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Ann Epidemiol. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Ann Epidemiol. 2015 June ; 25(6): 414–419. doi:10.1016/j.annepidem.2015.02.001.

Timing of Menarche Related to Carotid Artery Intima-Media Thickness in Black and White Young Adult Women: The Bogalusa Heart Study

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Abstract

Purpose—The early onset of menarche is related to the adulthood risk of cardiovascular (CV) disease. This study examines the relation of early onset of menarche to carotid artery intima-media thickness (IMT), which is a surrogate marker of cardiovascular (CV) disease, among asymptomatic young adult women in a black-white community.

Methods—A cohort of 461 women (31% black, 69 % white) aged 24-43 years (mean of 35.6 years) were participants in the Bogalusa Heart Study. The age at menarche was retrospectively collected. In addition to cardiovascular risk factor variable measurements B-mode ultrasound images of the far walls of carotid artery segments were obtained. The multivariate linear regression model along with mediating effect by Sobel test was applied to analyze menarcheal age effect on carotid artery IMT, adjusting for covariates.

Results—Waist/height ratio was significantly greater (p-value=0.01) in early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) in both black and white women. Homeostasis model assessment of insulin resistance (HOMA-IR) was significantly greater (p-value=0.01) in early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) in white women and also similar direction in black women. Internal carotid artery IMT was same in early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) in white women but higher (p-value=0.02) in black women. Given above these different associations, the mediation analysis by race was performed. The effect of early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) was mediated by waist/height ratio and HOMA-IR in white women after adjusting for parental education and age. The mediating effect of waist/height ratio (Sobel test-2.26 and p-value 0.02) and HOMA-IR (Sobel test -1.85 and p-valie

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Financial Disclosures: Authors have no financial relationships relevant to this article to disclose

Conflict of Interest: Authors have no conflict of interest to disclose

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0.06) on internal carotid artery IMT was noted in white women. The direct effect of early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) on internal carotid artery IMT (β= -0.150, p=0.01) was observed in black women.

Conclusions—The observed deleterious effect of early onset of menarche on carotid artery IMT in asymptomatic black and white younger adult women has biological, social and public health implications.

Keywords

Early onset of menarche; Internal carotid artery intima-media thickness; young adult women

Background

The menarcheal age is used to assess sexual maturation among females. There is no standard definition of early menarcheal age and various definitions exist within the literature (1-3). According to American Academy of Pediatrics, menarcheal age range is between 9-16 years of age. Most studies define menarcheal age at or below 12 years while others consider race specific 25th percentile of menarcheal age as early menarche. Early menarche is a widely used indicator of sexual maturation, more prevalent among US black girls than white girls (1-6). For example, in the Bogalusa Heart Study, the mean menarcheal ages of whites and blacks were similar (12.8 vs 12.9) but blacks were more likely (30% vs 25%), p= 0.10) to undergo a relatively early menarche below 12 years (7). Observation from a cross- sectional study in the Bogalusa Heart Study shows that early menarche is inversely associated with increased obesity in adulthood (8). Further, a longitudinal study within the Bogalusa Heart Study shows that early menarche is associated with metabolic syndrome in adulthood (8). Although it is known that early menarche is associated with metabolic risk factors for cardiovascular disease (CV) disease (7-9), there is a paucity of information in relation to early menarche and carotid artery intima media thickness (IMT) as a precursor of CV disease after consideration of the mediation effects of metabolic risk factors for CV disease in black-white young women (10-12). Racial composition of black-white reflects social constructs and proxy indicators of socioeconomic status (SES) (Ref 13-15). Even though race is social construct it has a large impact on biological mechanisms and health status (16, 17). Carotid artery IMT is a surrogate marker of CV disease morbidity and mortality (18, 19). B-mode ultrasonography is used to measure non-invasively the IMT of different segments of carotid artery. As part of Bogalusa Heart Study, a community-based study of the early natural history of CV disease (20), the present non-concurrent cohort study examines the direct and indirect effect of early menarche on carotid artery IMT in black-white women after controlling for parental education and age.

Materials and Methods

Study Population

During the 2001-2002 survey of black and white young adults, aged 18 to 45 years (n=1203; 70% white), ultrasonography of carotid artery IMT along with measurements of CV risk factor variables were performed as part of a longitudinal cohort study. Of these, 513 female participants (69% white, 31% black; mean age 35.6 years) who had data on menarcheal age

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were initially included in this study. The Tulane University Medical Center Institutional Review Board approved the study. Informed consent was obtained from all participants.

Menstrual History

As previously described (4), information on menarcheal age was obtained through interviews conducted by a nurse. Women were asked to identify the month and year when of first period occurred, with the help of questions such as, “Do you remember what grade you were in when you started having periods?” Participants who did not provide the month of menarche were considered menarche experienced at the midpoint of that specified year. Self-reported age of menarche was then calculated by subtracting month and year of birth from month and year of menstrual period. The reliability of self-reported age of menarche was reported in earlier studies (1, 7). Six participants were excluded from the analysis as their menstrual year was missing (n=3) or below 6 years (n=2) or above 20 yrs (n=1). They had similar distribution with the participants in terms of age distribution, education and parental education. The participants were also excluded if they were diabetes (n=11) or/both on antihypertensive (n=29) or/both cholesterol medications (n=11). Of 513 participants, 461 participants were included in the present study.

Participants were divided into two groups based on their menarcheal age: < 11 and ≥11 years as early maturers are found to be shorter but heavier in adulthood (1).

Carotid Artery Intima-Media Thickness

As previously described (21), carotid ultrasound measurements were recorded bilaterally using a Toshiba ultrasound instrument (Power Vision Toshiba SSH-380 ultrasound system, Toshiba America Medical System, Carrollton, TX) and a 7.5 MHz linear array transducer according to the protocol developed for the Atherosclerosis Risk in Communities Study (22). Images recorded on S-VHS tapes were read by certified readers from the Division of Vascular Ultrasound Research at Wake Forest University School of Medicine using a semi-automatic ultrasound image processing program developed by the California Institute of Technology and Jet Propulsion Laboratory (22, 23). The mean of the maximum carotid artery IMT readings of 3 right and 3 left far walls of common, bulb, and internal segments was used. If bilateral images could not be obtained, one side was used in the calculation.

General Examination

Standardized techniques and protocols were used by trained field observers (24). Replicate measurements of waist and height were made twice and the mean values were used to calculate waist/height ratio as a measure of visceral adiposity. Systolic and diastolic blood pressures were measured three times using a mercury sphygmomanometer by each of two randomly assigned observers. Mean arterial pressure was calculated as diastolic blood pressure plus one third pulse pressure. Information on smoking status was obtained using health habit questionnaires. The SES was assessed using both participants' and parental education. Those who smoked at least one cigarette per week during the past one year were identified as current smokers; those who smoked before past one year considered as ex-smoker and those who never smoked considered as non-smokers.

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Laboratory Measurements

Serum total cholesterol and triglycerides were assayed on fasting samples using an enzymatic procedure on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (25). The laboratory is being monitored for precision and accuracy of lipid measurements by the surveillance program of the Center for the Disease Control and Prevention (Atlanta, GA). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas, Pharmacia Diagnostics, Piscataway, NJ). Plasma glucose levels were measured by a glucose oxidase method as part of multiple chemistry profile (SMA20, Laboratory Corporation of America, Burlington, NC). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated based on the following formula: HOMA-IR=fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. This model is considered useful to assess insulin resistance in epidemiologic studies (26).

Statistical Analyses

All analyses were conducted using SAS software, version 9.1 (SAS institute, Cary, NC). For all comparisons, participants were divided into two groups based on their menarcheal age: < 11 and ≥11 years. A race specific t-test was used to determine differences in mean values of risk factor variables and carotid artery IMT by age of menarche: <11vs ≥11 years. The chi-square test and Fisher's exact were applied as needed for categorical variables. Log transformation was employed if continuous variables were not normally distributed. Normal distribution was examined using the Shapiro-Wilk normality test statistic. The test of effect modification by race was assessed between the relationship of menarcheal age and carotid artery IMT. To evaluate the mediator effect of wasit/height ratio or HOMA-IR in the causal pathway, race specific several simple and multiple regression analysis were performed (27). In model 1, dependent variable was carotid artery IMT and independent variables was early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) adjusted for parental education and age. In model 2, dependent variable was waist/height ratio or HOMA-IR and independent variable was early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) adjusted for parental education and age. In model 3, dependent variable was carotid artery IMT and independent variables were early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs), waist/height ratio or HOMA-IR adjusted for parental education and age. The Sobel test (28, 29) was conducted to test whether waist/height ratio or HOMA-IR carried the influence of early menarche on carotid artery IMT.

Results

The effect modification of race was significant (p-value=0.05). Therefore analysis was done separately by race. Table 1 shows race-specific risk factor variables and internal carotid artery IMT by menarcheal age. Early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) related significantly to higher waist/height ratio in both white and black women. Furthermore, early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) related significantly to higher HOMA-IR in white only. The early menarcheal age was significantly related to only higher internal carotid artery IMT in black women (p=0.02).

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Figure 2 displays the mediating effect of waist/height ratio and HOMA-IR adjusted for age and parental education in white women. The early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) influenced the effect on internal carotid artery IMT through the causal pathway of waist/height ratio (p-value for sobel test 0.02) and HOMA-IR ((p-value for sobel test 0.06).

In figure 3 displays no mediating effect of waist/height ratio ((p-value for sobel test 0.35) and HOMA-IR ((p-value for sobel test 0.99) for the effect of menarcheal age on internal carotid artery IMT in black women. The early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) direcly influenced the internal carotid artery IMT (p-value-0.01) after controlling for age and parental education

Discussion

The present community-based study demonstrates an inverse and independent association between early menarcheal age and internal carotid artery IMT in black women and indirect effect in white women. On average, internal carotid artery IMT decreased by 0.15 mm, (p-value 0.01) early menarcheal age (< 11 yrs) vs menarcheal age (≥11yrs) in black women after controlling for parental education and age. In white women, the early vs late menarcheal age has no direct effect (β= -0.019, p=-0.58), mediating through waist/height ratio (p-value= 0.02) and HOMA-IR (p-value= 0.06). This finding is consistent with recently-published longitudinal study with larger sample size measuring CV disease and mortality after 10.6-12.0 years follow-up (12). However, that study did not show the mediating effect of obesity and insulin resistance in relation to early menarchal age and CV disease. The mediating effect of obesity and insulin resistance was also observed in the literature (8, 10, 11). These studies explained the effect of obesity and insulin resistance in relation to early menarche with CV risk factors and carotid atherosclerosis.

The present study shows the relationship of menarcheal age with internal carotid artery IMT although menarcheal age was not related to other segments of carotid artery IMT. The atherosclerotic changes initiated at the internal carotid and bulb segments are more reflective of atherosclerosis (30). Therefore, including these segments are more sensitive and useful for early changes (21).

This observed deleterious association of early menarche with internal carotid artery IMT in black women was noted from a sub-sample of community-based cohort study. Early menarcheal age is associated with early life circumstances, namely birthweight, childhood obesity, childhood SES and psychological factors (31,32). On average, black girls experience increased levels of early life conditions when compared to white girls. The SES is inversely associated with menarcheal age in both black and white girls in the United States (33) although we did not find both participant's and parental education effect on menarcheal age. This finding is an agreement with previous study in terms of parental education (34). Race specific effect of carotid artery IMT by early menarcheal age may be also explained by genetic influence.

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The major strength of this study includes being community-based study of young adults of racial difference (white-.black women). However, our study has some limitations. For instance, this is a reconstructed non-concurrent longitudinal study. Concurrent cohort studies are needed to determine the effect of early menarche on carotid artery IMT. Moreover, the age at which menarche was self reported was recalled via memory by those who are 18-43 years of age which leaves the results subject to bias. However, self-reported menarcheal age is the most commonly used method in epidemiologic studies. Black-white differences in education may subject to differential misclassification bias that underestimates the prevalence of early menarcheal age in black women. Furthermore, we could not assess parental SES by income status which is inversely related to obesity but positively related to menarcheal age in both white and black girls in the United States (33-36). Lastly, the measurement of carotid artery IMT was assessed only once in each subject in their current individual states of adulthood.

In conclusion, the observed deleterious effect of early onset of menarche on carotid artery IMT in asymptomatic black young adult women has biological, socioeconomic and public health implications as black girls experience early menarche, which is related to obesity, CV disease morbidity and mortality (6,37,38). A recent study shows that the black/white difference in early life conditions such as childhood BMI explained about 18% of the overall difference in age of menarche while birth weight differences accounted for another 11%. (15) Further, longitudinal studies are needed to draw conclusions regarding this effect of early onset of menarche on carotid artery IMT after carefully considering early life conditions. The current observations show that timing of menarche can relate to early atherosclerosis directly to black young women and indirectly to white young women

Acknowledgments

The Bogalusa Heart Study is a joint effort of many individuals whose cooperation is gratefully acknowledged. We are especially grateful to the study participants.

Funding source: Supported by grants 546145G1 from Tulane University, 0855082E from the American Heart Association, AG-16592 from the National Institute on Aging, HL-38844 from the National Heart, Lung, and Blood Institute, R01-AG-16592-12 from National Institute on Aging and 1R01ES021724-01from National Institute of Environmental Health Sciences.

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List of abbreviations

SES	Socioeconomic Status
CV	Cardiovascular
IMT	Carotid artery intima-media thickness

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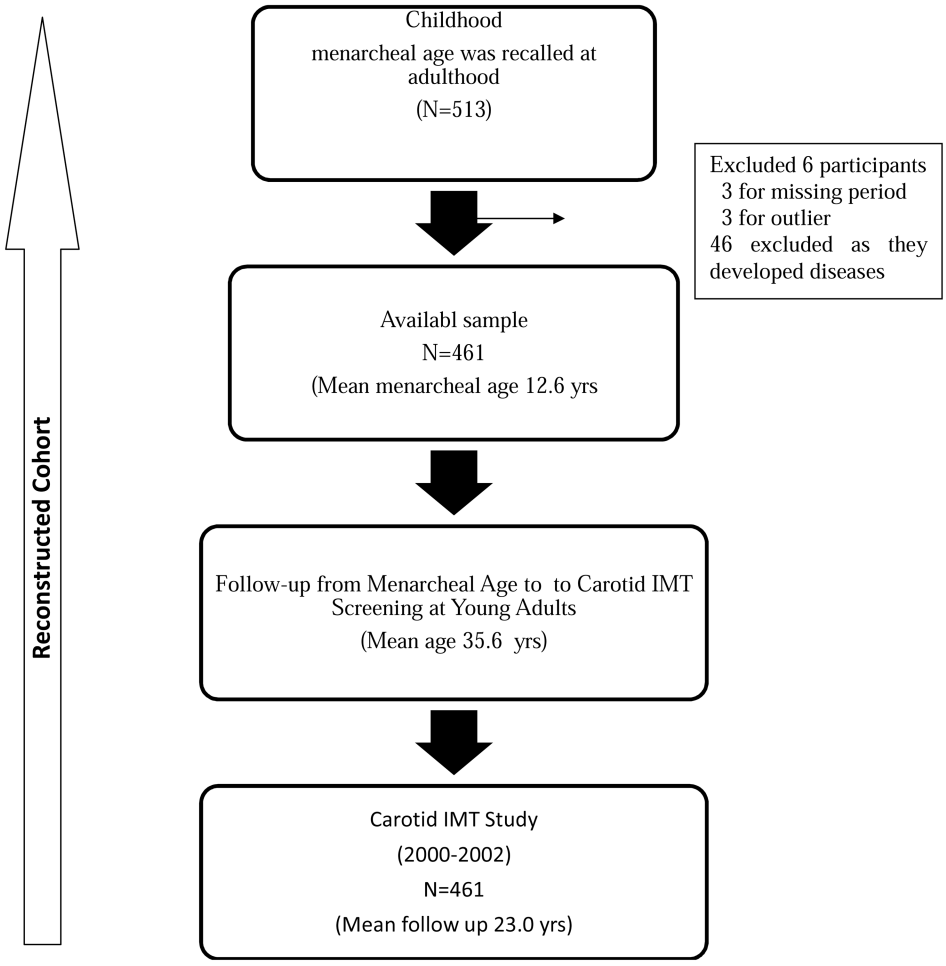

Figure 1. Diagram of reconstructed non-concurrent cohort study

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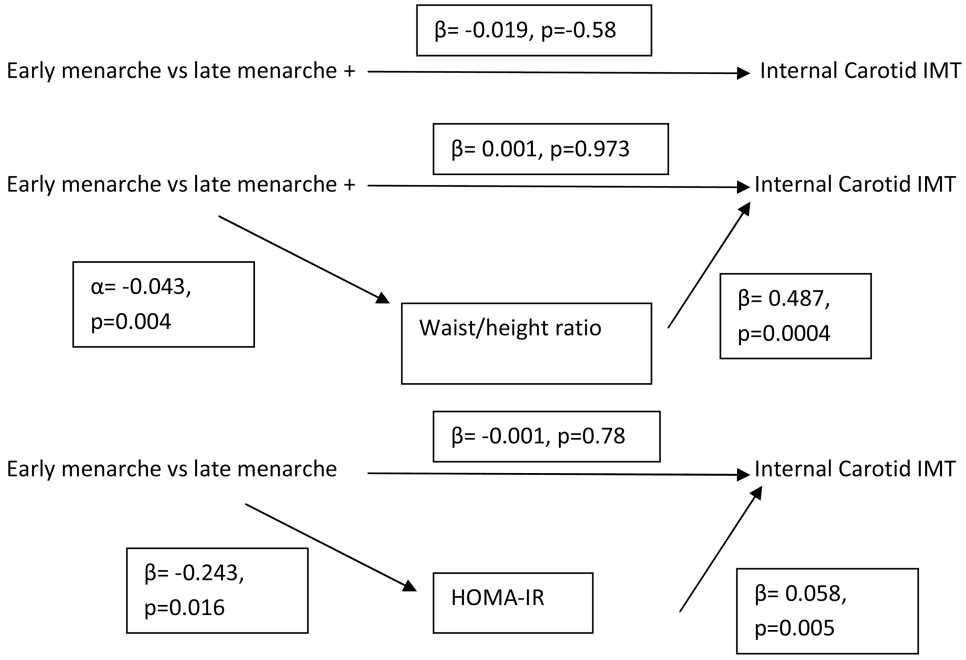

Sobel test for	Test Statistics	p-value
Waist/height ratio	-2.26000904	0.02382069
HOMA-IR	-1.84748767	0.06467649

Figure 2. Testing Mediating Effect on Internal Carotid Artery IMT for White Women

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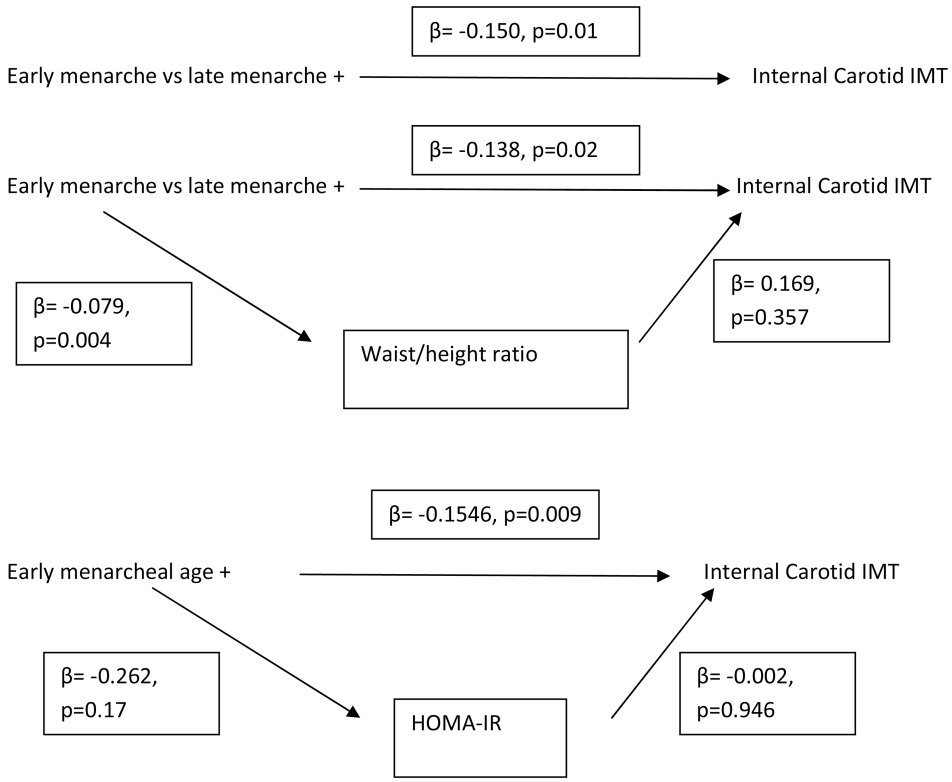

Sobel test for	Test Statistics	p-value
Waist/height ratio	-0.9368008	0.34886101
HOMA-IR	0.00211372	0.9983135

Figure 3. Testing Mediating Effect on Internal Carotid artery IMT for Black Women

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Table 1
Levels of risk factor variables by status of menarcheal age in whites vs blacks

	Menarcheal age < 11 yrs	Menarcheal age ≥11 yrs	p-value
White			
Age (yrs)	34.9±5.1	36.0±4.2	0.11
Participants' education (College or post graduate)	28 (15%)	157 (85%)	0.58
Parental education (College or post graduate)	16 (15%)	88 (85%)	0.87
Waist/ height ratio	0.56±0.1	0.52±0.1	0.01
Mean blood pressure (mmHg)	87.0±7.8	85.8±8.5	0.37
Triglycerides/HDL cholesterol ratio	2.7±1.4	2.6±2.2	0.18
HOMA-IR	2.9±2.3	2.2±1.6	0.01
Current smoker	9 (15.6%)	84 (12.5%)	.32
Ex smoker	7 (20%)	34 (31%)	
Internal carotid artery IMT (mm)	0.67±0.15	0.66±0.16	0.74
Carotid bulb IMT (mm)	0.89±0.10	0.90±0.20	0.96
Common carotid artery IMT (mm)	0.70±0.10	0.70±0.10	0.70
Black			
Age (yrs)	35.1±4.9	34.8±4.7	0.81
Participants' education (College or post graduate)	6 (15%)	46 (85%)	0.88
Parental education (College or post graduate)	2 (12%)	15 (88%)	0.72
Waist/ height ratio	0.63±0.13	0.56±0.10	0.006
Mean blood pressure (mmHg)	94.1±9.8	90.8±11.3	0.24
Triglycerides/HDL cholesterol ratio	2.0±0.7	1.8±1.0	0.18
HOMA-IR	3.9±3.3	3.4±5.6	0.19
Current smoker	9 (7.1%)	38 (30.1)	0.44
Ex smoker	1 (5.6)	3 (16.7%)	
Internal carotid artery IMT (mm)	0.79±0.20	0.67±0.14	0.02
Carotid bulb IMT (mm)	0.86±0.17	0.89±0.17	0.54
Common carotid artery IMT (mm)	0.72±0.11	0.74±0.10	0.46

Mean±SD for continuous variables

HOMA-IR=homeostasis model assessment of insulin resistance; ns=not significant; IMT=Intima media thickness