JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Impact of age at menarche on obesity and glycemic control in Japanese patients with type 2 diabetes: Fukuoka Diabetes Registry

Akiko Sumi[1], Masanori Iwase[1,2]*, Udai Nakamura[1], Hiroki Fujii[3], Toshiaki Ohkuma[1,4], Hitoshi Ide[1,5], Tamaki Jodai-Kitamura[1], Yuji Komorita[1], Masahito Yoshinari[1], Takanari Kitazono[1]

[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, [2]Diabetes Center, Hakujyuji Hospital, [3]Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia, and [5]Division of General Internal Medicine, School of Oral Health Science, Kyushu Dental University, Kitakyushu, Fukuoka, Japan

Keywords
Age at menarche, Glycemic control, Type 2 diabetes mellitus

***Correspondence**
Masanori Iwase
Tel.: +81-92-642-5256
Fax: +81-92-642-5271
E-mail address:
iwase@intmed2.med.kyushu-u.ac.jp

J Diabetes Investig 2018; 9: 1216–1223

doi: 10.1111/jdi.12839

Clinical Trial Registry
University Hospital Medical Information Network
UMIN000002627

ABSTRACT

Aims/Introduction: A younger age at menarche is associated with obesity and type 2 diabetes in adult life. The impact of early-onset menarche on obesity and glycemic control in type 2 diabetes has not been investigated. The present study examined the relationship between age at menarche and obesity and glycemic control in type 2 diabetes.

Materials and Methods: A total of 2,133 patients with type 2 diabetes aged ≥20 years were divided into groups according to age at menarche (≤11, 12, 13, 14 and ≥15 years). A retrospective cohort study examined the association of menarcheal age with adiposity and hemoglobin A_{1c}.

Results: Age at menarche was inversely associated with body mass index (BMI) and abdominal circumference ($P < 0.001$). Each 1-year decrease in age at menarche was associated with a 0.25-kg/m^2 and 0.6-cm increase in BMI and abdominal circumference, respectively, using a multivariate-adjusted model. Odds ratios for obesity and abdominal obesity significantly increased in participants with age at menarche ≤11 years after multivariable adjustments when age at menarche of 13 years was used as the reference (odds ratio 1.95, 95% CI 1.33–2.88, odds ratio 1.95, 95% CI 1.32–2.87, respectively). Younger age at menarche was significantly associated with higher hemoglobin A_{1c} ($P < 0.001$); however, the association was not statistically significant after adjusting for BMI.

Conclusions: Age at menarche of ≤11 years was associated with obesity after adjusting for confounding factors, and poor glycemic control associated with high BMI in type 2 diabetes. Age at menarche should be considered during clinical assessments.

INTRODUCTION

There is a trend towards a younger age at which people are reaching puberty, possibly associated with the impact of Westernization. In Japan, the mean age at menarche decreased from 13.2 years in 1961 to 12.2 years in 2011 in school-aged girls[1]. Earlier-onset menarche is reported to be associated with obesity[2–5], type 2 diabetes mellitus[4,6–11], cardiovascular disease[4,12–14], breast cancer[15] and increased all-cause mortality[4,13,16–18]. It is therefore possible that age at menarche can provide important information to help prevent non-communicable diseases.

Received 24 October 2017; revised 14 February 2018; accepted 28 February 2018

Obesity is a global health problem. Although the prevalence of obesity is lower in Japan than Western populations generally (prevalence of body mass index [BMI] ≥30: 3.7% in Japan vs 38.2% in the USA[19]), there has been an increase in the level of obesity in patients with type 2 diabetes in Japan (mean BMI increased from 24.1 kg/m^2 in 2002 to 25.0 kg/m^2 in 2013[20]).

It is reported that a younger age at menarche is associated with obesity in later life[2–5]. This raises the question as to the association between age at menarche and obesity in patients with type 2 diabetes, and whether early-onset menarche is associated with plasma glucose levels and could be used to predict the future onset of type 2 diabetes[4,6–11]. Against this background, the present retrospective cohort study examined the

relationship between age at menarche and obesity and glycemic control in Japanese patients with type 2 diabetes.

METHODS

Study participants

The Fukuoka Diabetes Registry was designed as a prospective, multicenter, observational study to investigate the effects of modern therapy on the prognosis of Japanese patients with diabetes mellitus[21]. Briefly, the Fukuoka Diabetes Registry cohort comprised patients aged ≥20 years who regularly attended educational research hospitals approved by the Japan Diabetes Society or certified diabetes clinics in Fukuoka Prefecture (UMIN Clinical Trial Registry 000002627) between April 2008 and October 2010. Exclusion criteria were people with drug-induced diabetes mellitus or receiving corticosteroid therapy; those who had undergone renal replacement therapy; those with serious diseases other than diabetes, such as advanced malignancy or decompensated liver cirrhosis; and those who were unable to visit a diabetologist regularly. Of the 2,263 women registered, after excluding those with type 1 diabetes, 2,133 female patients with type 2 diabetes mellitus remained, and were enrolled in the study. The study was approved by the Kyushu University Institutional Review Board and was carried out in accordance with the provisions contained within the Declaration of Helsinki. All patients provided written informed consent for participation in the study.

Clinical evaluation and laboratory measurements

Participants completed a self-administered questionnaire that sought information on age at diagnosis of diabetes, family history of diabetes, smoking habits, alcohol intake, physical activity, maximum bodyweight before enrollment, age at menarche and the occurrence of menopause. Smoking habits and alcohol intake were classified as either current use or not. Metabolic equivalent hours per week were calculated using Ainsworth's methods[22]. A dietary survey was carried out using a brief-type self-administered diet history questionnaire (Gender Medical Research, Inc., Tokyo, Japan) that sought information on the frequency of consumption of 58 items to assess the participants' dietary intakes. The dietary intake estimates for total energy and dietary fiber were calculated using an *ad hoc* algorithm developed for the brief-type self-administered diet history questionnaire based on the Standard Tables of Food Composition in Japan[23]. The medical records of participants were examined for medications including oral hypoglycemic agents and insulin therapy. Bodyweight and height were measured, and BMI was calculated. Obesity was defined as BMI ≥25 kg/m^2 according to the Japan Society for the Study of Obesity criteria[24]. Abdominal circumference at the umbilical level was measured in the standing position. Abdominal obesity was defined as an abdominal circumference of ≥90 cm according to the Japan Society for the Study of Obesity criteria[24].

Blood tests were carried out in either the fasting or postprandial state. Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography (Tosoh Corp., Tokyo, Japan), and serum C-peptide was determined using chemiluminescent immunoassays (Kyowa Medex, Tokyo, Japan). High-sensitivity C-reactive protein (HS-CRP) and serum adiponectin were determined by latex immunonephelometry (Siemens Healthcare Diagnostics, Tokyo, Japan; Mitsubishi Chemical Medience, Tokyo, Japan). β-Cell function (homeostatic model assessment of β-cell [HOMA2-%β] index) and insulin resistance (homeostatic model assessment of insulin resistance [HOMA2-IR] index) were estimated based on fasting glucose and C-peptide concentrations using a HOMA calculator (version 2.2.2; http://www.dtu.ox.ac.uk, accessed June 2012) after exclusion of individuals with unacceptable levels of plasma glucose (<3.0 mmol/L or >25 mmol/L) or C-peptide (<0.2 nmol/L or >3.5 nmol/L).

Statistical analysis

HOMA2-%β, HOMA2-IR, serum adiponectin and HS-CRP were log-transformed for statistical analyses because of their skewed distributions. They are presented with 95% confidence intervals (95% CI) that were back-transformed. Participants were divided into five categories according to age at menarche: ≤11, 12, 13, 14 and ≥15 years, as reported in previous studies[4,6,7,9]. Baseline characteristics by categories of age at menarche were explored using one-way analysis of variance and analysis of covariance to compare means of continuous variables, and using χ^2-tests to compare proportions of categorical variables. Trend associations for age at menarche were assessed using multivariable regression analyses, and included age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use as covariates. Associations between age at menarche and the prevalence of obesity, history of obesity and abdominal obesity were tested using multivariable logistic regression analyses. All analyses were carried out using the SAS software package (version 9.4; SAS Institute Inc., Cary, NC, USA). A P-value <0.05 was considered statistically significant.

RESULTS

Participant characteristics

Baseline characteristics of the study participants by categories of age at menarche are shown in Table 1. The mean age at menarche was 13.7 ± 1.8 years. Those with a younger age at menarche were diagnosed with diabetes at a younger age, had a shorter duration of diabetes, were more likely to be premenopausal, had lower energy and dietary fiber intake, and exercised less. These statistical differences were absent after adjusting for age.

Associations between age at menarche and obesity

The age at menarche was inversely associated with BMI (P for trend <0.001; Table 2). The association remained statistically significant after multivariable adjustments including age, duration of diabetes, current smoking, current drinking, leisure-time

Table 1 | Clinical characteristics of the study participants by categories of age at menarche

	Total	Categories of age at menarche (years)					*P* for trend	
		≤11	12	13	14	≥15	Unadjusted	Age-adjusted
Age at menarche (years)	13.7 (13.0–15.0)	10.7 (10.0–11.0)	12.0 (12.0–12.0)	13.0 (13.0–13.0)	13.9 (14.0–14.0)	15.8 (15.0–16.0)		
n	2,133	169	355	475	523	611		
Age (years)	65.8 ± 10.4	53.2 ± 11.4	61.1 ± 10.5	64.8 ± 9.8	67.7 ± 8.1	71.3 ± 7.7	<0.001	–
Age at diabetes diagnosis (years)	51.0 ± 11.9	40.3 ± 12.9	47.5 ± 11.5	50.9 ± 11.1	52.3 ± 10.7	55.0 ± 11.1	<0.001	NS
Duration of diabetes (years)	14.3 ± 9.8	12.4 ± 9.2	13.0 ± 9.5	13.4 ± 8.9	14.9 ± 10.2	15.8 ± 10.1	<0.001	NS
Family history of diabetes (%)	61.5	68.6	65.6	60.2	61.0	58.6	0.07	NS
Menopause (%)	92.3	63.9	86.8	92.6	97.3	98.7	<0.001	NS
Age at menopause (years)	49.4 ± 5.3	48.9 ± 5.4	49.5 ± 5.0	49.4 ± 5.0	49.4 ± 5.4	49.4 ± 5.4	NS	NS
Reproductive years	35.5 ± 5.5	38.2 ± 5.4	37.5 ± 5.0	36.4 ± 5.0	35.4 ± 5.4	33.5 ± 5.6	<0.001	<0.001
Current smoker (%)	6.8	10.7	6.2	6.1	7.8	5.9	NS	NS
Current drinker (%)	16.5	17.2	18.3	16.6	17.4	14.2	NS	NS
Energy intake (kcal/day)	1,509 ± 412	1,479 ± 384	1,510 ± 466	1,491 ± 392	1,510 ± 407	1,531 ± 407	<0.05	NS
Dietary fiber intake (g/1,000 kcal)	8.3 ± 2.2	7.6 ± 2.1	8.1 ± 2.0	8.4 ± 2.4	8.4 ± 2.1	8.4 ± 2.1	<0.001	NS
LTPA (MET h/week)	16.3 ± 16.4	13.4 ± 14.0	16.4 ± 20.1	16.0 ± 14.4	17.0 ± 16.1	16.8 ± 16.4	<0.05	NS
Oral hypoglycemic agents (%)	63.5	63.9	64.8	62.7	60.6	65.8	NS	NS
Insulin (%)	30.8	36.7	32.1	29.7	30.0	29.8	NS	NS

Data are mean ± standard deviation or percentage. Numbers in parenthesis represent interquartile range. LTPA, leisure-time physical activity; NS, not significant.

Table 2 | Association of categories of age at menarche with adiposity, stratified by age in Japanese patients with type 2 diabetes

	Categories of age at menarche (years)					*P* for trend	
	≤11	12	13	14	≥15	Unadjusted	Multivariate-adjusted
Age at menarche (years)	10.7 (10.0–11.0)	12.0 (12.0–12.0)	13.0 (13.0–13.0)	13.9 (14.0–14.0)	15.8 (15.0–16.0)		
BMI (kg/m^2)							
All	26.3 ± 6.1	24.7 ± 4.6	24.1 ± 4.5	23.4 ± 3.7	23.4 ± 3.8	<0.001	<0.001
<65 years	26.6 ± 6.3	25.2 ± 4.7	24.3 ± 5.0	23.5 ± 3.8	23.9 ± 4.3	<0.001	<0.001
≥65 years	24.5 ± 4.7	23.5 ± 3.9	23.9 ± 3.9	23.4 ± 3.6	23.2 ± 3.7	<0.05	<0.05
Maximum BMI (kg/m^2)							
All	29.7 ± 6.3	28.2 ± 4.9	27.4 ± 4.7	26.7 ± 3.8	26.7 ± 3.9	<0.001	<0.001
<65 years	29.9 ± 6.5	28.6 ± 5.3	27.4 ± 5.4	26.6 ± 3.8	26.8 ± 4.4	<0.001	<0.001
≥65 years	28.0 ± 5.3	27.4 ± 3.9	27.4 ± 3.9	26.8 ± 3.8	26.7 ± 3.8	<0.01	<0.01
Abdominal circumference (cm)							
All	89.0 ± 14.3	87.0 ± 11.7	86.0 ± 12.4	84.8 ± 10.5	85.3 ± 11.2	<0.001	<0.001
<65 years	89.3 ± 14.8	87.3 ± 12.3	84.7 ± 13.0	83.6 ± 10.9	84.0 ± 12.1	<0.001	<0.001
≥65 years	87.1 ± 10.9	86.2 ± 10.3	87.2 ± 11.6	85.5 ± 10.2	85.6 ± 11.0	NS	<0.05

Data are mean ± standard deviation. Numbers in parenthesis represent interquartile range. Multivariable adjustments include age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use. BMI, body mass index; NS, not significant.

physical activity, daily energy intake, oral hypoglycemic agent use and insulin use. The increase in BMI per 1-year earlier onset of menarche was 0.42 kg/m^2 in the crude and 0.25 kg/m^2 in the multivariate-adjusted models. An inverse association between age at menarche and BMI was evident in both participants aged <65 years and ≥65 years. Maximum BMI was significantly associated with age at menarche in all participants and those aged <65 years and ≥65 years. The increase in maximum BMI per 1-year earlier onset of menarche was 0.43 kg/m^2 in the crude and 0.33 kg/m^2 in the multivariate-adjusted models. Abdominal circumference was inversely associated with age at menarche. The association was significant in participants aged <65 years, whereas in those aged ≥65 years, it was significant after multivariate adjustments. The increase in abdominal circumference per 1-year earlier onset of menarche was 0.5 cm in the crude and 0.6 cm in the multivariate-adjusted models.

In all the participants, the prevalence of obesity was inversely related to the age at menarche, after adjusting for confounding factors (Table 3). Similarly, a history of obesity and abdominal obesity were more common in individuals who underwent menarche at an earlier age. There was a significant association between the prevalence of obesity and age at menarche in participants both aged <65 years and ≥65 years. Regarding a history of obesity and abdominal obesity, the association was significant in participants aged <65 years, but not in those aged ≥65 years. When 13 years-of-age was used as the reference, odds ratios (OR) for obesity, history of obesity and abdominal obesity significantly increased in those with age at menarche ≤11 years after multivariable adjustments (OR 1.95, 95% CI 1.33–2.88 for obesity; OR 2.01, 95% CI 1.31–3.15 for history of obesity; and OR 1.95, 95% CI 1.32–2.87 for abdominal obesity). In participants aged <65 years, the ORs for obesity, history of obesity and abdominal obesity were significantly higher in those who experienced menarche at ≤11 years and 12 years, whereas there were no significant differences in those aged ≥65 years.

Associations between age at menarche and glycemic control

Age at menarche was inversely associated with HbA_{1c} ($P < 0.001$). The increase in HbA_{1c} per 1-year earlier onset of menarche was 0.04% in the crude and 0.03% in the multivariate-adjusted models. However, the statistical significance was attenuated by age or multivariate adjustments, and absent with adjustment for BMI (Table 4). Analysis of glycemic control in participants aged <65 years yielded similar results, but there was no association in those aged ≥65 years. The insulin secretion parameter, HOMA2-%β, did not differ among the age at menarche categories. HOMA2-IR increased and serum adiponectin decreased at earlier onset of menarche ($P < 0.001$), although age adjustment removed the statistical significance. HS-CRP, a marker of systematic microinflammation, was inversely associated with age at menarche to a marginal degree in the age- and multivariate-adjustment models. For HOMA2-%β, HOMA2-IR, serum adiponectin and HS-CRP, similar results

Table 3 | Association of categories of age at menarche with obesity in Japanese patients with type 2 diabetes

	Categories of age at menarche (years)					*P* for trend
	≤11	12	13	14	≥15	
Age at menarche (years)	10.7 (10.0–11.0)	12.0 (12.0–12.0)	13.0 (13.0–13.0)	13.9 (14.0–14.0)	15.8 (15.0–16.0)	
Prevalence (%)						
All						
Obesity	55.0	40.3	35.0	29.8	28.3	<0.001
History of obesity	78.1	74.9	67.0	64.2	64.2	<0.001
Abdominal obesity	45.6	37.5	32.2	31.6	31.9	0.002
<65 years						
Obesity	58.2	44.0	33.0	28.7	36.7	<0.001
History of obesity	81.5	75.3	63.5	62.4	61.5	<0.001
Abdominal obesity	46.6	39.5	25.7	29.3	30.3	<0.001
≥65 years						
Obesity	34.8	32.1	36.7	30.4	26.5	0.014
History of obesity	56.5	74.1	70.2	65.2	64.7	0.11
Abdominal obesity	39.1	33.0	38.4	32.8	32.3	0.24
Multivariate-adjusted OR						
All						
Obesity	1.95 (1.33–2.88)	1.19 (0.88–1.59)	1.00 (ref)	0.85 (0.64–1.12)	0.79 (0.60–1.03)	<0.001
History of obesity	2.01 (1.31–3.15)	1.57 (1.15–2.15)	1.00 (ref)	0.89 (0.68–1.17)	0.82 (0.63–1.07)	<0.001
Abdominal obesity	1.95 (1.32–2.87)	1.30 (0.97–1.75)	1.00 (ref)	0.97 (0.74–1.27)	0.91 (0.69–1.19)	0.002
<65 years						
Obesity	2.78 (1.76–4.41)	1.58 (1.07–2.32)	1.00 (ref)	0.85 (0.54–1.31)	1.30 (0.79–2.14)	<0.001
History of obesity	2.98 (1.77–5.13)	1.81 (1.21–2.73)	1.00 (ref)	0.95 (0.62–1.44)	0.95 (0.58–1.55)	<0.001
Abdominal obesity	2.70 (1.69–4.35)	1.93 (1.29–2.89)	1.00 (ref)	1.21 (0.77–1.90)	1.31 (0.78–2.20)	<0.001
≥65 years						
Obesity	0.88 (0.34–2.17)	0.80 (0.48–1.30)	1.00 (ref)	0.77 (0.54–1.01)	0.62 (0.44–0.87)	0.022
History of obesity	0.56 (0.23–1.37)	1.24 (0.75–2.10)	1.00 (ref)	0.82 (0.57–1.17)	0.74 (0.52–1.03)	0.11
Abdominal obesity	1.06 (0.42–2.54)	0.78 (0.48–1.25)	1.00 (ref)	0.80 (0.56–1.13)	0.72 (0.52–1.00)	0.37

Data are mean ± standard deviation, percentage or odds ratios (OR). Numbers in parenthesis represent interquartile range or 95% confidence interval. Obesity was defined as body mass index ≥25 kg/m^2 and abdominal obesity as abdominal circumference ≥90 cm according to the Japan Society for the Study of Obesity criteria[22]. Multivariable adjustments include age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use.

were obtained in participants aged <65 years, whereas there were no associations in those aged ≥65 years.

DISCUSSION

In the present study, age at menarche was inversely associated with adiposity in patients with type 2 diabetes. To the best of the authors' knowledge, this is the first study to report on the association between age at menarche in patients with type 2 diabetes. It is reported that earlier-onset menarche is associated with obesity and the development of type 2 diabetes mellitus in later life[2–11]. The present results extend the association between age at menarche and obesity to patients with type 2 diabetes. Although people with obesity and type 2 diabetes are strongly urged to modify their lifestyle habits, including diet and exercise, there were twice as many patients in the ≤11 years-of-age at menarche group compared with the 13 years-of-age at menarche group. It is possible that obesity contributes to worsened glycemic control in those with age at menarche ≤11 years.

In a meta-analysis of 10 studies including 246,671 women[12], mostly from Western populations, early menarche (<12 vs 12 years) was associated with 0.34 kg/m^2 higher BMI. Of 303,000 women in the China Kadoorie Biobank, increases in BMI and abdominal circumference per 1-year earlier onset of menarche were reported to be 0.19 kg/m^2 and 0.38 cm, respectively[5]. In the current study, increases in BMI and abdominal circumference per 1-year earlier onset of menarche were 0.25 kg/m^2 and 0.6 cm in the multivariate-adjusted model. It appears that the impact of earlier-onset menarche on obesity is greater in the current study. This difference might be explained by the populations studied. For example, the general population vs patients with type 2 diabetes, or Western populations vs Asian populations, in whom those with type 2 diabetes are not typically obese.

The association between age at menarche and BMI was observed in both the <65 years and ≥65 years age groups. One of the mechanisms that has been proposed to explain the

Table 4 | Association of categories of age at menarche with glycemic control, insulin secretion, insulin resistance, adiponectin and microinflammation in Japanese patients with type 2 diabetes

	Categories of age at menarche (years)					*P* for trend		
	≤11	12	13	14	≥15	Unadjusted	Multivariate	Multivariate + BMI
Age at menarche (years)	10.7 (10.0–11.0)	12.0 (12.0–12.0)	13.0 (13.0–13.0)	13.9 (14.0–14.0)	15.8 (15.0–16.0)			
HbA_{1c} (%)								
All	7.77 ± 1.29	7.63 ± 1.16	7.59 ± 1.09	7.48 ± 0.97	7.47 ± 1.02	<0.001	<0.05	NS
<65 years	7.78 ± 1.31	7.72 ± 1.27	7.62 ± 1.12	7.49 ± 0.99	7.59 ± 1.18	<0.05	0.050	NS
≥65 years	7.70 ± 1.16	7.45 ± 0.85	7.56 ± 1.06	7.47 ± 0.97	7.45 ± 0.99	NS	NS	NS
HbA_{1c} (mmol/mol)								
All	59.8 ± 13.1	58.4 ± 11.8	58.0 ± 11.1	56.8 ± 9.9	56.8 ± 10.4	<0.001	<0.05	NS
<65 years	59.9 ± 13.3	59.2 ± 12.9	58.3 ± 11.3	56.9 ± 10.0	57.9 ± 12.0	<0.05	0.050	NS
≥65 years	59.1 ± 11.8	56.6 ± 8.7	57.7 ± 10.8	56.7 ± 9.8	56.5 ± 10.1	NS	NS	NS
HOMA2-%β								
All	39.6 (36.5–43.0)	38.9 (36.8–41.1)	39.5 (37.6–41.6)	40.8 (38.9–42.8)	41.1 (39.4–43.0)	NS	NS	NS
<65 years	42.3 (34.3–52.1)	37.6 (34.3–41.3)	39.6 (36.9–42.4)	41.6 (39.4–44.1)	41.4 (39.5–43.4)	NS	NS	NS
≥65 years	39.2 (35.7–43.0)	39.5 (36.8–42.4)	39.5 (36.7–42.5)	39.4 (36.2–42.8)	39.9 (35.8–44.5)	NS	NS	NS
HOMA2-IR								
All	1.12 (1.05–1.20)	1.02 (0.97–1.06)	0.98 (0.94–1.02)	0.95 (0.91–0.99)	0.98 (0.94–1.01)	<0.001	NS	NS
<65 years	1.14 (1.06–1.23)	1.06 (1.00–1.13)	0.99 (0.93–1.05)	0.96 (0.90–1.03)	1.03 (0.95–1.13)	<0.05	NS	NS
≥65 years	1.04 (0.88–1.24)	0.93 (0.86–1.00)	0.97 (0.92–1.03)	0.94 (0.90–0.99)	0.97 (0.93-1.00)	NS	NS	NS
Adiponectin (μg/mL)								
All	9.0 (8.2–9.8)	10.0 (9.5–10.7)	10.6 (10.1–11.2)	10.7 (10.2–11.2)	11.4 (10.9–11.9)	<0.001	NS	NS
<65 years	8.9 (8.1–9.8)	9.3 (8.6–10.0)	10.4 (9.6–11.2)	10.6 (9.7–11.5)	9.8 (8.7–10.9)	<0.05	NS	NS
≥65 years	9.6 (7.7–12.0)	11.9 (10.8–13.2)	11.0 (10.2–11.7)	10.7 (10.1–11.4)	11.8 (11.2–11.4)	NS	NS	NS
HS-CRP (mg/L)								
All	0.64 (0.52–0.79)	0.49 (0.42–0.56)	0.48 (0.43–0.55)	0.50 (0.44–0.56)	0.50 (0.45–0.56)	NS	<0.05	NS
<65 years	0.67 (0.54–0.84)	0.49 (0.41–0.58)	0.42 (0.35–0.50)	0.45 (0.37–0.55)	0.48 (0.37–0.62)	<0.05	NS	NS
≥65 years	0.48 (0.28–0.82)	0.49 (0.38–0.63)	0.56 (0.47–0.66)	0.53 (0.45–0.61)	0.51 (0.45–0.57)	NS	NS	NS

Data are mean ± standard deviation, percentage or odds ratios. Numbers in parenthesis represent interquartile range or 95% confidence. Multivariable adjustments include age, duration of diabetes, current smoking, current drinking, leisure-time physical activity, daily energy intake, oral hypoglycemic agent use and insulin use. BMI, body mass index; HbA_{1c}, hemoglobin 1c; HS-CRP, high-sensitivity C-reactive protein; HOMA2-%β homeostasis model assessment of β-cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; NS, not significant.

association between early age at menarche and obesity is that earlier-onset menarche might result in longer exposure to estrogen[25] and adrenal steroids[26], which tend to maintain adiposity. Furthermore, an overlap between single-nucleotide polymorphisms implicated in the timing of puberty and in determining BMI in adulthood has been reported[25]. These single-nucleotide polymorphisms include *TCF*, which was shown to be a risk factor for obesity and type 2 diabetes[27], and *LIN28B*, which is associated with insulin sensitivity and oxidative stress-related β-cell apoptosis[28]. Individuals who have these single-nucleotide polymorphisms tend to gain weight faster during infancy and early childhood, and show earlier-onset menarche[29].

Earlier age at menarche is associated with the future development of type 2 diabetes in Western and Asian populations[4,6–11], and was associated with elevated HbA_{1c}, secondary to high BMI in the current study. These associations can be largely explained by increased adiposity. In the current study, earlier age at menarche was not associated with insulin secretion, but was associated with increased insulin resistance, reduced serum adiponectin and increased systemic microinflammation (Table 4). However, adjusting for age and BMI removed these associations, being in line with HbA_{1c}.

Analyses stratified according to age (<65 years and ≥65 years) showed that there were significant associations between age at menarche and history of obesity or abdominal obesity in participants aged <65 years, but not in those aged ≥65 years (Table 3). This might be due to the small number of participants who went through menarche at ≤11 years (n = 23) among those aged ≥65 years. In addition, there were no significant interactions between the age of the participant (<65 and ≥65 years) and their age at menarche.

The present study had some limitations. First, there is the possibility of recall bias regarding age at menarche, although previous studies report that recalling age at menarche is reliable over many years[27]. Second, we could not clarify the influence of childhood or pubertal BMI on adulthood obesity because of a lack of information. Finally, the conclusions of the study should not be generalized to other ethnic populations, especially with high BMI, without caution.

In conclusion, age at menarche of ≤11 years was associated with obesity after adjusting for confounding factors, and poor glycemic control associated with BMI in type 2 diabetes. As obesity can accelerate the development and progression of diabetic complications, age at menarche should be a factor for consideration when determining clinical management of patients with obese type 2 diabetes.

ACKNOWLEDGMENTS

The authors thank Drs Yutaka Kiyohara, Yasufumi Doi, Toshiharu Ninomiya, Yoichiro Hirakawa, Shigenobu Kanba, Dongchon Kang, Shuzo Kumagai, Shinako Kaizu, Chisa Matsumoto (Kyushu University), Michiaki Kubo (RIKEN), Nobutaka Tsutsu, Nobuhiro Sasaki (Fukuoka Red Cross Hospital), Kiyohide Nunoi, Yuichi Sato, Yuji Uchizono, Ayumi Yamauchi, Kaori Itoh, Chie Miyakawa (St. Mary's Hospital), Sakae Nohara, Hirofumi Imoto, Kazushi Amano, Chie Kitaoka (Steel Memorial Yawata Hospital), Daisuke Gotoh, Toshitaka Himeno, Masae Toyonaga (Kyushu Central Hospital), Noriyasu Shinohara, Ayako Tsutsumi (Fukuoka Higashi Medical Centre), Yasuhiro Idewaki, Masahiro Nakano, Mina Matsuo, Shoko Morimoto, Tomoko Hyodo (Hakujuji Hospital), Masae Minami (Clinic Minami Masae), Miya Wada (Wada Miya Naika Clinic), Yoshifumi Yokomizo (Yokomizo Naika Clinic), Yohei Kikuchi, Masanori Kikuchi (Kikuchi Naika Clinic), Riku Nomiyama (Suzuki Naika Clinic), Shin Nakamura (Nakamura Naika Clinic), Kenji Tashiro (Oshima Eye Hospital), Mototaka Yoshinari (Yoshinari Naika Clinic), Kojiro Ichikawa (Fukutsu Naika Clinic) and Teruo Omae (Hisayama Research Institute For Lifestyle Diseases); clinical research coordinators Chiho Ohba, (Hisayama Research Institute For Lifestyle Diseases) and Yoko Nishioka (Kyushu University); and administrative staff Tomoko Matake (Hisayama Research Institute For Lifestyle Diseases) and Junko Ishimatsu (Kyushu University). We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. This work was supported, in part, by the Japan Society for the Promotion of Science KAKENHI (grant numbers 23249037 and 23659353 to MI and 16K00861 to HF) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Hinobayashi T, Kato M, Akai S, *et al.* The change of interests of Japanese schoolgirls around puberty. Proceeding of 15th European Conference on Developmental Psychology. Pianoro, Bologna: Medimond-Monduzzi; 2012; 441–444.
2. Pierce MB, Leon DA. Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. *Am J Clin Nutr* 2005; 82: 733–739.
3. Feng Y, Hong X, Wilker E, *et al.* Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis* 2008; 196: 590–597.
4. Lakshman R, Forouhi NG, Sharp SJ, *et al.* Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab* 2009; 94: 4953–4960.
5. Yang L, Li L, Millwood IY, *et al.* Adiposity in relation to age at menarche and other reproductive factors among 300 000 Chinese women: findings from China Kadoorie Biobank study. *Int J Epidemiol* 2017; 46: 502–512.
6. Lakshman R, Forouhi N, Luben R, *et al.* Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. *Diabetologia* 2008; 51: 781–786.
7. He C, Zhang C, Hunter DJ, *et al.* Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. *Am J Epidemiol* 2010; 171: 334–344.

8. Pierce MB, Kuh D, Hardy R. The role of BMI across the life course in the relationship between age at menarche and diabetes, in a British Birth Cohort. *Diabet Med* 2012; 29: 600–603.
9. Elks CE, Ong KK, Scott RA, *et al*. Age at menarche and type 2 diabetes risk: the EPIC-InterAct study. *Diabetes Care* 2013; 36: 3526–3534.
10. Hwang E, Lee KW, Cho Y, *et al*. Association between age at menarche and diabetes in Korean post-menopausal women: results from the Korea National Health and Nutrition Examination Survey (2007-2009). *Endocr J* 2015; 62: 897–905.
11. Lim JS, Lee HS, Kim EY, *et al*. Early menarche increases the risk of Type 2 diabetes in young and middle-aged Korean women. *Diabet Med* 2015; 32: 521–525.
12. Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int J Obes (Lond)* 2013; 37: 1036–1043.
13. Charalampopoulos D, McLoughlin A, Elks CE, *et al*. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *Am J Epidemiol* 2014; 180: 29–40.
14. Canoy D, Beral V, Balkwill A, *et al*. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation* 2015; 131: 237–244.
15. Hsieh CC, Trichopoulos D, Katsouyanni K, *et al*. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer* 1990; 46: 796–800.
16. Jacobsen BK, Heuch I, Kvale G. Association of low age at menarche with increased all-cause mortality: a 37-year follow-up of 61,319 Norwegian women. *Am J Epidemiol* 2007; 166: 1431–1437.
17. Jacobsen BK, Oda K, Knutsen SF, *et al*. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976-88. *Int J Epidemiol* 2009; 38: 245–252.
18. Tamakoshi K, Yatsuya H, Tamakoshi A, *et al*. Early age at menarche associated with increased all-cause mortality. *Eur J Epidemiol* 2011; 26: 771–778.
19. OECD.org. OECD OBESITY UPDATE 2017; 2017. Available from: http://www.oecd.org/health/obesity-update.htm Accessed September 21, 2017.
20. JDDM. Available from: http://jddm.jp/data/index-2013.html Accessed September 21, 2017.
21. Ohkuma T, Fujii H, Iwase M, *et al*. Impact of sleep duration on obesity and the glycemic level in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Diabetes Care* 2013; 36: 611–617.
22. Ainsworth BE, Haskell WL, Whitt MC, *et al*. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; 32: S498–S504.
23. Kobayashi S, Honda S, Murakami K, *et al*. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. *J Epidemiol* 2012; 22: 151–159.
24. Examination Committee of Criteria for Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66: 987–992.
25. LeBlanc ES, Kapphahn K, Hedlin H, *et al*. Reproductive history and risk of type 2 diabetes mellitus in postmenopausal women: findings from the Women's Health Initiative. *Menopause* 2017; 24: 64–72.
26. Thankamony A, Ong KK, Ahmed ML, *et al*. Higher levels of IGF-I and adrenal androgens at age 8 years are associated with earlier menarche in girls. *J Clin Endocrinol Metab* 2012; 97: E786–E790.
27. Tong Y, Lin Y, Zhang Y, *et al*. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: a large Human Genome Epidemiology (HuGE) review and meta-analysis. *BMC Med Genet* 2009; 10: 15.
28. Perry JR, Day F, Elks CE, *et al*. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature* 2014; 514: 92–97.
29. Flom JD, Cohn BA, Tehranifar P, *et al*. Earlier age at menarche in girls with rapid early life growth: cohort and within sibling analyses. *Ann Epidemiol* 2017; 27: 187–193.e2.