Association Between Age at Menarche and Metabolic Syndrome in Southwest Iran: A Population-Based Case Control Study

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Research Article

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Abstract

Background: Age at menarche (AAM) affects women's health outcomes and could be a risk factor for some diseases such as Metabolic Syndrome (MetS). We assessed the association between age at menarche and metabolic syndrome components (obesity, hypertension, type 2 diabetes and cardiovascular disease) in women aged 35 to 70 years in Hoveyze, southwest Iran.

Methods: This is a case-control study conducted on 5830 women 35 to 70 years in Hoveyze cohort study (HCS), a part of the PERSIAN cohort study, between 2016 to 2018. The case group were women with MetS while the controls were women without MetS. Metabolic syndrome is determined based on standard NCEP-ATP III criteria. Demographic, socioeconomic and reproductive history data were gathered face to face by trained interviews. Also, lab, anthropometrics and blood pressure measurements were assayed for participants. Multiple Logistic Regression was used to estimate the association between age at menarche and metabolic syndrome, with adjustment for potential confounding variables.

Results: The overall mean age at menarche was 12.60 ± 1.76 years old. Urban and rural women differed in their age at menarche (at age 12.58 ± 1.71 and 12.63 ± 1.83 years, respectively). Comparison of the four menarche age groups (≤ 10 , 11-12, 13-14, 15-16 years) was statistically different showed between age at menarche and MetS. The odds of having metabolic syndrome for groups with menarche age of 13-14 years and 16-15 years, compared to women with a menstrual age ≤ 10 years, decreased by 21% and 20%, respectively.

Conclusion: The present study showed the effect of age at menarche on odds of having MetS in women 35-70 years.

Background

Menarche, defined as the first menstrual period in a woman's life that is a marker of female puberty and the onset of ovarian and other endocrine functions related to reproductive capacity (1, 2). In recent decades, the mean age at menarche has decreased (1, 3). Early menarche is often defined as menarche ≤ 11 years old but some investigators base definition on menarche at ≤ 12 years (4). Many factors including race, genetic, geographical location, climate, lifestyle, socioeconomic status, physical activity and nutrition affect the early or late age at menarche (5–8). Bratke et al proposed a downward trend in the mean age at menarche results from the increase in the prevalence of overweight and obesity (9).

Age at menarche affects women's health outcomes (10) but the results of the studies were inconsistent. Also the average age of menarche (AAM) in many countries has been reported differently. Some studies showed that Age at menarche can be a risk factor for disease (1) as metabolic syndrome (11–14), ovarian cancer (15), blood pressure (16–18), type 2 diabetes (T2D) (19), gestational diabetes mellitus (20) and cardiovascular disease (21). However, some other studies have shown that there is no statistically significant relationship between menarche age and diabetes (10) and metabolic syndrome (2, 22).

Metabolic syndrome (MetS) consists of hypertension, hyperglycemia, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), and abdominal obesity, and is a major predictive variable for CVD (2). Over the past two decades, the prevalence of metabolic syndrome has increased significantly, especially in developing countries (23). The results of a systematic review showed the overall prevalence of MetS 29% in Iran (24). The findings in Hoveyze cohort study demonstrated that the prevalence of MetS was 39.1% (25). Some factors such as age, weight, menopause, age at menarche, and genetic factors might be risk factors in MetS development (26). Previous studies have shown inconsistent results for the relationship between age at menarche and MetS. Understanding this association can be effective in therapeutic and preventive interventions design and reducing metabolic syndrome and other cardiovascular diseases. Thus, the goal of the present study was to assess the association between age at the onset of menarche and metabolic syndrome and its components in women 35–70 years in HCS.

Methods

Study design and participants:

This study was an unmatched case-control study. The participants were women aged 35–70 years who entered the enrolment phase of the Hoveyze cohort study (HCS). The HCS is a population-based cohort study conducted in Hoveyze County. In this study to assess NCDs in the Arab ethnicity in southwest of Iran in 10009 adults (age 35–70 years) that recruited from May 2016 to August 2018 (25). The Hoveyze cohort study center is one of the sites of the Prospective Epidemiological Research Studies in Iran (the PERSIAN Cohort Study), including 180 000 Iranian adults. All the steps of registration, implementation and quality control of this study have been performed according to the PERSIAN protocol. (27).

The participants were categorized in two groups with MetS as cases ($n = 2660$) and without MetS as controls ($n = 3170$). Then, relationship of presence or absence of MetS with the age at menarche in the two groups were evaluated. Anthropometric measurements, Blood pressure, Triglycerides, HDL, type 2 of diabetes mellitus were measured at the first visit. Also participants were asked about their age at the first menstrual. Women who did not have information about menarche age or whose metabolic syndrome criteria were not measured were excluded from this study. Outcome and exposures were measured equally in the two groups. Informed written consent was obtained from the participants on the day of registration.

Assessment of anthropometric measurements and Blood pressure (BP):

Assessment of anthropometric measurements was done while the participants wearing light clothes and no shoes. Height was measured to the nearest 0.5 cm by a stadiometer (Seca 206), weight was measured to the nearest 1 kg using a standing scale (Seca 755). Waist, hip, and wrist circumferences (in cm)

were measured by Seca locked tape meters. BMI was calculated as weight (kg) divided by squared height (m2). BP was measured by Riester sphygmomanometers, twice (10 min interval) on each arm based on PERSIAN cohort protocol (27).

Assessment of biological measurements:

In Hoveyzeh Cohort Study (HCS) was collected 25 cc of fasting blood from each participant. Blood samples were centrifuged (Sigma, Germany) at 3000 rpm for 10 minutes to separate serum. Then, the required serum levels were measured by BT 1500 autoanalyser (Biotechnica Instruments, Italy). A complete blood count (CBC) was done by the hematology autoanalyser (Nihon Kohden 6510-k, Japan). Urine tests (urine pH, specific gravity) and analysis were also performed (27).

Metabolic syndrome criteria:

Based on the National Cholesterol Education Program-Adult Treatment Panel III guidelines (NCEP ATP3) (28) participants with 3 or more of the 5 below criteria diagnosed as MetS. Abdominal obesity (waist circumference ≥ 102 in men and ≥ 88 in women), serum TG ≥ 150 mg/dL, take hypertriglyceridemia medications, HDL < 40 mg/dL in men and < 50 in women, take drug treatment for low HDL-C, BP $\geq 130/85$ mmHg, or take hypertension drugs, FBS ≥ 100 mg/dL, take hyperglycemia drugs.

Statistical Analysis:

To describe the variables, mean and standard deviation (SD) for continuous variables and the number and percent for categorical variables were used. The categorical variables were compared by chi-square test. The independent t-test was used to compare continuous variables between the two groups. Multiple logistic regression was used to assess the association between age at menarche and the MetS by controlling confounder factors. The analyses were carried out with SPSS version 23.0. The Statistical significance was declared if the p-value was less than 0.05.

Results

In this study, we recruited 5830 women participants of Hoveyzeh Cohort Study .The mean $\pm$ SD age at menarche in our study was 12.60 ± 1.76 years old .Mean age at menarche differed in Urban and rural women (at ages 12.58 ± 1.71 and 12.63 ± 1.83 years, respectively). Based on wealth index, the prevalence of early age of menarche (≤ 10 years) in poorest groups more than richest groups (26.1% vs. 11.1%). The overall prevalence of MetS in the enrollment phase in women 35-70 years in Hoveyzeh cohort study was 45.62% (25). The characteristics of women with or without Mets were reported in Table 1. Participants with MetS were older than without MetS group. Women with MetS had a less than mean age at menarche and HDL level. Controversy women with MetS had a greater mean BMI, height, weight, waist circumference, hip circumference, SBP, DBP, PR, TC, TG, FBS, ALK, AST, ALT levels.The results of the Chi-square test showed that there was a significant relationship between the variables of Wealth index, Use Alcohol, Smoker, Education, Contraceptive use ,and metabolic syndrome ($P < 0.0001$). Also the results demonstrated that the difference between mean age of menarche and mean weight, Waist circumference, Hip circumference, Wrist circumference, SBP, DBP, PR, TC, TG, FBS, ALK, AST, ALT, Gravity, Parity in two groups with and without Metabolic syndrome was significant ($P < 0.0001$). (Table1)

Table 1: Characteristics of study population by metabolic syndrome

Variables		Cases(n=2660)	Controls(n=3170)	P_value
Age, (years)		51.12 ± 9.17	46.28 ± 8.54	<0.001*
Age at menarche , (years)		12.51 ± 1.78	12.67 ± 1.74	<0.001*
Height, (cm)		158.97 ± 5.66	158.77 ± 5.68	0.18*
Weight, (kg)		78.87 ± 13.95	72.00 ± 15.11	<0.001*
BMI, (kg/m2)		31.18 ± 5.31	28.52 ± 5.60	<0.001*
Waist circumference, (cm)		105.67 ± 10.33	97.73 ± 12.28	<0.001*
Hip circumference, (cm)		107.90 ± 10.07	104.89 ± 10.33	<0.001*
Wrist circumference, (cm)		17.47 ± 1.34	16.93 ± 1.29	<0.001*
SBP, (mm Hg)		116.43 ± 20.06	106.08 ± 15.53	<0.001*
DBP, (mm Hg)		72.59 ± 11.42	67.82 ± 10.02	<0.001*
PR		80.47 ± 9.66	78.78 ± 9.27	<0.001*
FBS, (mg/dL)		130.61 ± 60.75	96.37 ± 28.98	<0.001*
HDL-C, (mg/dL)		48.21 ± 10.93	57.17 ± 11.82	<0.001*
TG, (mg/dL)		197.47 ± 103.05	111.57 ± 46.97	<0.001*
TC, (mg/dL)		195.74 ± 43.31	186.93 ± 37.93	<0.001*
AST		17.79 ± 11.32	17.22 ± 7.71	0.02*
ALT		19.21 ± 12.67	16.76 ± 11.54	<0.001
ALK		224.87 ± 65.71	197.64 ± 63.41	<0.001*
Gravity		6.64 ± 3.15	5.70 ± 2.87	<0.001*
Parity		6.07 ± 2.70	5.24 ± 2.47	<0.001*
Wealth index	poorest	568 (21.35)	740 (23.34)	0.002**
	poor	529 (19.89)	736 (23.21)	
	moderate	546 (20.53)	587 (18.52)	
	rich	537 (20.19)	586 (18.48)	
	richest	480 (18.04)	521 (16.43)	
Use Alcohol	Yes	4 (0.15)	2 (0.06)	0.30**
	No	2656 (99.85)	3168 (99.94)	
Smoker	Yes	228 (8.57)	206 (6.50)	0.003**
	No	2432 (91.43)	2964 (93.50)	
Education	Illiterate	2132 (80.15)	2324 (73.31)	<0.001**
	Primary school	333 (12.52)	471 (14.86)	
	Secondary school	73 (2.74)	133 (4.20)	
	Diploma	74 (2.79)	124 (3.91)	
	University	48 (1.80)	118 (3.72)	
Use Contraceptive	Yes	1582 (59.47)	1987 (62.68)	0.01**
	No	1078 (40.53)	1183 (37.32)	

*Independent T -test

**Chi-square test

Abbreviations

MetS: Metabolic Syndrome,T2D: Type 2 diabetes,TG: Triglyceride,CVD: Cardiovascular Disease,GDM: Gestational Diabetes Mellitus,BP: Blood Pressure,SBP: Systolic Blood Pressure,DBP: Diastolic Blood Pressure,PR: Pulse Rate,HDL-C: High-Density Lipoprotein Cholesterol,ALT: Alanine Transaminase,FBS: Fasting Blood Sugar,TC: Total Cholesterol,AST: Aspartate Transaminase,ALP: Alkaline Phosphatase,BUN: Blood Urea Nitrogen

The frequency of the four menarche age groups ($\leq 10, 11-12, 13-14, 15-16$ years) were statistically different between the case and the control groups. This were seen for its all components except for Triglyceride (Table 2).

Table 2. Metabolic syndrome components in women 35-70 years old in the Hoveyzeh Cohort Study(HCS)

Category of age at menarche	N	Metabolic syndrom	P_value	TG (mg/dl) $\geq$ 150 mg/dL	P_value	HDLc (mg/dl) <50	P_value	BP $\geq 130/85$ mmHg	P_value	FBS ≥ 100 mg/dL	P_value	Abdon circun
≤ 10 years	832	412(49.5)	0.01	309(37.1)	0.58	386(46.4)	0.01	257(30.9)	0.03	386(46.4)	0.004	737(81)
11-12 years	2001	939(46.9)		794(39.7)		864(43.2)		565(28.2)		883(44.1)		1768(1)
13-14 years	2018	880(43.6)		781(38.7)		836(41.4)		517(25.6)		805(39.9)		1753(1)
15-16 years	979	429(43.8)		390(39.8)		382(39)		275(28.1)		406(41.5)		816(8)

*Chi-square test

Table 3 shows the odds ratio (OR) and 95% confidence interval (CI) for MetS according to age at menarche of the women in the four groups (≤ 10 years, 11-12 years, 13-14 years, 15-16 years), using age at menarche 15-16 years as the reference category. Model 1 shows crude odds ratios of metabolic syndrome for four menarche age groups, so that the odds of metabolic syndrome at menstrual age of ≤ 10 years 1.25 (95% CI (1.04-1.51); $P=0.015$) times more than age at menarche 15-16 years. Model 2 is adjusted for demographic variables (age, education) and life-style (smoking, and physical activity). The odds of having MetS in at menstrual age of ≤ 10 and 11-12 years were 1.27 (95% CI (1.04-1.54); $P=0.01$) and 1.20 (95% CI (1.02-1.41); $P=0.02$) times more than age at menarche 15-16 years, respectively. Model 3 is adjusted for biological measurements (FBS, TG, TCHOL, HDL, SGOT, SGPT and ALK) and DPB, SPB and PR. The odds of having MetS in at menstrual age of ≤ 10 years was 1.34 (95% CI (1.03-1.74); $P=0.02$) times more than menstrual age 15-16 years group. Also results in models 4 demonstrated the odds of having MetS in women with age menarche of ≤ 10 years was 1.30 (95% CI (1.07-1.58); $P=0.008$) times more than menstrual age 15-16 years group, after adjustment for reproductive variables (gravidity, parity, gestational diabetes and pregnancy hypertension, use of oral contraceptives, use of hormone replacement therapy) (Table3)

Table 3: Odds Ratios (and 95% Confidence Intervals) for MetS by Menarcheal Age in Participants

Menarche (Years)	N	Case	Model 1			Model 2			Model 3			Model 4			M
			OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	
			OddsRatio			OddsRatio			OddsRatio			OddsRatio			
≤10	832	412	1/25	1/04-1/51	0/015	1/27	1/04-1/54	0/01	1/34	1/03-1/74	0/02	1/30	1/07-1/58	0/008	1/
11-12	2001	939	1/13	0/97-1/32	0/11	1/20	1/02-1/41	0/02	0/95	0/76-1/194	0/70	1/15	0/98-1/36	0/07	0/
13-14	2018	880	0/99	0/85-1/15	0/91	1/12	0/95-1/32	0/15	0/92	0/740-1/152	0/48	1/02	0/86-1/20	0/78	0/
15-16	979	429	1	-	-	1	-	-	1	-	-	1	-	-	1

Model 1: Unadjusted. **Model 2:** Adjusted demographic variable (Age, Education) AND Life-style (smoking, and Physical activity). **Model 3:** Adjusted biological FBS, measurements (TG, TCHOL, HDL, SGOT, SGPT, ALK) AND DPB, SPB and PR. **Model 4:** Adjusted Reproductive variable (Gravidity, parity, has gestational diabetes and pregnancy hypertension, use of oral contraceptives and use of hormone replacement therapy). **Model 5:** Adjusted Model 2, Model 3 and Model 4

Discussion

Our study demonstrates the mean age at menarche 12.60 ± 1.76 years in women participants of Hoveyzeh Cohort Study. Some studies reported the mean menarche age 12.81 years (95% CI: 12.56–13.06) in Iranian girls (29), in the United States 12.8 years (30), 13 years in the Netherlands, 12.60 years in Turkey, 13.15 years in Dutch girls (31), 13.6 ± 1.2 years among Indian women (32) and in China 15.4 ± 1.9 years (21).

One of the reasons for the early age of menarche in some areas is the hot climate mentioned in the Khatoon study (33). Hoveyze has a warm climate in southwestern Iran. This might be the reason for lower the mean age of menarche in this region than Iranian women and women live in cold regions.

This study demonstrated mean age at menarche in urban regions slightly lower than in rural areas. This result is almost confirmed by different studies. Rihlat et al reported urban and rural women differed in their age at menarche (at ages 12.7 and 14.5 years, respectively) (34). Ajong et al showed the strength of association of the urban/rural setting with early menarche (35). Another study reported an earlier age at menarche in the urban and suburban dwellers of Northern Ghana region (36). Also, Marván et al showed urban women had statistically significant earlier ages at menarche than rural women (37). Overnutrition, obesity and overweight in urban girls may be the cause for this difference in menarche age. Inverse Ramalingam et al (38) showed there was no statistical difference between menarche age in urban and rural regions.

In our study, early age menarche was lower than in the richest women. Inversely Marván et al reported in high SES women reached menarche the earliest and low SES women the latest. The historical decline in age at menarche for high and medium SES groups occurred relatively early, whereas that for the low SES observed last. In a US study found income status to be related to the timing of menarche over time when the proportion of girls experiencing early menarche (<11 years old) increased over a 50 year time period only for those girls of a low socioeconomic position (39). In contrast, another study reported in the United Kingdom (UK) spanning an 85 year time period found a decline in the timing of menarche across all socioeconomic groups (40).

The results of studies on the relationship between menarche age and metabolic syndrome is not certain (13, 22, 41-43). The most suggested explanation is that early menarche in adolescents and MetS in adulthood are consequences of childhood obesity (13). Our study showed that early age at menarche is associated with a higher risk of MetS in women aged 35 to 70 years in HCS. Elsehly et al reported the statistically significant association between age at menarche in women with and without MetS (11.6±1.1 years vs. 13.2 ±1.8 years respectively, $P<0.001$) (14). Hyse et al demonstrated in women with an age at menarche below 12.5 years Odds ratio of 1.49 (CI: 1.22-1.82) for the MetS (43). Feng et al in Chinese women reported age at menarche was inversely associated with the total number of MetS components (41).

Lee et al suggested the risk of MetS was significantly increased at ≤ 12 years of age at menarche (OR = 1.91, $P < 0.05$) (1). Gloeck et al showed menarche age had a curvilinear ('U' shaped) relationship with MetS in adulthood. Late menarche and early menarche are risk factors for MetS, and cardiometabolic abnormalities in adults (44). Cho et al showed no association between age at menarche and MetS (22). Also Hwang et al reported early or late menarche was not associated with an increased risk of MetS in premenopausal Korean women (2).

Janghorbani et al. showed that there is a strongly association between younger age at menarche and an increased risk of T2D (45). The results of a study in Brazil showed a relationship between menarche age (less than 11 years) and a high risk of diabetes (46). Iwase M et al in a retrospective cohort study on the relationship between menarche age and obesity and glycemic control in T2D showed that there was an inverse relationship between age at menarche and BMI and abdominal circumference (47). Yang et al. reported that menarche age has a linear and inverse relationship with the incidence of diabetes for each year of delay (48). Another study by Qiu et al demonstrated that no significant association between menarche age and diabetes. But there was a significant relationship between late menarche age (18 years) and lower CVD risk (10).

Lee et al reported Women with age at menarche ≤ 12 years had significantly higher levels of triglycerides (β coefficient = 37.83, $P = 0.02$). Beside that hypertriglyceridemia was significantly increased at early menarche with 1.99 (95% CI: 1.16–3.41, $P < 0.01$) (1). Hozoori et al suggested Body mass index, waist circumference (WC), and Weight were inversely and significantly associated with the age of menarche ($P<0.01$) (49). Also Wronka was showed a significant relationship between weight and BMI with the age at menarche (50).

Strengths and Limitations of the Study:

A major strength of the present study is the large study population. Another advantage was the use of high-reliability cohort study data. A limitation of our study is not having the actual menarche dates of the girls. However previous studies showed that self-reporting for menarche dates is reliable.

Conclusion

The present study showed the association between age at menarche and MetS in a large representative population.

Declarations

Ethics approval and consent to participate:

The study was confirmed by the ethics committee of Ahvaz Jundishapur University of Medical Sciences with a code of ethics IR.AJUMS.REC.1398.272. This study was conducted according to the Helsinki Declaration. On the day of the referral, we informed participants about all procedures involved, clearly. Informed written consent was obtained from the participants on the day of registration and notified participants can withdraw from the study whenever they wish.

Consent for Publication: Not applicable

Competing interests: None to declare

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Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

NN and BCh were principal investigators of the study and drafted the manuscript. SJH, NS and ASH were advisors of the study. ASM, ZR and SS performed the statistical analysis. JK had role in data gathering. All authors contributed to the design and data analysis and assisted in the preparation of the final version of the manuscript. All authors read and approved the final version of the manuscript.

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