BMJ Open Diabetes Research & Care

Breakfast skipping is associated with persistently increased arterial stiffness in patients with type 2 diabetes

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To cite: Mita T, Osonoi Y, Osonoi T, *et al*. Breakfast skipping is associated with persistently increased arterial stiffness in patients with type 2 diabetes. *BMJ Open Diab Res Care* 2020;**8**:e001162. doi:10.1136/bmjdrc-2019-001162

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2019-001162).

Received 27 December 2019
Revised 11 January 2020
Accepted 28 January 2020

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ABSTRACT

Objective While certain lifestyle habits may be associated with arterial stiffness, there is limited literature investigating the relationship between lifestyle habits and longitudinal changes in arterial stiffness in patients with type 2 diabetes mellitus (T2DM). This is an exploratory study to determine whether lifestyle habits, in addition to conventional atherosclerotic risk factors, are associated with increased arterial stiffness.

Research design and methods The study participants comprised 734 Japanese outpatients with T2DM and no history of apparent cardiovascular diseases. Lifestyle habits were analyzed using self-reported questionnaires, and brachial-ankle pulse wave velocity (baPWV) was measured at baseline, and at years 2 and 5. A multivariable linear mixed-effects model was used to determine the predictive value of lifestyle habits and possible atherosclerotic risk factors for longitudinal change in baPWV.

Results Over 5 years of follow-up, baPWV values significantly increased. In a multivariable linear mixed-effects model that adjusted for age and gender, a low frequency of breakfast intake was significantly associated with persistently high baPWV, independently of other lifestyle habits. Furthermore, in a multivariable linear mixed-effects model that included both lifestyle habits and possible atherosclerotic risk factors, a low frequency of breakfast intake remained the only independent predictive factor for persistently high baPWV. Subjects who ate breakfast less frequently tended to have additional unhealthy lifestyle habits and atherosclerotic risk factors.

Conclusions Our analyses suggest that breakfast skipping is an independent lifestyle habit that is associated with persistently increased arterial stiffness in patients with T2DM.

Trial registration number UMIN000010932.

Significance of this study

What is already known about this subject?

- Cross-sectional studies demonstrated that certain lifestyle habits such as poor sleep quality and low physical activity may be associated with arterial stiffness.
- A recent cross-sectional study demonstrated that breakfast skipping was associated with a higher prevalence of subclinical atherosclerosis in the general population, not in patents with type 2 diabetes mellitus (T2DM).

What are the new findings?

- A low frequency of breakfast intake was significantly associated with persistently high brachial-ankle pulse wave velocity independently of other lifestyle habits and possible atherosclerotic risk factors.

How might these results change the focus of research or clinical practice?

- Asking about the frequency of breakfast intake in clinical practice may be a simple and useful method to help identify patients at high risk of developing cardiovascular diseases.
- Eating breakfast more frequently may improve arterial stiffness in patients with T2DM.

INTRODUCTION

Patients with type two diabetes mellitus (T2DM) are at high risk of developing cardiovascular diseases (CVD), which are also one of the main causes of death in this population.[1] In general, patients with T2DM have increased arterial stiffness,[2] which may be one of the mechanisms linking T2DM to cardiovascular morbidity and mortality.[3] In patients with T2DM, increased arterial stiffness is associated with the incidence of CVD.[4 5] Identifying patients with a high probability of developing CVD by evaluating arterial stiffness is important in order to reduce the morbidity and mortality of these diseases. The brachial-ankle pulse wave velocity (baPWV) is a non-invasive technique that is often used clinically to assess arterial wall stiffness, evaluate the severity of atherosclerosis and predict CVD in patients with T2DM.[4 5]

Previous cross-sectional studies demonstrated that increased arterial stiffness in patients with T2DM was associated with conventional atherosclerotic risk factors such as age, gender, body mass index (BMI), duration of T2DM, glycemic control, dyslipidemia, systolic blood pressure (BP), estimated glomerular filtration rate (eGFR), elevated uric acid levels and albuminuria.[2 6 7] Other recent cross-sectional

studies showed that in addition to these conventional atherosclerotic risk factors, poor sleep quality and low physical activity was correlated with increased arterial stiffness in patients with T2DM.[8–10] By assessing serial changes in arterial stiffness, a recent study demonstrated that chronic hyperglycemia, older age, female gender, increased systolic BP and pulse rate and the presence of dyslipidemia and retinopathy were associated with the progression of arterial stiffness in patients with T2DM.[6] However, in that study, lifestyle-related problems were not assessed, and thus it remains largely unknown how factors such as energy intake, physical activity, sleep duration, sleep quality, chronotype, dietary habits such as skipping breakfast and/or eating late-night dinners and depressive state are associated with the progression of atherosclerosis.

Lifestyle habits have potential to cause arterial stiffness through deteriorating cardiometabolic risk profiles and/or altering hormone levels as follows. Previous reports demonstrated that increased counter-regulatory hormones due to duration of sleep and/or poor sleep quality may be associated with progression of arterial stiffness in the general population.[11 12] Recent studies showed that evening chronotype may be associated with poor glycemic control in patient with T2DM.[13 14] Depressive status could also have a negative impact on glucose metabolism through increased counter-regulatory hormones.[15] Eating late-night dinners may cause higher postprandial glucose levels in the following morning.[16] In addition to those lifestyle habits, breakfast skipping is becoming a major potential target for preventing lifestyle-related diseases. Previous studies demonstrated relationships between breakfast skipping and increases in both body weight[17] and risk of T2DM[18] in the general population. A recent cross-sectional study demonstrated that breakfast skipping was associated with a higher prevalence of subclinical atherosclerosis in the general population.[19] Furthermore, three cohort studies demonstrated that breakfast skipping was associated with increased risks of CVD and stroke in members of the general population without a history of CVD.[20–22] Patients with T2DM are at high risk of developing CVD,[1] but it has remained largely unknown whether like the general population, they are more likely to develop atherosclerosis if they skip breakfast.

As mentioned above, lifestyle habits are potential targets for primary CVD prevention strategies in addition to conventional atherosclerotic risk factors. However, there is limited literature addressing this issue in patients with T2DM. This is an exploratory study to bring insight on the lifestyle habits that are associated with longitudinal changes in arterial stiffness in patients with T2DM free of apparent CVD.

METHOD

Subjects

The subjects of this cohort study were recruited from the Diabetes Outpatient Clinic of Juntendo University (Tokyo, Japan), Secomedic Hospital (Funabashi, Japan) and Naka Kinen Clinic (Naka, Japan), as previously described.[8 23 24] This is an ongoing, observational, prospective cohort study that aims to investigate the relationships between lifestyle habits and the onset of CVD over an 8-year follow-up period. This study is an exploratory subanalysis of the cohort study. The study design, inclusion criteria and exclusion criteria have been published previously.[8 23 24] A total of 736 outpatients with T2DM and no history of apparent CVD were recruited between June 2013 and January 2014. However, two patients withdrew their consent.

Questionnaire survey

Questionnaire surveys were administered at baseline and at 2 and 5 years as previously described.[8 23 24] Sleep quality was evaluated with the use of the Pittsburgh Sleep Quality Index (PSQI).[25] Based on PSQI scores, patients were divided into three groups as follows: the 'poor sleep quality group' had PSQI scores ≥9, the 'average sleep quality group' had PSQI scores of 6–8 and the 'good sleep quality group' had PSQI scores ≤5.[26] Morningness/eveningness was evaluated with the Morningness-Eveningness Questionnaire (MEQ).[27] Scores of 65–86 were classified as morning type, scores of 53–64 as neither type and scores of 16–52 as evening type.[23] Depression-related symptoms were evaluated with the use of the Beck Depression Inventory (BDI)-II.[28] Higher scores represent a depressive state. The dietary intake of 56 food and beverage items was estimated with the use of brief, self-administered diet history questionnaire.[29] Physical activity level was assessed with the use of the International Physical Activity Questionnaire (IPAQ).[30]

Subjects were asked about their average nightly sleep duration over the past month. Subjects were divided into three groups as follows: long sleep duration group, 8.5 hours or more; intermediate sleep duration group, 5.5–8.5 hours and short sleep duration group, <5.5 hours.[31] Subjects were also asked about excessive daytime sleepiness, as follows: "Have you ever had excessive daytime sleepiness?" Workers were defined as full-time employees or shift workers as previously described.[8 23 24] Subjects were asked whether they were current smokers or had smoked previously. They were classified as never-smokers, former smokers or current smokers.

Finally, the questionnaire addressed each individual's dietary schedule. Subjects were asked about the times at which they ate breakfast, lunch, dinner and snacks, as follows: "What time do you have each meal?" Subjects were asked about the number of meals they ate per day, as follows: "How many meals do you have per day? One, 2, 3, 4 or 5 or more". Subjects were asked about the number of regular snacks they ate per day, as follows: "How many times do snack per day? Almost never, 1, 2, 3, 4 or 5 or more". Snacking after dinner was evaluated by the following question: "Do you eat fruits or other sweet snacks after dinner?" Subjects were asked about the amount of time between their last meal (either dinner or a snack) and bedtime. They were also asked about their average frequency of breakfast consumption, as follows:

"How many times per week do you eat breakfast?" Finally, they were asked about the average frequency with which they ate dinner out, as follows: "How many times per week do you eat dinner out and/or eat ready-made dinners at home? Almost never, 1 to 2, 3 to 4 or 5 or more".

Biochemical tests

From baseline to 5 years, fasting blood samples were obtained from participants once per year. Hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program), liver and renal function tests, lipid levels and uric acid level were measured with standard techniques. Using a spot urine, sample urinary albumin excretion (UAE) was measured by latex agglutination assay. The eGFR was calculated by the formula.[32]

Measurement of baPWV

Using an automatic waveform analyzer (BP-203RPE; Colin Medical Technology, Komaki, Japan), baPWV was measured at baseline and at 2 and 5 years, as described previously.[23] The average value of right baPWV and left baPWV was used as an individual representative value. The validity and reproducibility of baPWV measurements were confirmed in a previous study.[33] The ankle-brachial index was also measured. The baPWV data of patients with a resting ankle-brachial index ≤0.90 were excluded as they were considered to have peripheral artery disease.

Statistical analysis

Results are presented as mean±SD or median (IQR) for continuous variables, and as number (proportion) for categorical variables. Natural log-transformed values for triglycerides and UAE were used to approximate normal distribution. Patient characteristics, lifestyle habits and clinical variables over the study period were assessed with the mixed-effects model for repeated measures (MMRM), including time (years) as a factor with unstructured within-subject correlation. Longitudinal baPWV was analyzed using a linear mixed-effects model that included time, patient characteristics, lifestyle habits and possible atherosclerotic risk factors at baseline as fixed effects, and patient as a random effect to account for the inherent correlation of repeated measures on the same individual over time. We added the interaction term between time and each covariate in the mixed-effects model.

We further investigated the demographic and other characteristics of the subjects according to the frequency of breakfast intake at baseline. Since the majority of subjects ate breakfast 7 times per week, the rest of the subjects were almost equally divided into two groups for comparison based on the frequency of breakfast intake. Trend association across these three breakfast intake groups was evaluated by linear regression analysis for continuous variables and logistic regression analysis for categorical variables. The adjusted mean of baPWV was estimated using the MMRM method, taking into account the breakfast intake group, time, its interaction, baseline age and gender.

Statistical tests were two-sided with a 5% significant level. All analyses were performed using SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient demographic and background characteristics during the study period

At baseline, the data of 734 patients were available. Among them, a total of 99 subjects did not visit any of the study institutions at 5 years: 49 were transferred to another medical institution due to changes in work or house address, 45 subjects dropped out and 5 subjects died. The baseline clinical characteristics of the 734 patients with T2DM are summarized in table 1. The mean age was 57.8±8.5 years, 63% were male, HbA1c was 7.0%±1.0% (52.6±10.9 mmol/mol) and the estimated duration of T2DM was 9.9±7.2 years. Over 5 years of follow-up, modest but significant increases were seen in HbA1c levels, and with respect to lifestyle habits, in both the MEQ score and PSQI score. With respect to conventional atherosclerotic risk factors, modest but significant changes occurred in BMI, systolic and diastolic BP, high-density lipoprotein (HDL) cholesterol and logarithm of triglycerides. Renal function evaluated by eGFR and albuminuria slightly deteriorated, while baPWV significantly increased.

Relationships between longitudinal brachial-ankle pulse wave velocity and lifestyle habits

First, we used a linear mixed-effects model to examine the relationships between longitudinal baPWV, adjusted for age and gender and each lifestyle habit. We found a significant interaction between time and excessive daytime sleepiness (see online supplementary table S1), suggesting that baPWV in subjects with excessive daytime sleepiness significantly decreased with time compared with those without. On the other hand, there were no significant interactions between time and other lifestyle habits, including chronotype, sleep quality, sleep duration, depressive status, physical activity, caloric intake, alcohol consumption, smoking status, shift worker status, the frequency of breakfast skipping or time of dinner for longitudinal baPWV throughout the study period (see online supplementary tables S2–4; other data not shown). However, this analysis demonstrated that poor sleep quality was significantly associated with persistently high baPWV (see online supplementary table S2). Also, less frequent breakfast intake was significantly associated with persistently high baPWV (see online supplementary table S3). In addition, shift workers had significantly and persistently higher baPWV than non-shift workers (see online supplementary table S4).

Predictors of longitudinal brachial-ankle pulse wave velocity during 5-year follow-up

Next, we aimed to identify lifestyle habits associated with longitudinal changes in baPWV using a multivariable

Table 1 Patient demographic and background characteristics during the study period

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	P value
Age (years)	57.8±8.5 (n=734)						–
Male gender (%)	463 (63)						–
Body mass index (kg/m^2)	24.6±4.0 (n=729)	24.5±4.0 (n=724)	24.4±4.0 (n=676)	24.3±3.9 (n=671)	24.3±3.9 (n=660)	24.2±3.8 (n=629)	<0.001
Estimated duration of diabetes (years)	9.9±7.2 (n=726)						–
Diabetic retinopathy	267 (36.8)						
Diabetic neuropathy Normoalbuminuria/microalbuminuria/ macroalbuminuria	572 (79.2)/124 (17.2)/23 (3.6)						
Diabetic neuropathy	193 (26.5)						
Systolic BP (mm Hg)	127±14 (n=729)	128±14 (n=724)	128±15 (n=676)	129±14 (n=671)	130±15 (n=660)	129±14 (n=633)	<0.001
Diastolic BP (mm Hg)	77±10 (n=729)	79±11 (n=724)	79±11 (n=676)	78±10 (n=671)	79±10 (n=660)	78±10 (n=633)	<0.001
HbA1c (%)	7.0±1.0 (n=727)	7.0±1.1 (n=718)	7.0±1.1 (n=678)	7.0±1.1 (n=660)	7.0±1.0 (n=646)	7.1±1.0 (n=635)	0.029
HbA1c (mmol/mol)	52.6±10.9 (n=727)	52.6±11.8 (n=718)	53.2±11.5 (n=678)	53.3±12.4 (n=660)	53.2±11.9 (n=646)	53.9±12.1 (n=635)	0.029
Total cholesterol (mg/dL)	185±28 (n=726)	185±27 (n=713)	185±29 (n=676)	188±30 (n=654)	184±28 (n=635)	184±31 (n=627)	0.009
HDL cholesterol (mg/dL)	59±14 (n=727)	57±13 (n=713)	57±13 (n=677)	60±15 (n=660)	59±14 (n=643)	59±14 (n=635)	<0.001
Triglyceride: log-transformed value (actual value, median (IQR) (mg/dL)	4.66±0.56 (100 (70, 152)) (n=720)	4.63±0.55 (98 (71, 144)) (n=713)	4.61±0.54 (96 (70, 137)) (n=677)	4.69±0.58 (104 (74, 152)) (n=660)	4.65±0.56 (101 (72, 144)) (n=643)	4.66±0.56 100 (71, 142)) (n=635)	<0.001
Uric acid (mg/dL)	5.5±1.2 (n=727)	5.5±1.2 (n=714)	5.5±1.3 (n=677)	5.4±1.3 (n=660)	5.5±1.3 (n=644)	5.5±1.2 (n=633)	0.76
eGFR (mL/min/1.73 m^2)	78±18 (n=723)	75±17 (n=701)	73±18 (n=681)	71±18 (n=656)	69±19 (n=643)	68±18 (n=630)	<0.001
UAE: log-transformed value (actual value, median (IQR): mg/g creatinine)	2.64±1.31 (10 (6, 23)) (n=722)	2.61±1.45 (10 (5, 24)) (n=702)	2.63±1.38 (10 (5, 25)) (n=651)	2.66±1.48 (10 (5, 26)) (n=645)	2.63±1.43 (10 (5, 29)) (n=623)	2.65±1.46 (10 (5, 26)) (n=613)	0.23
Insulin therapy (n/%)	80 (11)						–
Hypotensive drugs (n/%)	348 (47.7)						–
Lipid-lowering drugs (n/%)	444 (60.9)						–
Antiplatelet agents (n/%)	24 (3.3)						–
Morningness-Eveningness Questionnaire score	57.4±7.3 (n=732)		57.6±6.9 (n=672)			58.5±7.0 (n=597)	<0.001
Pittsburgh Sleep Quality Index score	5.1±3.0 (n=733)		5.3±3.0 (n=669)			5.4±3.1 (n=600)	0.044
Beck Depression Inventory-II score	9.9±7.6 (n=734)						–
Caloric intake (kcal/day)	1,719±585 (n=733)						–
Physical activity (METs·h/week)	43.7±73.9 (n=732)						–
Sleep duration (hours)	6.5±1.2 (n=733)		6.5±1.1 (n=671)			6.5±1.2 (n=601)	0.15

Continued

Table 1 Continued

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	P value
Frequency of breakfast intake (times a week)	6.6±1.3 (n=733)		6.5±1.4 (n=668)			6.6±1.3 (n=601)	0.26
Current smoker (yes)	177 (24.1)						–
Alcohol consumption (g/day)	12.4±21.6 (n=733)						–
baPWV (cm/s)	1545±280 (n=726)		1578±290 (n=668)			1656±315 (n=601)	<0.001

Data are mean±SD, median (IQR) or number of patients. P values are derived using a mixed-effects model with repeated measures.
baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; UAE, urinary albumin excretion.

linear mixed-effects model adjusted for age and gender. As shown in table 2, the lower frequency of breakfast intake was significantly associated with persistently high baPWV, independent of other lifestyle habits. Although shift workers tended to have persistently higher baPWV than non-shift workers, and poor sleep quality tended to be associated with persistently higher baPWV than good sleep quality, lifestyle habits including excessive daytime sleepiness showed no significant association with longitudinal changes in baPWV. Furthermore, we investigated whether lifestyle habits in patients with T2DM were associated with persistently increased arterial stiffness independent of conventional atherosclerotic risk factors.

In a multivariable linear mixed-effects model that included both lifestyle habits and conventional atherosclerotic risk factors, the frequency of breakfast intake was still an independent predictive factor for persistently higher baPWV, in addition to older age, longer estimated duration of T2DM, lower BMI, higher systolic BP, higher logarithm of triglycerides, higher uric acid microalbuminuria and use of antiplatelet agents (table 3).

Characteristics of each group at baseline by frequency of breakfast intake

We further investigated subjects' demographic and other characteristics classified by the frequency of breakfast intake. As the majority of subjects ate breakfast 7 times a week, the remaining subjects were almost equally divided into two groups for comparison. According to this classification, the weekly breakfast intake was 7 times a week in 639 subjects, <4 times a week in 42 subjects and ≥4 and<7 times a week in 52 subjects, as shown in table 4.

Subjects who ate breakfast <4 times a week had significantly and persistently higher estimated baPWV than those who ate breakfast ≥4 and<7 times a week and those who ate breakfast 7 times a week (figure 1). The baPWV in all three groups tended to increase throughout the study period. Even when replacing continuous variables with categorical variables in the multivariable linear mixed-effects model, subjects who ate breakfast <4 times a week had still persistently higher baPWV than those who ate breakfast ≥4 and<7 times a week and those who ate breakfast daily (see online supplementary table 5). As shown in table 4, subjects who ate breakfast <4 times a week tended to be young and obese; had a low mean MEQ score, high mean PSQI score and high mean BDI-II score; had high alcohol consumption and ate dinner late, frequently ate late-evening snacks and frequently ate out and/or ate ready-made meals at home for dinner. There were no significant trends in other lifestyle habits, including energy intake, sleep time and mean IPAQ scores. In terms of metabolic-renal parameters, patients who ate breakfast <4 times a week had higher HbA1c levels, higher diastolic BP, higher triglyceride levels, higher uric acid levels and less frequent nephropathy and neuropathy, and also tended to have lower HDL cholesterol levels (see online supplementary table 6). However, there were no significant differences in both frequency of nephropathy and

Table 2 Predictors of longitudinal brachial-ankle pulse wave velocity during 5-year follow-up

	Comparison	Regression coefficient (95% CI)	P value
Intercept		838 (423 to 1254)	<0.001
Time	1 year	23.0 (19.9 to 26.1)	<0.001
Age	1 year	15.5 (13.2 to 17.8)	<0.001
Gender	Male vs female	39.3 (–5.7 to 84.2)	0.09
Morningness-Eveningness Questionnaire score	Neither type vs evening type	30.1 (–16.5 to 76.8)	0.21
	Morning type vs evening type	23.5 (–40.1 to 87.1)	0.47
Pittsburgh Sleep Quality Index score	Average vs good	32.9 (–12.1 to 78.0)	0.15
	Poor vs good	68.0 (–1.33 to 137.4)	0.05
Sleep duration	Intermediate vs short	–11.6 (–66.0 to 42.8)	0.68
	Long vs short	14.1 (–88.3 to 117.1)	0.78
Beck Depression Inventory-II score	1 point	–0.65 (–3.20 to 1.90)	0.62
Caloric intake	1 kcal/day	–0.02 (–0.06 to 0.01)	0.18
Physical activity	1 METs·h/week	–0.08 (–0.32 to 0.16)	0.52
Alcohol consumption	1 g/day	0.49 (–0.45 to 1.44)	0.31
Current smoker	Former smoker vs current smoker	–27.4 (–78.1 to 22.5)	0.28
	Former smoker vs never-smoker	–21.8 (–71.5 to 27.9)	0.39
Frequency of breakfast intake	One time a week	–25.3 (–40.6 to –10.0)	0.001
Time of dinner	1 hour	–0.85 (–18.5 to 16.8)	0.92
Excessive daytime sleepiness	Yes vs no	–21.1 (–61.4 to 19.3)	0.31
Shift worker	Yes vs no	52.9 (–7.49 to 113.2)	0.09

Longitudinal brachial-ankle pulse wave velocity was analyzed with a linear mixed-effects model using time and lifestyle habits at baseline as fixed effects, and patient as a random effect.

neuropathy among three groups after adjusting for age, gender, duration of T2DM and HbA1c levels at baseline. Throughout the study period, subjects who ate breakfast <4 times a week tended to be obese with a low mean MEQ score and high mean PSQI score. Also, they tended to have higher triglyceride levels and uric acid levels, and lower HDL cholesterol levels, than subjects who ate breakfast ≥4 and <7 times a week or 7 times a week.

DISCUSSION

In this study, we demonstrated for the first time that breakfast skipping was associated with persistently high baPWV in patients with T2DM. Although the mechanisms by which breakfast skipping induces arterial stiffness remain largely unknown, we propose the following possible scenarios. First, breakfast skipping causes a sensation of hunger, and leads to overeating later in the day, causing weight gain, insulin resistance and poor glycemic control.[34 35] In this study, while the subjects who ate breakfast <4 times a week did not have a significantly different daily energy intake than subjects in the other two groups, they consumed more calories later in the day; specifically, they tended to eat late dinners, frequently ate late-evening snacks and often ate out and ate ready-made meals at home for dinner (table 4). A previous cross-sectional study reported that eating at night was positively associated with BMI in middle-aged subjects,[36] and therefore greater daily energy intake late in the day may be associated with deterioration of metabolic controls through weight gain, leading to worsening of arterial stiffness. A second mechanism by which breakfast skipping may induce arterial stiffness is by causing overactivity in the hypothalamic-pituitary-adrenal axis due to prolonged fasting, resulting in elevation of BP.[37] Third, individuals who skip breakfast are more likely to make other unfavorable choices regarding lifestyle habits. In this study, subjects who ate breakfast <4 times a week tended to have an evening chronotype, poor sleep quality and more depression-related symptoms. Due to social norms, individuals with an evening chronotype may be forced to be awake at times they do not prefer, and this may cause stress that activates the sympathetic adrenal nervous system.[38] Subsequent excess release of stress hormones, including cortisol and catecholamines, may lead to the progression of atherosclerosis. In addition, a previous report showed that high levels of catecholamines caused by poor sleep quality may be associated with progression of arterial stiffness in healthy middle-age adults.[12] Thus, a cluster of unhealthy habits may contribute to persistently high baPWV in subjects who eat breakfast infrequently.

Table 3 Results of multiple linear regression analysis for variables associated with longitudinal brachial-ankle pulse wave velocity during 5-year follow-up

Variable	Comparison	Adjusted ORs (95% CI)	P value
Intercept		213 (–281 to 706)	0.40
Time (years)	1 year	23.3 (20.2 to 26.4)	<0.0001
Age (years)	1 year	13.4 (10.9 to 15.9)	<0.0001
Gender	Male vs female	4.2 (–41.2 to 49.5)	0.86
Morningness-Eveningness Questionnaire score	Neither type vs evening type	19.5 (–23.3 to 62.3)	0.37
	Morning type vs evening type	19.2 (–39.9 to 78.4)	0.52
Pittsburgh Sleep Quality Index score	Average vs good	32.5 (–9.2 to 74.3)	0.13
	Poor vs good	42.7 (–21.2 to 106.5)	0.19
Sleep duration	Intermediate vs short	–2.06 (–51.8 to 47.7)	0.93
	Long vs short	–7.65 (–104.1 to 88.8)	0.88
Beck Depression Inventory-II score	1 point	–1.85 (–4.25 to 0.55)	0.13
Caloric intake	1 kcal/day	–0.02 (–0.05 to 0.01)	0.22
Physical activity	1 METs·h/week	–0.11 (–0.34 to 0.13)	0.36
Alcohol consumption	1 g/day	0.24 (–0.70 to 1.17)	0.62
Current smoker	Former smoker vs current smoker	–8.19 (–55.8 to 39.4)	0.74
	Former smoker vs Never-smoker	–5.97 (–53.2 to 41.2)	0.80
Frequency of breakfast intake	One time a week	–25.5 (–39.5 to –11.5)	0.0004
Time of dinner	1 hour	–7.56 (–24.1 to 8.9)	0.37
Excessive daytime sleepiness	Yes vs no	–13.8 (–51.3 to 23.7)	0.47
Shift worker	Yes vs no	38.1 (–18.0 to 94.2)	0.18
Estimated duration of diabetes	1 year	3.59 (1.02 to 6.15)	0.006
Body mass index	1 kg/m^2	–14.3 (–19.4 to –9.16)	<0.0001
Systolic BP	1 mm Hg	5.35 (4.09 to 6.62)	<0.0001
HbA1c	1 mmol/mol	1.26 (–0.51 to 3.03)	0.16
Total cholesterol	1 mg/dL	0.23 (–0.50 to 0.96)	0.54
HDL cholesterol	1 mg/dL	–0.89 (–2.51 to 0.73)	0.28
Triglyceride: log-transformed value	1 unit	56.0 (13.9 to 98.0)	0.009
eGFR	1 $mL/min/1.73\,m^2$	1.08 (–0.04. 2.19)	0.06
Uric acid (mg/dL)	1 mg/dL	25.8 (–9.27 to 42.3)	0.002
Diabetic retinopathy	Yes vs no	20.1 (–16.8 to 56.9)	0.29
Diabetic nephropathy	Macroalbuminuria vs normoalbuminuria	25.5 (–20.2 to 71.3)	0.27
	Microalbuminuria vs normoalbuminuria	100.6 (5.2 to 196.0)	0.04
Diabetic neuropathy	Yes vs no	–26.1 (–65.3 to 13.1)	0.19
Insulin therapy	Yes vs no	3.03 (–56.5 to 62.6)	0.92
Antihypertension drugs	Yes vs no	–3.76 (–39.5 to 32.0)	0.84
Antihyperlipidemia drugs	Yes vs no	–25.7 (–61.0 to 9.7)	0.16
Antiplatelet drugs	Yes vs no	127.2 (33.8 to 220.7)	0.008
Sleep apnea syndrome	Yes vs no	1.68 (–97.3 to 100.6)	0.97

Longitudinal brachial-ankle pulse wave velocity was analyzed with a linear mixed-effects model using time, lifestyle habits and possible atherosclerotic risk factors at baseline as fixed effects, and patient as a random effect.
BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein.

Table 4 Characteristics of each group at baseline by frequency of breakfast intake

Variable	Frequency of breakfast intake at baseline			Est	P value
	<4 times a week (n=42)	≥4 and <7 times a week (n=52)	7 times a week (n=639)		
Frequency of breakfast intake (times a week)	1.9±1.5	5.5±0.5	7.0±0.0		
Age (years)	53.0±8.7	53.9±9.7	58.4±8.3	5.13	<0.001
Male gender (%)	32 (76.2)	31 (59.6)	397 (62.5)	1.36	0.17
Morningness-Eveningness Questionnaire score	51.0±7.0	52.3±7.3	58.2±7.0	8.05	<0.001
Pittsburgh Sleep Quality Index score	6.0±3.2	6.1±2.6	5.0±3.0	–2.94	0.003
Sleep duration (hours)	6.4±1.2	6.3±1.2	6.5±1.2	1.03	0.3
Beck Depression Inventory score	13.8±7.7	11.9±7.4	9.5±7.6	–4.10	<0.001
Caloric intake (kcal/day)	1712±507	1695±802	1722±570	0.23	0.82
Carbohydrate intake (g/day)	219±71	214±90	227±75	1.09	0.28
Fat intake (g/day)	47±19	49±31	49±21	0.51	0.61
Protein intake (g/day)	61±24	64±39	67±29	1.53	0.13
Physical activity (METs·h/week)	34.2±54.1	32.2±46.6	45.3±76.7	1.34	0.18
Smoker (current/former/never)	13/16/13 (31.0/38.1/31.0)	16/11/25 (30.8/21.2/48.1)	148/184/307 (23.2/28.8/48.0)	1.91	0.06
Alcohol consumption (g/day)	20.2±27.4	17.1±29.2	11.5±20.3	–3.00	0.003
Worker (yes)	31 (73.8)	46 (88.5)	461 (72.1)	–1.32	0.19
Shift worker (yes)	4 (9.5)	6 (11.5)	68 (10.6)	0.10	0.91
Regular snacking (time a week)	0.6±0.6	0.8±0.7	0.7±0.7	0.41	0.69
Late evening snacks (yes)	19 (45.2)	22 (42.3)	248 (38.8)	–0.93	0.35
Time from last meal to bedtime (hours)	3.1±1.3	3.7±1.7	3.4±1.6	0.56	0.58
Time of dinner (hour)	19.8±1.2	19.8±1.2	19.2±1.1	–4.75	<0.001
Eating out and/or eating ready-made meals at home for dinner (almost never/1 to 2/3 to 4/5 or more times a week	16 (38.1)/13 (31.0)/10 (23.8)/3 (7.1)	16 (30.8)/28 (53.8)/4 (7.7)/4 (7.7)	370 (57.9)/209 (32.7)/35 (5.5)/25 (3.9)	–4.56	<0.001
Excessive daytime sleepiness (yes)	16 (38.1)	18 (34.6)	199 (31.2)	–1.02	0.31
Estimated duration of diabetes (years)	7.2±4.4	9.4±6.8	10.1±7.3	2.40	0.02
Body mass index (kg/m^2)	26.6±4.6	25.9±5.0	24.4±3.9	–4.13	<0.001
Diabetic retinopathy (number) (%)	13 (31.0)	21 (40.4)	232 (36.8)	0.43	0.67
Diabetic nephropathy (number) (%) Normoalbuminuria/microalbuminuria/macroalbuminuria	29 (70.7)/10 (24.4)/2 (4.9)	36 (70.6)/12 (23.5)/3 (5.9)	200 (31.5)/507 (80.6)/101 (16.1)	–2.03	0.04
Diabetic neuropathy (number) (%)	6 (14.3)	11 (21.2)	175 (27.6)	2.07	0.04
Antidiabetes drugs (yes)	37 (88.1)	44 (84.6)	541 (85.3)	–0.37	0.71

Continued

Table 4 Continued

Variable	Frequency of breakfast intake at baseline			Est	P value
	<4 times a week (n=42)	≥4 and <7 times a week (n=52)	7 times a week (n=639)		
Insulin therapy (yes)	3 (7.1)	7 (13.5)	69 (10.9)	0.40	0.69
Antihypertension drugs (yes)	22 (52.4)	23 (44.2)	302 (47.6)	−0.31	0.75
Antihyperlipidemia drugs (yes)	25 (59.5)	34 (65.4)	384 (60.6)	−0.18	0.86
Antiplatelet drugs (yes)	0 (0.0)	2 (3.8)	22 (3.5)	0.96	0.34
Sleep apnea syndrome (yes)	2 (4.8)	0 (0.0)	23 (3.6)	0.25	0.80

Data are mean±SD or number (proportion) of patients. Est is the regression coefficient for linear trends across quintiles and is based on linear regression analysis for continuous variables or logistic regression analysis for categorical variables.

Fourth, subjects in this study who ate breakfast <4 times a week tended to be obese and had higher HbA1c levels, higher diastolic BP, higher triglyceride and uric acid levels and lower HDL cholesterol levels than subjects who ate breakfast more frequently. The accumulation of such conventional atherosclerotic risk factors could certainly contribute to the worsening of arterial stiffness.

More interestingly, even after adjusting for potential conventional atherosclerotic risk factors (table 3) and unfavorable lifestyle habits such as eating out and/or eating ready-made meal at home for dinner (data not shown), we found that a low frequency of breakfast intake was associated with persistently increased arterial stiffness in patients with T2DM. It is assumed that breakfast skipping affects additional atherosclerotic risk factors. For example, breakfast skipping impacts glucose regulation by reducing sensitization and activation of β-cells mediated by insulin and/or incretin. A previous study demonstrated that breakfast skipping affected postprandial glucose regulation throughout the day and was associated with impaired insulin secretion and lower incretin response in patients with T2DM.[39] In the same study, extended fasting as a result of breakfast skipping resulted in the prolonged elevation of plasma free fatty acids that caused insulin resistance. Therefore, conditions triggered by breakfast skipping may play an important role in the pathogenesis of arterial stiffness.

Since breakfast skipping was associated with increased arterial stiffness, one might expect that eating breakfast more frequently would improve arterial stiffness. Indeed, the above-mentioned study demonstrated that eating breakfast reversed the deleterious effects triggered by breakfast skipping.[39] Unfortunately, our study design did not allow us to clarify how changes in breakfast-eating habits impact arterial stiffness.

Limitations

The present study has certain limitations. First, the observational cohort study design made it impossible to evaluate whether lifestyle habits and/or risk factors for atherosclerosis had a causal relationship with arterial stiffness. Second, we used only evaluation of arterial stiffness as a marker of CVD. In this regard, we are currently conducting a long-term follow-up study in the same cohort that focuses on lifestyle and onset of primary CVD. Third, we evaluated lifestyle using self-reported questionnaires. Although these have been widely used in many studies, the results could have been influenced by social desirability and recall bias. In particular, the frequency of breakfast intake was also self-reported, as in other studies,[21 22] and hence was prone to a subjective interpretation of the definition of 'breakfast'. Furthermore, the number of subjects who ate breakfast <7 times a week was relatively small. However, this proportion was not largely different from that of a recent study.[40] Fourth, our data probably cannot be generalized to a broader population because we investigated a limited number of subjects and used specific inclusion and exclusion

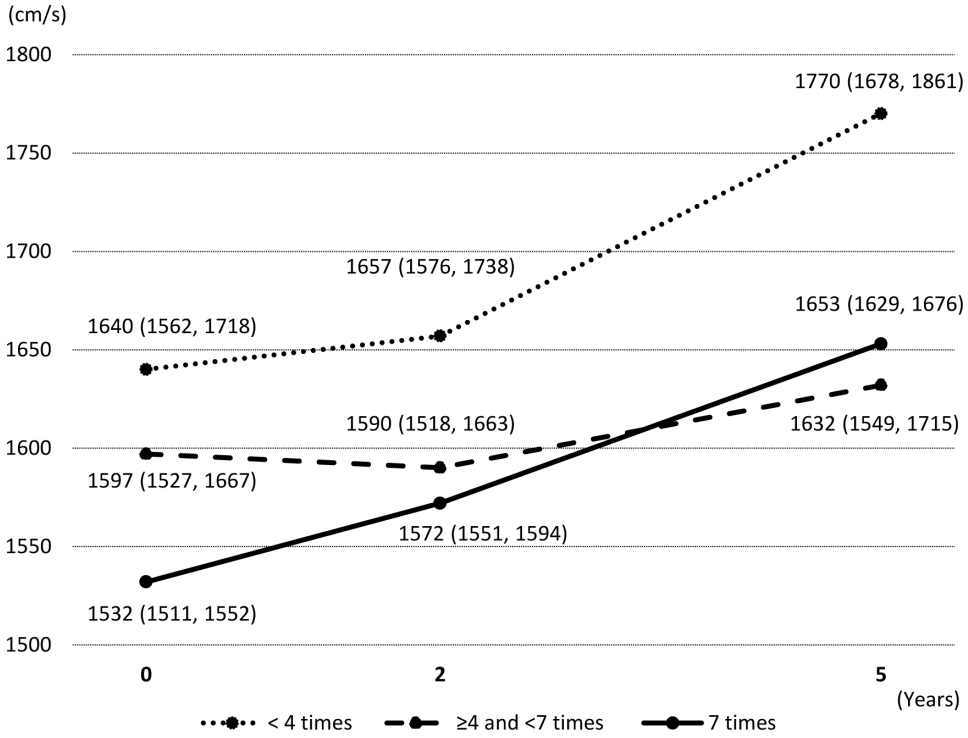

Figure 1 Adjusted means of brachial-ankle pulse wave velocity by breakfast intake group (95% CI: lower value and upper value) derived by a mixed-effects model for repeated measures method using the group, time, their interaction, baseline age and gender.

criteria.Fifth, there may be other lifestyle patterns that should be considered. Finally, the adherence of the drugs such as antidiabetes drugs, antihypertension drugs, antihyperlipidemia drugs and antiplatelet drugs that could be potential confounding factors should be considered. Especially, drug adherence may decrease in the individuals who skip breakfast because they are more likely to make other unfavorable choices.

CONCLUSIONS

In conclusion, the present study demonstrated that breakfast skipping was a lifestyle habit that was independently associated with persistently increased arterial stiffness. Therefore, asking about the frequency of breakfast intake in clinical practice may be a simple and useful method to help identify patients at high risk of developing CVD.

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Acknowledgements The authors would like to thank the following staff who participated in this trial and provided excellent technical support: Yayoi Uchiyama and Emi Ito (Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine), and Satako Douguchi, Norie Watahiki, Nana Shiozawa, Misato Ojima, Akiko Haginoya and Katuhiro Kawauchi (Naka Kinen Clinic).

Contributors All authors contributed to the study design and were involved in all stages of manuscript development. TM and YO drafted the manuscript. MG, a statistician, was primarily responsible for data analysis. TM, YO, TO, MS, SN, YS, HI, MG and HW also collected, analyzed and interpreted the data, reviewed and edited the manuscript and approved the final manuscript. HW is the principal guarantor of this work; he has full access to all study data and takes responsibility for the integrity of the data and the accuracy of data analysis. All authors have read and agreed to the publication of the manuscript.

Funding This study was conducted through a research grant from the Manpei Suzuki Diabetes Foundation (to TM).

Disclaimer This funding agency had no role in study design, data collection or analysis, decision to publish or preparation of the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the institutional review board of Juntendo University Hospital and conducted in accordance with the principles described in the Declaration of Helsinki. All patients provided written informed consent prior to participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The analyzed datasets are available from the corresponding author (tom-m@juntendo.ac.jp) on reasonable request.

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