA_{1c} level agreed with those of previous studies.

Walking speed and MCI

We examined the association between the diagnosis of sarcopenia and/or its criteria and MCI in Japanese patients with type 2 diabetes. On the criteria of AWGS [17], we defined sarcopenia by low ASM (skeletal mass index < 7.0 kg/m² in men and < 5.7 kg/m² in women) along with a low muscle strength (handgrip strength < 28 kg for men and < 18 kg for women) or low physical performance (walking speed < 1.0 m/s). Interestingly, only walking speed (not muscle loss or weakness) is an independent determinant of MCI after adjusting for multiple factors, such as age, gender, BMI, duration of diabetes, hypertension, dyslipidemia, smoking, drinking, eGFR, HbA_{1c}, and history of coronary heart diseases and stroke. Limited reports have evaluated the association between cognitive dysfunction and the criteria for sarcopenia in diabetic patients. In Japanese type 2 diabetic patients with cognitive dysfunction, the skeletal muscle strength and walking speed were lower [26, 27]. These results were consistent with our results, and we also found that walking speed is the sole determinant for MCI among the three criteria for sarcopenia.

Why is reduced walking speed associated with MCI?

The mechanism of cognitive dysfunction in diabetes has been suggested to be related to: (1) insulin resistance in the local brain (7, 34); (2) chronic inflammation, deposition of advanced glycation end-products (AGE), and mitochondrial dysfunction; (3) τ (tau) deposition; (4) low adiponectin level in blood (35); and (5) hypoglycemia due to exogenous and endogenous insulin (37, 38). Brain atrophy due to impaired glucose metabolism, including hypoglycemia, is suggested to be linked to the onset of MCI (36).

There are four possible mechanisms due to which walking speed could be linked to the onset of MCI. First, a slow walking speed might reflect an average decrease in physical activity. Patients who exercise regularly have a lower risk of Alzheimer's disease and dementia (39,40). However, there was no difference in the habits of regular exercise between our MCI and non-MCI groups. Second, a slow walking speed might indicate sarcopenia (muscle loss), decreased muscle quality, or reduced overall physical function. Type 2 diabetic patients with visceral fat accumulation have been reported to have poor muscle quality (41). Decreased skeletal muscle mass is likely to occur in patients with decreased insulin secretion. In

such cases, muscle mass and quality might be reduced. Third, the walking function might reflect metabolism in the brain. Holtzer and colleagues suggested that elderly patients with diabetes exhibit altered frontal lobe function during walking and are at a risk of falling (42). Fourth, it is possible that hypoglycemia caused by SU drugs and insulin preparations is linked to abnormalities in brain metabolism and a reduced walking speed. However, in this study, walking speed was still a determinant of MCI, and was not related to hypoglycemia, even after adjusting the use of SU or insulin, which had a risk of hypoglycemia.

Study limitations

This study has several limitations. First, this study was done using a relatively small number of cases at a single hospital. However, our data can be considered as relatively valid because these were collected using standardized and uniform methods. Second, the data were limited to only the Japanese population and our results cannot be extended to other races. Third, this was a retrospective observational study and the cause and result relationship between MCI and its risk factors could not be determined in this study.

Conclusions

This study was the first to show that slow walking speed is a determinant for the presence of MCI in patients with type 2 diabetes. It was suggested that walking speed is an important factor, when considering the prediction and prevention of MCI development in patients with diabetes mellitus.

Abbreviations

MCI

mild cognitive impairment; BMI:body mass index; HbA1c:hemoglobin A1c; LDL cholesterol:low-density lipoprotein cholesterol; HDL cholesterol:high-density lipoprotein cholesterol; eGFR:estimated glomerular filtration rate; SMF-BIA:segmental multi-frequency bioelectrical impedance analysis; MoCA-J:the Japanese version of Montreal cognitive assessment; ASM:appendicular skeletal muscle mass; OD:odds ratio; AWGS:Asian working group for sarcopenia; SMI:skeletal mass index.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Fukushima Medical University Ethics Committee (Number 29118). Written informed consent was obtained from the patients recruited between January 2018 and May 2019 in the Department of Diabetes, Endocrinology and Metabolism, School of Medicine, Fukushima Medical University Hospital.

Competing interests

There was no involvement of the funding sources acknowledged in this study in any aspect of the study design, data collection, data analysis and interpretation, or writing of or decision to publish this manuscript.

Funding

This study was supported by Japan Society for the Promotion of Science (JPSP) (Grant Number JP16K01823 to M.S. and JP17K00924 to A.K and M.S.) and a grant from Japan Agency for Medical Research and Development (AMED, 965304 to M.S.)

Authors' contributions

NM and MS designed the study. NM, AK, HS, HT, MI, HH, and MS collected data. HM advised for Discussion. NM and MS analyzed the data and wrote the manuscript with input from all authors. MS is the guarantor of this work, and as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Acknowledgments

The authors sincerely thank Mses. Hiroko Ohashi and Ryuko Sato for their assistance with data sampling and the staff in the Department of Diabetes, Endocrinology and Metabolism, Fukushima Medical University for their support with recruitment of participants. We would like to thank Editage () for English language editing.

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Figures

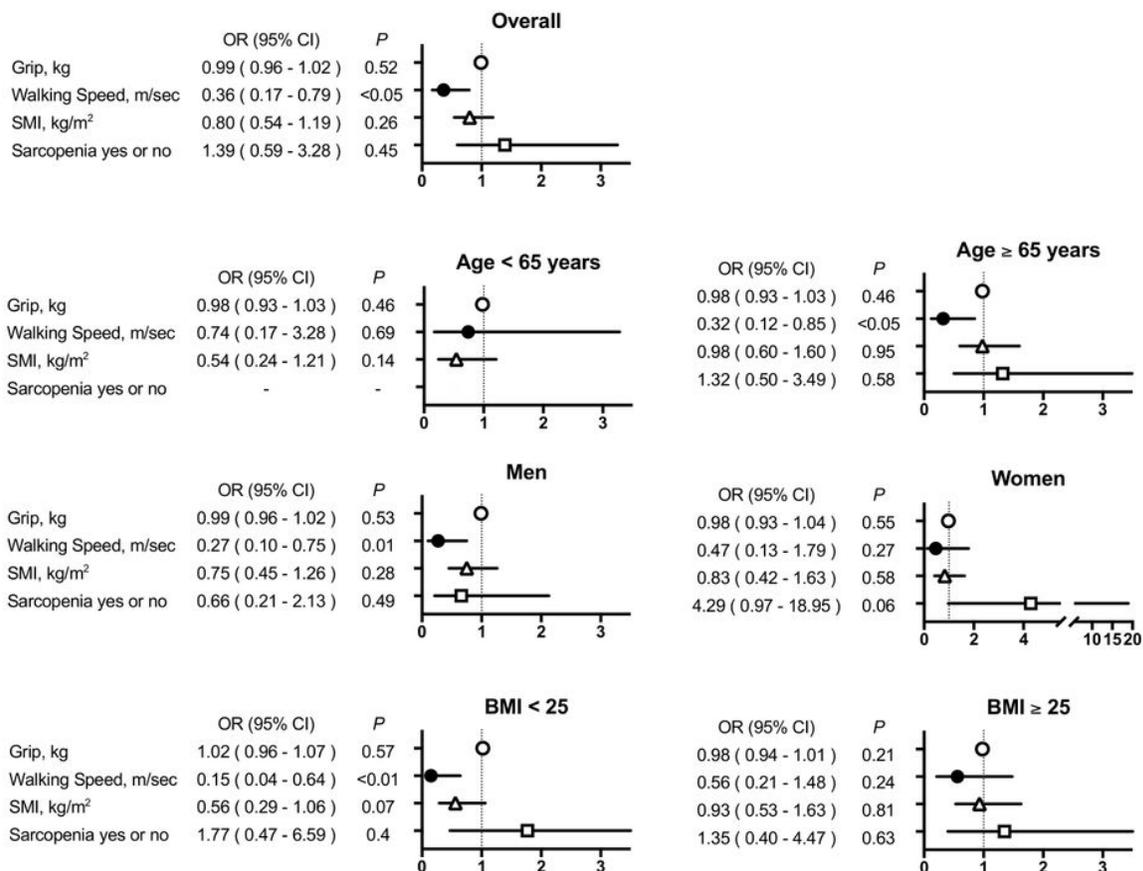


Figure 1

Figure 1

Adjusted odds ratio (OR) for mild cognitive impairment (MCI) (Model 4). ORs (5% confidential intervals) for MCI were calculated for hand grip strength (kg), walking speed (m/s), skeletal muscle index (kg/m²), and sarcopenia (yes or no) in overall patients with type 2 diabetes mellitus (n = 438), with respect to age <65 years or age ≥65 years, men or women, and BMI <25 or BMI ≥25. MCI was defined if MoCA-J (the Japanese version of Montreal Cognitive Assessment) score was <26. Model 4: adjusted for age, gender, BMI, duration of diabetes, hypertension, dyslipidemia, smoking, drinking, eGFR, HbA1c, and history of coronary heart diseases and stroke

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