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Age at menarche, type 2 diabetes and cardiovascular disease complications in US women aged under 65 years: NHANES 1999–2018

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ABSTRACT

Background Diabetes and diabetes complications are on the rise in US adults aged <65 years, while onset of menarche at a younger age is also increasing. We examined the associations of age at menarche with type 2 diabetes among women aged <65 years and with cardiovascular disease (CVD) complications among women with diabetes.

Methods Using the nationally representative cross-sectional National Health and Nutrition Examination Survey 1999–2018, women aged 20–65 years free of cancer were included in the current analysis. Diabetes was defined as a self-reported diabetes diagnosis. CVD was defined as coronary heart disease or stroke. Age at menarche was self-reported age of first menstruation and categorised into ≤10, 11, 12, 13, 14 and ≥15 years.

Results Of 17 377 women included in the analysis, 1773 (10.2%) reported having type 2 diabetes. Earlier age at menarche was associated with type 2 diabetes compared with median age at menarche of 13 years, after adjustment for age, race/ethnicity, education, parity, menopause status and family history of diabetes, smoking status, physical activity, alcohol consumption and body mass index (p for trend=0.02). Among women with diabetes, earlier age at menarche was associated with stroke with similar adjustment (p for trend=0.03), but not with total CVD. Extremely early age at menarche (≤10 years) was significantly associated with stroke (adjusted OR 2.66 (95% CI 1.07 to 6.64)) among women aged <65 years with diabetes with similar adjustment.

Conclusions Earlier age at menarche was associated with type 2 diabetes among young and middle-aged women in the USA and with stroke complications among these women living with diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The median age of diabetes complications is decreasing, in parallel with the decreasing age at menarche in the USA and globally.

⇒ Age at menarche has been associated with a higher risk of diabetes and with cardiovascular disease (CVD) independently, but it remains unclear whether age at menarche is a risk factor for CVD complications among younger women with diabetes.

WHAT THIS STUDY ADDS

⇒ Age at menarche seems to be an early life risk factor for stroke complications among younger women with diabetes.

⇒ Earlier ages at menarche were associated with premature stroke events among women aged <65 years with diabetes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Women with early-life exposures such as early age at menarche need to be further examined for diabetes and prevention research and strategies for progression of diabetes complications.

INTRODUCTION

The prevalence of diabetes complications among younger adults is increasing.[1–4] Diabetes-related vascular events among middle-aged adults now account for a higher proportion of total diabetes cardiovascular complications in the USA.[5] In parallel with the observed younger age of onset of diabetes complications, secular trends have also shown earlier age at menarche in the USA and worldwide.[6–10] Age at menarche, the age at onset of first menstruation in girls, is frequently used as an indicator of the timing of puberty in epidemiological studies to explore the association between adolescent pubertal development and later disease risk.[11]

Previously, earlier age at menarche has been associated with adverse outcomes including obesity,[12 13] type 2 diabetes,[14–16] cardiovascular disease (CVD)[17–21] and mortality.[19 22] While several studies have assessed the relationship between age at menarche and type 2 diabetes previously, these studies were largely conducted in white American and European populations.[14 15] In terms of the association between cardiovascular health and age at menarche, analyses were often conducted

only on postmenopausal older women.[20 23 24] For example, the Million Women Study from the UK, a cohort study analysing data from more than 1 million women aged 50 years and over, reported an association between age at menarche and vascular disease risk, but it only included women aged 50–64 years at baseline and, as a result, most of the cardiovascular events were only observed in postmenopausal women.[23]

Age at menarche has been associated with diabetes and with CVD independently,[13 16 19] but it remains unclear whether age at menarche is a risk factor for CVD complications among younger women with diabetes. With the increasing prevalence of diabetes complications among young and middle-aged adults, it will be beneficial to investigate the earlier life risk factors for early-onset diabetes complications. The objectives of this study are to assess (1) the association of age at menarche with diabetes among women aged <65 years and (2) the association of age at menarche with CVD among women aged <65 years with diabetes using National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2018.

METHODS

Study population

This study used data from the NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016 and 2017–2018. The NHANES is a nationally representative cross-sectional survey that collects information among the non-institutionalised US population.[25 26] The survey employs a multistage probabilistic design to collect a wide range of health information through household interviews and physical examinations. In this analysis, the inclusion criteria were women, age 20–65 years, who responded to the reproductive health question asking their age at menarche. The age inclusion criterion was chosen to be able to focus on younger adults, as they now account for the higher proportion of total diabetes CVD complications in the country.[5] The exclusion criteria included a history of cancer, to reduce the potential of confounding through the well-known cardiovascular and diabetes comorbidities in patients with cancer.[27] A total sample size of 17 377 women was included in the current analysis.

Ascertainment of diabetes

All participants answering 'yes' or 'borderline' to the NHANES question asking if they have ever been told by a health practitioner that they had diabetes or sugar diabetes outside of pregnancy were defined as a diabetes case.[26] If the participant refused or did not know the answer, the response was counted as missing.

Ascertainment of CVD

CVD was defined as coronary heart disease (CHD), non-fatal or fatal myocardial infarction (MI), and non-fatal or fatal stroke. If the participant had a history of CHD, MI or stroke, they were defined as a CVD case.

CHD was ascertained by asking the participant if the doctor had ever told them that they had CHD; MI was ascertained by asking the participants if the doctor had ever told them that they have had a heart attack; and stroke was ascertained asking the participants if the doctor had ever told them that they had had a stroke. If the participant responded 'yes', they were counted as a case.[26]

Assessment of age at menarche

Age at menarche was assessed from the question 'How old were you when your first menstrual period occurred?'[26] Age of menarche was categorised into six groups (≤10, 11, 12, 13, 14 and ≥15 years of age) for main regression analyses.

Covariates

A number of potential confounders were included in this analysis based on previous literature[20 25 28] and availability of data in the NHANES: (1) demographic and socioeconomic status including age (<30, 30–39, 40–49, 50–59, 60–69, ≥70 years old or missing), race/ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic and others), education (<high school, high school, >high school or missing), poverty income ratio (<1.0, 1.0–1.99, ≥2.0, or missing, where a ratio of <1 means that the income is less than the poverty level, a ratio of 1 means the income and poverty level are the same, and a ratio of >1 means the income is higher than the poverty level) and marital status (married, not married or missing); (2) smoking status (current smoker, former smoker, non-smoker or missing); (3) physical activity (yes, had moderate recreational activities or vigorous recreational activities, no or missing); (4) family history of diabetes (yes, no, missing); (5) body mass index (BMI) (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 or missing); and (6) menopause status (premenopause, postmenopause without hormone therapy and postmenopause with hormone therapy, or missing).[26] We included all causes of menopause as long as they had 12 consecutive months without a menstrual period, per the NHANES question, as defined by the three established staging systems: Study of Women's Health Across the Nation (SWAN), Stages of Reproductive Aging Workshop (STRAW) and Penn Ovarian Staging Study (PENN-5).[29]

Statistical analysis

To account for the complex survey design of the NHANES, a 20-year weight was calculated by dividing the original 2-year weight by 10 for each woman and appropriate sample weights were used for 1999–2000 and 2001–2002, according to the NHANES analytical guidelines.[26] Weighted linear and logistic regression models were performed to investigate the associations between age at menarche and diabetes, in addition to age at menarche and CVD among participants with diabetes. The reference value for exposure was defined as 13 years old as it was the median age at menarche in our sample. Four sets of models were used, adjusting for previously

known risk factors[16 19] including adjusting for age (model 1); additionally adjusting for race/ethnicity, education, parity, menopause status and family history of diabetes (model 2); further adjusting for smoking status, physical activity and alcohol consumption (model 3); and adjusting for model 3 in addition to BMI (model 4). The missing indicator method was used to treat missing data in covariates. Only physical activity and alcohol consumption had more than 5% missing values; indicator variables were used to control for missingness. We performed stratified analyses to examine its association with age at menarche controlling for the potential confounders mentioned above by race/ethnicity and by menopausal status. Furthermore, we assessed the interactions of age at menarche with parity, menopause status, hypertension and family history of diabetes by adding an interaction term to the statistical model. Odds ratios (ORs), 95% CIs and linear p trends were calculated. Tests for trend were conducted by assigning a median value to each category and modelling this value as a continuous variable. All analyses were conducted using the statistical analysis software SAS V.9.4.

RESULTS

Among 17 377 women aged 20–65 years included in this analysis, 1773 (10.2%) reported having type 2 diabetes. A flow chart of participant inclusion is shown in online supplemental figure 1. The mean (SD) age at menarche was 12.68 (0.02) years. Table 1 shows the demographic characteristics of the participants.

Assessment of association of age at menarche and type 2 diabetes

Earlier age at menarche was associated with higher odds of type 2 diabetes (p for trend <0.0001; table 2) with adjustment for age. With additional adjustment for race, education, parity, menopause, family history of diabetes, alcohol consumption, physical activity, smoking and BMI, the association remained significant (p for trend=0.03; table 2). Associations remained significant with additional adjustment for age at menopause (p for trend=0.04). No statistical interactions of age at menarche with parity, menopause status, hypertension and family history of diabetes were present (p for interaction >0.05).

We performed stratified analysis by race/ethnicity (see online supplemental table 1A-C). For white participants, the ORs ranged from 2.05 (95% CI 1.43 to 2.94) for age at menarche ≤10 years to 0.98 (95% CI 0.61 to 1.58) for age at menarche 15 years compared with those with age at menarche 13 years (linear p-trend=0.0002). For Hispanic women, ORs ranged from 1.42 (95% CI 0.95 to 2.13) for age at menarche ≤10 years to 0.91 (95% CI 0.62 to 1.33) for age at menarche ≥15 years compared with those with age at menarche 13 years (linear p-trend=0.06). For non-Hispanic black participants, ORs ranged from 1.50 (95% CI 1.07 to 2.11) for age at menarche ≤10 years to 0.94 (95% CI 0.70 to 1.28) for ≥15 years compared with those with age at menarche 13 years (linear p-trend=0.003).

Stratified analysis by menopausal status was conducted (see online supplemental appendix table 1D,E). In postmenopausal women, ORs ranged from 1.72 (95% CI 1.22 to 2.42) for age at menarche ≤10 years to 1.14 (95% CI 0.84 to 1.57) for age at menarche ≥15 years compared with those with age at menarche 13 years (linear p-trend 0.006). In premenopausal women, ORs ranged from 2.16 (95% CI 1.50 to 3.12) for age at menarche ≤10 years to 0.76 (95% CI 0.48 to 1.21) for age at menarche ≥15 years compared with those with age at menarche 13 years (linear p-trend <0.001).

Assessment of association of age at menarche and CVD among women with diabetes

Among women with diabetes (n=1773), 205 (11.56%) had CVD defined as self-reported responses to questions on CHD (n=75), non-fatal or fatal MI (n=89) or stroke (n=109) (table 3). Nine participants had both CHD and stroke. Age at menarche was not significantly associated with the total CVD or CHD among women with diabetes. Age at menarche was associated with stroke among women with diabetes (linear p-trend=0.02) with adjustment for race, education, parity, menopause, family history of diabetes, alcohol consumption, physical activity smoking and BMI (table 3). Associations remained significant with additional adjustment for age at menopause (linear p-trend=0.03). Furthermore, for women with age at menarche of 10 years or younger, the weighted OR was 2.66 (95% CI 1.07 to 6.64) compared with women with age at menarche of 13 years. No statistical interactions of age at menarche with parity, menopause status, hypertension and family history of diabetes were present (p for interaction >0.05).

Stratified analysis by race was performed and similar trends were observed across non-Hispanic white, non-Hispanic black and Hispanic subjects (see online supplemental appendix table 2A–C). For non-Hispanic white subjects, ORs for stroke were 2.10 (95% CI 0.71 to 6.23) for age at menarche ≤10 years, 1.30 (95% CI 0.48 to 3.53) for 11 years, 0.45 (95% CI 0.14 to 1.41) for 12 years, 0.36 (95% CI 0.04 to 3.60) age at menarche 14 years, and 0.43 (95% CI 0.18 to 0.99) for age at menarche ≥15 years compared with those with age at menarche 13 years (linear p-trend=0.02). For non-Hispanic black subjects, ORs for stroke were 4.06 (95% CI 2.11 to 7.80) for age at menarche ≤10 years, 2.40 (95% CI 1.09 to 5.27) for 11 years, 1.91 (95% CI 1.01 to 3.65) for 12 years, 4.33 (95% CI 2.12 to 8.88) for 14 years, and 1.69 (95% CI 0.94 to 3.04) for ≥15 years compared with those with age at menarche 13 years (linear p-trend=0.009). For non-Hispanic black subjects, ORs for stroke were 1.10 (95% CI 0.29 to 4.11) for age at menarche ≤10 years, 2.23 (95% CI 0.61 to 8.20) for 11 years, 6.55 (95% CI 1.93 to 22.25) for 12 years, 2.30 (95% CI 0.48 to 10.89) for 14 years and 4.30 (95% CI 0.81 to 22.87) for age at menarche ≥15

Table 1 Weighted characteristics of women aged 20–65 years by age at menarche in NHANES 1999–2018

		Age at menarche (years)					
	Total	**≤10**	**11**	**12**	**13**	**14**	**≥15**
N (%)	17 377	1566 (9.0)	2316 (13.3)	4567 (26.2)	4174 (24.0)	2333 (13.4)	2432 (13.9)
Age, n (%)							
20–30	4240	434 (28.7)	621 (25.9)	1195 (23.9)	974 (23.2)	543 (23.4)	473 (20.3)
30–39	3821	349 (22.6)	532 (22.8)	1020 (23.3)	942 (23.5)	497 (23.1)	481 (21.6)
40–49	3791	335 (22.2)	473 (23.5)	978 (23.7)	932 (23.8)	511 (24.2)	562 (25.4)
50–59	3192	262 (17.7)	414 (20.5)	805 (19.7)	769 (20.2)	444 (19.9)	498 (21.7)
60–65	2344	186 (8.8)	276 (7.2)	569 (9.4)	557 (9.5)	338 (9.4)	418 (11.0)
Race/ethnicity, n (%)							
Hispanic	5017	476 (18.9)	746 (18.3)	1312 (15.1)	1079 (12.5)	711 (13.8)	693 (14.9)
White	6773	496 (55.3)	891 (62.8)	1822 (65.6)	1823 (69.9)	922 (66.9)	819 (60.8)
Black	3917	476 (19.9)	516 (12.9)	1018 (12.6)	855 (10.7)	452 (11.1)	600 (14.6)
Other race	1681	118 (5.8)	163 (5.8)	415 (6.5)	417 (6.7)	248 (7.9)	320 (9.6)
Education, n (%)							
<High school	3964	328 (16.1)	502 (14.7)	923 (13.9)	926 (14.3)	608 (15.8)	677 (18.0)
High school	3743	358 (22.5)	480 (21.8)	1018 (23.2)	893 (22.8)	448 (20.2)	546 (23.4)
>High school	9672	879 (61.4)	1333 (63.4)	2625 (62.8)	2353 (62.7)	1274 (63.6)	1208 (58.4)
Smoking status, n (%)							
Current smoker	3439	361 (23.2)	486 (21.4)	883 (20.8)	843 (22.5)	429 (19.9)	437 (20.8)
Former smoker	2787	255 (15.4)	388 (18.3)	719 (18.0)	731 (19.1)	365 (18.5)	329 (16.5)
Non-smoker	11 154	950 (61.3)	1441 (60.1)	2963 (61.0)	2599 (58.2)	1537 (61.4)	1664 (62.5)
BMI, kg/m^2, n (%)							
<25.0	5392	279 (19.4)	553 (27.2)	1284 (32.7)	1469 (39.7)	850 (41.4)	957 (48.1)
25.0–29.9	4777	373 (24.7)	607 (26.5)	1257 (27.0)	1157 (26.6)	679 (28.0)	704 (25.9)
30.0–34.9	3451	379 (23.8)	525 (20.7)	977 (19.8)	764 (16.0)	436 (15.9)	370 (12.2)
≥35	3622	523 (31.1)	610 (24.6)	997 (19.4)	758 (17.0)	354 (13.8)	380 (12.9)
Menopausal status/hormone therapy, n (%)							
Premenopause	10 096	931 (57.3)	1357 (58.4)	2732 (58.1)	2407 (58.9)	1340 (59.0)	1329 (57.1)
Postmenopause w/o hormone therapy	5139	461 (29.6)	639 (25.8)	1279 (26.4)	1246 (26.5)	698 (26.0)	816 (29.1)
Postmenopause w/ hormone therapy	2151	174 (13.0)	319 (15.7)	556 (15.3)	521 (14.4)	295 (14.9)	286 (13.7)
Nulliparity, n (%)							
Yes	2888	286 (21.6)	413 (22.6)	766 (19.6)	702 (19.7)	369 (19.2)	352 (18.2)
No	14 484	1278 (78.1)	1898 (77.4)	3799 (80.3)	3471 (80.2)	1962 (80.6)	2076 (81.7)
Physical activity,* n (%)							
Yes	5289	444 (25.8)	686 (26.6)	1410 (29.5)	1284 (28.0)	726 (31.4)	739 (30.2)
No	5677	564 (27.4)	760 (24.6)	1443 (23.0)	1312 (22.8)	753 (23.3)	845 (25.2)
Current alcohol consumption, n (%)							
Yes	11 426	1032 (69.3)	1606 (73.9)	3082 (73.4)	2761 (71.9)	1494 (72.8)	1451 (67.7)
No	2724	266 (15.0)	354 (13.1)	686 (12.7)	697 (15.3)	354 (12.4)	367 (13.1)
Family history of diabetes, n (%)							
Yes	8321	893 (57.1)	1202 (48.7)	2188 (46.7)	1916 (46.7)	1063 (42.2)	1059 (40.4)
No	8801	654 (41.7)	1084 (49.9)	2305 (51.8)	2189 (51.7)	1244 (56.5)	1325 (57.0)

*Moderate or vigorous recreational activities.
BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

Table 2 Weighted OR and 95% CI of diabetes by age at menarche in NHANES 1999–2018 in women aged 20–65 years

	Age at menarche (years)						
Type 2 diabetes	**≤10**	**11**	**12**	**13**	**14**	**≥15**	**P trend* (linear)**
Cases/total n	217/1565	259/2314	488/4566	360/4171	206/2331	243/2430	
Model 1	1.90 (1.50 to 2.39)	1.36 (1.06 to 1.73)	1.39 (1.12 to 1.72)	1	0.95 (0.73 to 1.24)	1.01 (0.78 to 1.32)	<0.0001
Model 2	1.64 (1.29 to 2.08)	1.31 (1.01 to 1.70)	1.37 (1.10 to 1.71)	1	0.95 (0.72 to 1.24)	0.93 (0.71 to 1.23)	<0.0001
Model 3	1.63 (1.28 to 2.08)	1.34 (1.03 to 1.74)	1.37 (1.10 to 1.71)	1	0.95 (0.72 to 1.25)	0.93 (0.70 to 1.23)	<0.0001
Model 4	1.32 (1.03 to 1.69)	1.14 (0.88 to 1.49)	1.29 (1.03 to 1.61)	1	0.99 (0.74 to 1.31)	1.05 (0.80 to 1.37)	0.03

Model 1: adjusted by age. Model 2: model 1 + race/ethnicity, education, parity, menopause status/hormone therapy, family history of diabetes. Model 3: Model 2 + smoking status, physical activity, alcohol consumption. Model 4: Model 3 + body mass index.
*Cochran–Armitage statistical test was performed to test for trend.
NHANES, National Health and Nutrition Examination Survey.

years compared with those with age at menarche 13 years (linear p-trend=0.007).

DISCUSSION

Earlier age at menarche was associated with type 2 diabetes among young and middle-aged US women after adjusting for age, race/ethnicity, education, parity, menopause status, family history of diabetes, smoking status, physical activity, alcohol and BMI. Further, earlier ages at menarche were associated with premature stroke events among women aged <65 years with diabetes.

This is the first study to our knowledge to investigate age at menarche as a risk factor for CVD complications among younger women with diabetes, using NHANES data to allow the inclusion of racial and ethnic variations representing US young and middle-aged women. The findings on the association between age at menarche and type 2 diabetes are similar to previous findings of the Nurse's Health Study (NHS) and NHS II, where younger age at menarche was associated with a higher relative risk of type 2 diabetes of up to 18% for those aged 34–59 years at baseline and after 26 years of follow-up in NHS, and up to 40% higher risk in NHS II for women aged 26–46 years at baseline and after 14 years of follow-up.[14] Adding to findings from these previous studies showing the association of age at menarche with diabetes or CVD independently,[17–20 29 30] we report here that younger age at menarche was associated with a higher risk for stroke complications among younger women with diabetes.

Earlier age at menarche may be one of early life indicators of the cardiometabolic disease trajectory in women. One potential pathway explanation may be that women with an earlier age at menarche are exposed to oestrogen for longer periods of time, and early menarche has been associated with higher oestrogen levels.[31 32] A meta-analysis suggested that endogenous sex hormones play important roles in the pathogenesis of diabetes.[33] Studies in both men and women show that sex hormone binding globulin, bioavailable testosterone and oestradiol, and high plasma oestradiol are all associated with insulin resistance and glucose levels independent of adiposity.[33] An in vivo study showed that high oestradiol levels inhibited insulin signalling owing to decreased phosphorylation of insulin receptor substrate-1,[34] and a recent in vitro study showed that oestradiol-induced insulin receptor cleavage causes cellular insulin resistance, and its molecular mechanisms are shared with those with high glucose levels.[35] In terms of diabetes-related cardiometabolic outcomes, earlier age at menarche in women may contribute to an increased risk of metabolic syndrome, which is associated with an increased risk of CVD.[36] Therefore, the positive association of early age at menarche with type 2 diabetes and diabetes-related CVD complications observed in this study might be explained by the prolongation of the potential inhibition effects of oestrogen on insulin signalling and its role in cellular insulin resistance.

Table 3 Weighted OR and 95% CI of cardiovascular disease by age at menarche in NHANES 1999–2018 among patients with diabetes aged 20–65 years

	Age at menarche (years)						P* trend (linear)
	≤10	11	12	13	14	15	
Total CVD							
Cases/ total, n	34/217	36/259	57/488	32/360	23/206	23/243	
Model 1	1.90 (0.97 to 3.74)	1.27 (0.64 to 2.49)	0.85 (0.45 to 1.60)	1	1.12 (0.52 to 2.43)	0.85 (0.37 to 1.95)	0.07
Model 2	1.84 (0.94 to 3.61)	1.15 (0.59 to 2.25)	0.80 (0.42 to 1.54)	1	1.07 (0.49 to 2.31)	0.82 (0.36 to 1.86)	0.09
Model 3	1.93 (0.98 to 3.81)	1.18 (0.60 to 2.32)	0.90 (0.47 to 1.72)	1	1.13 (0.51 to 2.49)	0.87 (0.38 to 1.98)	0.09
Model 4	1.90 (0.96 to 3.77)	1.11 (0.55 to 2.23)	0.84 (0.45 to 1.60)	1	1.15 (0.52 to 2.56)	0.77 (0.34 to 1.73)	0.09
CHD							
Cases/ total, n	7/216	13/258	22/486	16/359	10/206	7/243	
Model 1	0.80 (0.23 to 2.76)	1.18 (0.39 to 3.53)	0.90 (0.38 to 2.13)	1	1.33 (0.42 to 4.19)	0.79 (0.22 to 2.81)	0.97
Model 2	0.75 (0.23 to 2.44)	0.93 (0.31 to 2.76)	0.80 (0.33 to 1.93)	1	1.37 (0.42 to 4.53)	0.78 (0.23 to 2.70)	0.66
Model 3	0.71 (0.20 to 2.57)	0.90 (0.29 to 2.79)	0.92 (0.34 to 2.48)	1	1.57 (0.44 to 5.60)	0.83 (0.25 to 2.76)	0.52
Model 4	0.70 (0.18 to 2.72)	0.86 (0.26 to 2.83)	0.96 (0.35 to 2.64)	1	1.60 (0.44 to 5.80)	0.80 (0.26 to 2.43)	0.51
Stroke							
Cases/ total, n	21/216	20/258	33/488	13/360	10/206	12/242	
Model 1	2.58 (0.98 to 6.81)	1.89 (0.78 to 4.58)	1.34 (0.55 to 3.25)	1	1.13 (0.37 to 3.51)	1.00 (0.33 to 3.09)	0.04
Model 2	2.53 (0.96 to 6.65)	1.85 (0.76 to 4.51)	1.34 (0.54 to 3.29)	1	1.08 (0.35 to 3.36)	0.92 (0.30 to 2.85)	0.03
Model 3	2.80 (1.11 to 7.05)	1.95 (0.82 to 4.63)	1.50 (0.64 to 3.52)	1	1.14 (0.37 to 3.52)	1.02 (0.33 to 3.17)	0.02
Model 4	2.66 (1.07 to 6.64)	1.81 (0.76 to 4.31)	1.32 (0.57 to 3.05)	1	1.15 (0.37 to 3.61)	0.90 (0.28 to 2.92)	0.02

Model 1: adjusted by age. Model 2: Model 1 + race/ethnicity, education, parity, menopause status/hormone therapy, family history of diabetes. Model 3: Model 2 + smoking status, physical activity, alcohol consumption. Model 4: Model 3 + body mass index.
*Cochran–Armitage statistical test was performed to test for trend.

The association between age at menarche and stroke complications attenuated slightly after adjustment for BMI but remained significant. Therefore, adiposity may also play a role in the observed association between early age at menarche and stroke complications, as higher childhood adiposity is associated with earlier age at menarche and with cardiometabolic diseases later in life.[37]

Our study has several limitations. Selection bias in NHANES might be present; however, analyses have showed that any errors of representation resulting from sample location characteristics and non-response were minimised with enhanced weighting adjustments.[38] While reverse causality is likely not to be an issue as menarche precedes CVD, causality cannot be established due to the cross-sectional nature of the study design. The cross-sectional evidence presented in this study supports the need for further research using a longitudinal design. Additionally, a large proportion of the sample of women were not eligible to be included in the analysis as they did not have age at menarche data available, potentially causing selection bias in our results. Further, potential misclassification of age at menarche exists as it was recalled; however, other studies using self-reported age at menarche as exposure all report associations with similar magnitudes and directions for outcomes such as diabetes and CVD,[16 19 20] and a study comparing data recorded prospectively with self-reports in middle age reported no significant difference between self-reported age at menarche and prospective measurement.[39] Furthermore, if present, this type of measurement error would result in an underestimation of the association. The self-report of cardiovascular and diabetes also poses a limitation to the study as it could introduce misclassification through recall bias and social desirability bias; however, a validation has shown that agreement between self-report and medical records is high (kappa 0.71–0.80) for diabetes and CVD.[40]

CONCLUSION

In this nationally representative racially and ethnically diverse US population, women with earlier ages at menarche have higher odds of having type 2 diabetes than those with age at menarche of 13 years. Among young and middle-aged women with diabetes, earlier age at menarche is associated with progression of disease to premature stroke. These findings support the possibility that age at menarche may be incorporated into early-life

strategies for preventing diabetes and progression of diabetes complications.

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Contributors SHL conceptualised the research question and planned the analysis. MPS and YL conducted the data analysis. MPS drafted the initial paper. All authors, MPS, YL, SHL, LAB, JH, and KMR, contributed to critically reviewing and editing the paper. SHL is the guarantor of this paper.

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