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Original Article

Is There any Association between Age at Menarche and Risk of Metabolic Syndrome? The Tehran Lipid & Glucose Study

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Abstract

Background: There is controversial data available regarding the impact of age at menarche on cardio-metabolic parameters. This community-based study aimed to assess this association among Iranian women.

Methods: We recruited 5,344 eligible women out of 7718, aged 10–50 years who participated in the Tehran lipid and glucose study (TLGS), conducted in 1999–2000. Based on their age at menarche, these women were subdivided into five groups: <11 years, 11–12 years, 13–14 years, 15–16 years and ≥17 years. The status of metabolic syndrome (MetS) and its components were compared among study subgroups.

Results: The crude prevalence of MetS was 11.9, 95% CI: 11.0–13.0. Prevalence values for MetS components were 20.1 for central obesity (95% CI: 19.0–21.3), 15.7 for high fasting blood sugar (FBS), (95% CI: 14.5–17.1), 15.1 for high triglycerides, (95% CI: 14.1–16.3), 53.5 for low high density lipoproteins (HDL) (95% CI: 51.9-55.0) and 9.5 for high blood pressure (BP) (95% CI: 8.5–10.4). After adjustment for covariates, menarche age <11 years, compared to 13–14 years, was significantly associated with higher risk of Mets (odds ratio [OR] = 2.3, 95% CI: 1.1–5.4) and its components; i.e. central obesity (OR = 2.5, 95% CI: 1.5–4.2), BP (OR = 2.9, 95% CI: 1.4–6.0) and FBS (OR = 3.0, 95% CI: 1.4–6.0). To compare our results with other studies, we calculated the standardized prevalence of MetS which was based on the WHO standardized population 11.5, 95%CI: 10.7–12.5 and the standardized prevalence of MetS by the population in Tehran was 11.7, 95% CI: 10.7–12.6.

Conclusion: Early menarche can be associated with an increase in metabolic disturbances later in life.

Keywords: Adiposity, Cardiovascular risk, Menarche age, Metabolic syndrome, Reproductive age

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Introduction

Metabolic syndrome (MetS) is a category of risk factors that enhance the risk of cardiovascular diseases[1]; over 50% of individuals with Acute Coronary Syndrome have three or more components of MetS.[2] The prevalence of MetS among adults in developed countries (U.S.) increased by >35% from the period 1988–1994 to the period 2007–2012 and remained unchanged during 2007–2014. However, it remained prevalent particularly among the old population.[3] Over the previous two decades, there has been a sharp worldwide increase in the prevalence of MetS, especially in developing countries. The results of a systematic review in Iran (2017) showed the overall prevalence of MetS and its gender-stratification in women and men at 29% (95% CI: 22–36), 37% (95% CI: 26–48) and 29% (95% CI: 23–36), respectively.[4] The findings of a population-based study in Iran (2014) demonstrated that the prevalence of MetS was 42.3% (36.5% men and 47.1% women[5] and in 2012, the overall prevalence was 23.7%).[6] Many factors such as age, weight, menopause, age at menarche and genetic factors may play a role in MetS development.[7-11]

In women, age at menarche varies and is dependent on the interaction between environmental and genetic factors and lifestyles.[12,13] Lifestyle changes resulting from industrialization, i.e. reduced levels of physical activity and enhanced consumption of energy substrates in developing countries, have lowered the age at onset of menarche recently.[14-16] The association of menarche onset with metabolic disturbances indicates feedback mechanisms that can affect women across their lifespan.[17] Previous studies have shown early menarche to be a risk factor for cardiovascular disease; furthermore, early menarche has been related to pre-diabetes and diabetes,[18-20] obesity[16, 21] and MetS.[17,22,23]

In several developing countries, the prevalence of MetS tends to be higher in women than men.[9,24] Considering gender differences, identification of women at risk for these diseases earlier in life could play a critical role in facilitating more effective interventions and hence, more favorable outcomes. To the best of our knowledge, despite several publications on the association between

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menarcheal age and Mets and its components, this is the first population-based study done among Iranian women to explore this association considering several relevant confounders. We, therefore, conducted this study to investigate the association between early age at menarche and risk of MetS in a population-based cohort of the Tehran Lipid and Glucose Study (TLGS).

Materials and Methods

Subjects

For the purpose of our study, we used the baseline data of female participants of the TLGS – an ongoing prospective study, initiated in 1998, with the purpose of determining the prevalence of non-communicable disease risk factors. Of the 7718 women, aged 13–50 years in the TLGS, we excluded all those with no information on menarche age and/or MetS or its components (incomplete data) and women who reached menopause before or during the study (n = 1170). Of these, 17 (0.3%) could not recall their menarcheal age. Furthermore, those with pathological late-onset puberty, such as those with hypothyroidism (n = 3), chronic renal failure (n = 1), and type 1 diabetes (n = 2) were also excluded. Finally, 5344 women met our inclusion criteria and remained in the final analysis.

The participants' socio-demographic variables, as well as information on several risk factors for non-communicable diseases and reproductive histories, were gathered by trained staff pending face-to-face interviews.

Physical Examination and Laboratory Tests

The follow-up included a general physical examination, height and weight measurements and blood sampling. Detailed information on measurements has been published in a previously study.[20]

A modifiable activity questionnaire was used to evaluate the physical activity pattern achieved[24]; the participants were asked to report the physical activities in which they had participated within the past 12 months. "Leisure time physical activity" was described as three or more days of severe-intensity activity of at least 20 minutes, or ≥5 days of moderate-intensity activity or walking at least 30 minutes, or ≥5 days of any combination of walking, moderate or severe-intensity activities, achieving a minimum of at least 600 metabolic equivalent task minutes per week.[25,26] Parity was addressed in two questions of the TLGS questionnaire, i.e. how many live born children + how many stillbirths. After determining the contraceptive method used, the duration of OCP use was determined with the question: how long have you used contraception method? (months). Smoking status was categorized as ever and never smokers.

Definitions

MetS was defined based on the Joint Interim Statement,[25] as the presence of any three out of the five following risk factors: 1) Abdominal obesity: WC ≥95 cm for women based on population- and country-specific cutoffs for Iranians[26]; 2) fasting blood sugar (FBS) ≥100 mg/dL or drug treatment; 3) Fasting triglycerides ≥150 mg/dL or drug treatment; 4) Fasting high density lipoprotein cholesterol (HDL-C) <50 mg/dL in women or drug treatment and 5) Elevated blood pressure (BP) defined as systolic blood pressure (SBP) ≥130 mm Hg, diastolic blood pressure (DBP) ≥85 mmHg or antihypertensive drug treatment.[27] Age at menarche was defined as age at the first menstrual bleeding. All data were taken in interviews.

Statistical Analysis

We used baseline collected data; however, in order to identify MetS, we only used data collected in the 4th phase of TLGS (2009–2011). We used the ANOVA test with Dunnett post hoc test for continuous variables, and χ^2 test for categorical variables to compare the demographic and reproductive characteristics between groups based on their age at menarche.

We divided age at menarche into five groups, i.e. >11 years, 11–12 years, 13–14 years (reference group), 15–16 years and 17–19 years; women with menarcheal age of 13–14 years were considered the reference group as this group constituted 49.5% of our participants.

The risk of age at menarche on MetS and its components was assessed using the logistic regression method before and after adjustment for confounding variables. We entered all those relevant variables available that had an association with different menarcheal age subgroups, using a cutoff value of 0.2 for *P*. We used two adjusted models; adjustment for parity, education and age (model 2); adjustment for parity, education, age and body mass index (BMI) (model 3). We re-analyzed our data considering the cluster effect; however, the results were not significantly different from those obtained when not considering this effect. This can partly be explained by the family-based nature of our study and recruitment of only women. Additionally, because the size of clusters was quite low (1–3) and the number of clusters very high, many clusters were created (3472), and the cluster effect was not significant. We used SPSS 15 (SPSS Inc. Chicago, IL, USA) ($P < 0.05$) for data analysis.

Results

Table 1 presents the demographic and reproductive characteristics of the subjects stratified by age at menarche. The results show that mean age at menarche was 13.27 ± 1.5 years, and that mean age ($P = 0.001$), BMI ($P = 0.046$) and WC ($P = 0.001$) differed significantly between these 5 menarcheal age groups. Out of 5344 reproductive-aged women, 525 (12.8%) had MetS.

Logistic regression analysis demonstrated that the risk of MetS in women with age at menarche <11 years was 1.8 times higher after adjustment for parity and education, 2.4 times higher after adjustment for parity and education

Table 1. Mean and Standard Deviation of Demographic and Reproductive Characteristics by Menarcheal Age in Participants

Variables	<11 Years n = 102	11–12 Years n = 1532	13–14 Years n = 2656	15–16 Years n = 954	17–19 Years n = 100	*P* Value
Age (y)[a]	33.6 ± 10.4	28.1 ± 12.7	29.5 ± 11.3	35.4 ± 9.1	36.9 ± 9.0	<0.0001
BMI (kg/m^2) [a]	27.1 ± 6.1	25.7 ± 5.3	25.8 ± 5.4	25.4 ± 5.0	26.4 ± 5.6	0.046
WC (cm) [a]	88.3 ± 14.3	84.9 ± 13.1	86.3 ± 13.1	85.8 ± 11.9	88.5 ± 13.7	0.001
Parity [a]	0.8 ± 1.5	0.8 ± 1.4	1.3 ± 1.7	1.3 ± 1.7	1.3 ± 1.5	<0.0001
Physical activity [a]	837.7 ± 1019.6	1466.2 ± 2358.2	1538.5 ± 2626.5	1694.2 ± 2479.7	1554.1 ± 2079.2	0.9
Smoking history, yes[b]	7 (6.9)	79 (5.2)	172 (6.5)	70 (7.4)	6 (6.0)	0.4
Duration of OCP use (mon)[a]	3.2 ± 1.2	4.1 ± 5.9	4.4 ± 7.4	4.4 ± 6.1	2.7 ± 0.8	0.9
Education[b]						
High school or lower	44 (43.8)	435 (28.4)	567 (21.4)	167 (17.5)	25 (25.0)	<0.0001
High School Diploma	46 (45.0)	707 (46.1)	1340 (50.5)	498 (52.2)	42 (42)	
University degree	12 (11.3)	390 (25.5)	749 (28.2)	289 (30.3)	33 (33)	

Abbreviations: BMI, body mass index; WC, waist circumference; OCP, oral contraceptive pill.
[a] Mean ± SD, comparison using ANOVA test.
[b] Number(%), comparison using chi-square test.

and age, and 4 times higher after adjustment for parity and education, age and BMI than in women with age at menarche13–14 years (reference group) (Table 2). The risk of high BP was also significantly higher among women with earlier menarche (group 1) than those with age at menarche 13–14 years (reference group), only after adjustment for covariates such as parity, education, age, and BMI ($P < 0.05$). Group one showed a significant association with high triglyceridemia and low HDL compared to group 3, although the latter also differed significantly before adjustment ($P < 0.05$). Using logistic regression analysis, there was a statistically significant difference in the risk of high FBS (as a component of MetS) between group 1 and the reference group before ($P = 0.002$) and after adjustment for covariates ($P < 0.05$) (Table 3).

We re-analyzed our data, considering the difference between age at menarche and age at recruitment. Our final results, however, were not significantly changed (data has not been shown).

The age-adjusted crude rates (and 95% CI) of MetS and its components were estimated for each menarcheal age group, using logistic regression. The marginal means are shown in Table S1.

The age-adjusted crude rates of MetS by menarcheal age were 21.3 (95% CI: 13.4–32.1), 11.2 (95% CI: 9.5–13.1), 12.2 (95% CI: 10.8–13.7), 11.4 (95% CI: 9.3–14.1), and 13.2 (95% CI: 7.0–23.6), respectively. The exact *P* values of these associations in menarcheal age groups were 0.03, 0.09, 1 (Ref), 0.9, and 0.4, respectively.

We stratified and presented these results by age in three categories (group 1: 13–25 y, group 2: 26–37 y & group 3:38–50 y); these findings are reported in the supplementary section (see Supplementary file 1, Tables S2-S4).

Discussion

Our findings showed that early menarche (<11 years) was associated with a 2.3-fold increase in the risk of MetS after adjustment for potential confounders, which is in agreement with the findings of other studies in Western countries[11,28] and the United States.[17,29,30] These results demonstrate an inverse association between age at menarche and MetS, indicating that early age at menarche may raise the prevalence of MetS, regardless of ethnicity and race. However, the results of a Korean study, conducted in 2005 on 892 post-menopausal Korean women, showed no association between age at menarche and MetS[31]; their results could have been highly influenced by menopausal status of their participants, while in our study and in as study by Feng et al, menopausal women were excluded.[32] In addition, a study conducted on 7,349 Chinese women, aged 50–92 years reported an odds ratio of 1.49 for MetS among women with menarcheal age <12.5 years.[33]

Table 2. Odds ratios (and 95% Confidence Intervals) for MetS by Menarcheal Age in Participants

Variables	Groups				
	<11 years n = 102	11–12 years n = 1532	13–14 years n = 2656	15–16 years n = 954	17–19 years n = 100
MetS					
Model 1	1.8 (1.1–3.2)*	0.8 (0.6–1.01)	1.0 (Ref)	0.9 (0.7–1.2)	1.4 (0. 8–2.6)
Model 2	4.0 (2.0–7.9)*	1.0 (0.8–1.4)	1.0 (Ref)	0.7 (0.5–1.01)	1.2 (0.6–2.4)
Model 3	2.3 (1.0–5.4)*	0.9 (0. 6–1.2)	1.0 (Ref)	0.8 (0. 6–1.2)	1.3 (0.6–2.9)

Abbreviations: MetS, metabolic syndrome; BP, blood pressure; HDL-C, high density lipoproteins cholesterol; FBS, fasting blood sugar.
Analysis was conducted using logistic regression.
*Statistically significant.
Model 1: No adjustment; Model 2: Adjusted for Age, Parity, and Education; Model 3: Adjusted for variables in model 2 and Body mass index.

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

Variables	Groups				
	<11 Years n = 102	11-12 Years n = 1532	13-14 years n = 2656	15-16 Years n = 954	17-19 Years n = 100
Central obesity					
Model 1	1.5 (1.0–2.3)	0.8 (0.7–1.02)	1.0 (Ref)	0.8 (0.7–1.01)	1.2 (0.8-1.9)
Model 2	1.9 (1.2–3.1)*	0.9 (0.8–1.1)	1.0 (Ref)	0.7 (0.5–1.01)	1.02 (0. 6-1.7)
High BP					
Model 1	1.7 (0.96–3.1)	0.8 (0. 6–1.0)	1.0 (Ref)	0.9 (0.7–1.2)	1.3 (0.7–2.6)
Model 2	3.9 (1.9–7.7)*	1.0 (0.8–1.4)	1.0 (Ref)	0.8 (0.5–1.1)	1.1 (0.5–2.4)
Model 3	2.9 (1.4–6.0)*	0.9 (0.7–1.2)	1.0 (Ref)	0.8 (0.6–1.2)	1.2 (0.5–2.6)
High triglyceridemia					
Model 1	1.6 (0.99–2.7)	0.8 (0. 7–1.0)	1.0 (Ref)	1.0 (0.8–1.3)	0.9 (0.5–1.7)
Model 2	1.8 (1.08–3.1)*	1.05 (0.9–1.2)	1.0 (Ref)	0.96 (0.8–1.2)	1.08 (0.7–1.8)
Model 3	1.5 (0.9–2.7)	1.0 (0.8–1.1)	1.0 (Ref)	1.0 (0.8–1.3)	1.1 (0. 7–1.8)
Low HDL-C					
Model 1	1.7 (1.1–2.7)*	1.0 (0. 9–1.1)	1.0 (Ref)	1.0 (0.8–1.1)	1.0 (0.6–1.5)
Model 2	1.8 (1.1–3.0)*	1.0 (0.9–1.2)	1.0 (Ref)	1.0 (0.8–1.2)	1.1 (0.7–1.8)
Model 3	1.5 (0.9–2.6)	1.0 (0.8–1.1)	1.0 (Ref)	1.0 (0.9–1.3)	1.1 (0. 6–1.8)
High FBS					
Model 1	2.9 (1.6–5.4)*	1.1 (0.9–1.4)	1.0 (Ref)	0.8 (0.6–1.1)	1.1 (0. 6–2.1)
Model 2	3.6 (1.8–7.2)*	1.2 (0.96–1.6)	1.0 (Ref)	0.8 (0.6–1.0)	1.1 (0.5–2.1)
Model 3	3.0 (1.4–6.0)*	1.2 (0.9–1.5)	1.0 (Ref)	0.8 (0.6–1.1)	1.1 (0. 6–2.2)

Abbreviations: MetS, metabolic syndrome; BP, blood pressure; HDL-C, high density lipoproteins cholesterol; FBS, fasting blood sugar.
Analysis was conducted using logistic regression.
*Statistically significant.
Model 1: No adjustment; Model 2: Adjusted for Age, Parity, and Education; Model 3: Adjusted for variables in model 2 and Body mass index.

MetS is believed to be a bridge between diabetes and cardiovascular disease.[9] The findings of our previous study showed that menarcheal age was inversely associated with the prevalence of pre-diabetes and diabetes.[20] The results of the 2012 Atherosclerosis Risk in Communities (ARIC) study, conducted in the United States, also confirmed these findings only in white women, with authors suggesting that race or ethnicity may contribute to developmental factors in the etiology of type 2 diabetes although this hypothesis needs more studies for confirmation.[34]

The results of our study showed that age at menarche was negatively associated with components of MetS including high BP, high levels of plasma triglycerides, low HDL-C, high FBS and central obesity. Similarly, another study on 9000 Chinese women aged 25–64 years showed that age at menarche was inversely associated with MetS and some of its components after adjustment for covariates such as BMI (at age 25).[32] The findings of the Aktor et al study on 1423 Bangladeshi women, aged 15–75 years showed that age at menarche was inversely associated with the prevalence of MetS and some of its components, i.e. high triglycerides and low HDL-C, after adjustment for covariates[23]; in this study, the results were not adjusted for BMI and waist circumference (WC) although our current study revealed an increase in prevalence of high triglycerides and low HDL-C after adjustment for BMI and WC.

A study by Heys et al on 7349 post-menopausal Chinese women (the Guangzhou Biobank Cohort Study) reported that early age at menarche, compared to age at menarche >14.5 years, was associated with higher prevalence of MetS and some of its components, including central obesity, high BP, high FBS and high triglycerides after adjustment for age, education and number of pregnancies; adding WC to this model, decreased these effects although these associations stayed statistically significant.[33] According to our findings, there is no association between late menarche age and MetS. However, the findings of another study that followed women from suburban areas of Ohio for over 26 years showed that early and late menarche were both associated with MetS.[17] The results of the current study showed that the menarche age had a curvilinear ('U' shaped) association with MetS in later life. Late menarche and early menarche are risk factors for adult MetS and cardio-metabolic disorders. Women with early (≤10 years) and those with late (≥16 years) menarche age could be at high risk for adult cardio-metabolic disorders. In our study, which included non-menopausal women, due to the small size of samples in the late menarche age group, we did not find any association between this group and MetS and its components; however, in the Glueck et al study, women aged > 26 years were investigated.[17]

Dreyfus et al, in a study conducted on 1333 African American and 1250 white women, reported that each year of earlier onset of menarche was related to elevated glucose, triglycerides and MetS only among white women.[30] The results of other studies show that girls with earlier onset of age at menarche demonstrate earlier increases in BMI during childhood[35] and adolescence.[36,37] Also, Sun et al

reported early maturation in both genders, accompanied by higher BMI, WC, fasting plasma triglycerides and fasting plasma insulin, compared to those with late maturation.[38] The results of another study, conducted on 2,417 males and 2641 females from northern Finland, showed earlier puberty to be associated with higher BMI, fasting insulin, diastolic BP and reduced HDL-C during adulthood in both sexes.[39] Furthermore, other studies have reported an association between age at menarche and components of MetS. In this regard, we reported that early menarche, compared to the reference group, was significantly associated with higher risk of central obesity, BP, and FBS after adjustment for covariates. Also, the findings of studies showing the role of menarche in relation to the increased risk of MetS is not yet clear.[28]

Current data suggest that approximately over 50% of differences in the timing of menarche are caused by genetic factors,[40] indicating a genetic base for the phenotypic relationships between age at menarche and BMI[12,41]; nevertheless, the role of menarche in the increased risk of MetS is not clear yet. Apparently, early menarche is only a marker for childhood obesity; whether or not it functions as a risk factor by itself or via sex hormone differences during the life span needs to be investigated.[28]

To the best of our knowledge, despite several publications on association between age at menarche and Mets and its components, this is the first population-based study conducted among Iranian women to explore this association following adjustment for several relevant confounders. The major strength of our study is the methodology in terms of reliable measurements of general anthropometric measurements and blood sampling. Also, the quantity of intra-assay variability is presumably minimal as all laboratory measurements were made together in the same laboratory by the same person.

In conclusion, our results indicate that a history of early age at menarche (<11 years) could help to identify women at risk for MetS. Therefore, early recognition of these women may result in preventing MetS and minimizing their cardiovascular risk.

Study Limitations

Our study was not adjusted for confounders such as pre-menarcheal BMI; over-time lifestyle changes may influence our results rather than age at menarche. Perhaps recall bias poses a difficulty with self-reporting of age at menarche; however, in the TLGS, age at menarche was evaluated every three years which indicated good confirmation. It can be presumed that in a conservative and religious society such as the Islamic Republic of Iran, menarche is a major developmental landmark that is precisely recalled by women and this is an asset of this study.

Authors' Contribution

MF contributed to the study design and execution, data analysis, manuscript drafting and critical discussion. FRT contributed to the study design and execution, data analysis, manuscript drafting and critical discussion. SBG contributed to the manuscript drafting. FA contributed to the study design and execution and manuscript drafting.

Conflict of Interest Disclosures

None.

Ethical Statement

The ethics committee of the Research Institute for Endocrine Sciences (RIES) approved the study proposal and informed consent was obtained from all participants (Approval number: 409/3492, 2017).

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Supplementary Materials

Supplementary file 1 contains Tables S1-S4.

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