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Earlier menarche is associated with non-alcoholic fatty liver disease and abdominal ectopic fat in midlife, independent of young-adult BMI: The CARDIA Study

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Abstract

Objective—We test the hypothesis that earlier menarche is associated with higher non-alcoholic fatty liver disease (NAFLD) and ectopic adiposity, independent of young-adult BMI.

Design and Methods—We use data from 1,214 black and white women in the Coronary Artery Risk Development in Young Adults (CARDIA) study who reliably reported menarche age at exam years 0 and 2, had multiple-slice abdominal computed tomography (CT) at exam year 25, and had no known liver disease or secondary causes of steatosis. Women were aged 18–30 at year 0 and 43–55 at year 25. Liver attenuation, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and inter-muscular adipose tissue (IMAT) were derived from CT. NAFLD was defined as liver attenuation <51 Hounsfield units.

Results—One-year earlier menarche was associated with higher NAFLD (RR=1.15; 95% CI: 1.07–1.24), and VAT (6.7; 95% CI: 4.3–9.0cc), IMAT (1.0; 95% CI: 0.6–1.4cc), and SAT (19.3; 95% CI: 13.2–26.0cc) after confounder adjustment. Associations remained significant (p<0.05) after further adjustment for year-0 BMI. Only VAT remained significant (p=0.047) after adjustment for weight gain between year 0 and 25.

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Conflicts of Interest Statement

The authors have no conflict of interest with the submitted work.

Conclusion—Earlier menarche is positively associated with NAFLD and ectopic fat independent of confounders and young-adult BMI. Weight gain between young adulthood and midlife explains some of this association.

Keywords

Puberty; Visceral Fat; Subcutaneous Fat; Hepatic Steatosis; Nonalcoholic fatty liver disease; Racial Disparity

Introduction

Non-alcoholic fatty liver disease (NAFLD) – a spectrum of liver disease from steatosis to cirrhosis – has risen to epidemic proportions in the U.S.[1] In addition to being a leading cause of chronic liver disease,[1] NAFLD is associated with significant cardiometabolic disease and disability. The formidable challenge of sustained behavior change once NAFLD manifests make its prevention a public health priority.[2]

One preventive avenue is through identification of antecedents of NAFLD. Puberty represents an important event during human growth in which patterns of adult health are established. Its timing, influenced by myriad genetic and environmental factors,[3] may provide an early-life window into altered metabolic trajectories, and thereby facilitate a path to primordial prevention.

Menarche is the most easily distinguishable marker of pubertal timing in females. Whether due to genetics or environment, earlier age at menarche has been associated with higher risk of obesity,[4] metabolic syndrome,[5–7] type 2 diabetes,[8–11] and cardiovascular disease.[8] Moreover, we found early menarche was associated with a marker of liver dysfunction, alanine aminotransferase.[12] Yet, whether age at menarche is related to NAFLD has not been studied, and only one study[13] has investigated whether age at menarche is specifically related to visceral (VAT) and subcutaneous abdominal adipose tissue (SAT); they did not assess inter-muscular adiposity (IMAT).

In this light, the objective of the current study is to test the hypothesis that earlier menarche is associated with higher risk of NAFLD, and levels of intra-abdominal fat, independent of confounders and young adult BMI.

Methods

Data Source

Coronary Artery Risk Development in Young Adults (CARDIA) is an ongoing multi-center, community-based study that was undertaken to study the evolution of cardiovascular disease risk factors in 5,115 young adults (2,787 women) initially aged 18–30 years at baseline (year 0) examination in 1985/6. Young black and white adults were recruited from the population in Birmingham, AL; Chicago, IL; Minneapolis, MN; and from a health maintenance organization in Oakland, CA. Participants were balanced on race (black vs. white), age (18–24 vs. 25–30 years), and education (≤12 vs. >12 years schooling).[14] The current study used data from the year 0, 2, and 25 clinic visits. The retention rates among survivors at the year 2

and 25 exams were 91 and 72%, respectively. Signed informed consent was obtained from all participants at each exam, and the institutional review board at each of the clinical centers approved all protocols.

Inclusion Criteria

We analyzed a subset of the 1,981 women who attended the CARDIA year 25 exam and were eligible to have computed tomography (CT) of the abdomen and thorax at that exam. Participants were not included in CT if they were pregnant (*n*=17), weighed more than the 450 lbs (*n*=5), refused (*n*=8), or if CT scheduling was inconvenient or available funds for CT were used before their visit (*n* = 151). We then excluded those who secondary to surgical or other artifacts, typically spinal hardware, had degraded images of liver fat VAT, SAT or IMAT (*n* = 13). We further excluded those missing baseline diet (*n*=1), with self-reported history of liver disease at year 25 (*n*=51); those with secondary causes of fatty liver at year 25: self-reported HIV (*n*=4), or a history of intravenous drug use (*n*=37), or alcohol consumption ≥20 g/day (*n*=198)[15]; those taking hormone therapy at year 25 (*n*=132); and those missing age at menarche measurement (*n*=7). Finally, we excluded women whose self-report of age at menarche was unreliable (i.e., difference between year 0 and year 2 self-report was greater than 2 years apart, *n*=142) or >18 years (*n*=1). These exclusions left 1,214 women for analysis. Results obtained after these exclusions were not materially different than those before exclusions (data not shown).

Independent Variable Measurements

Data collected at exam years 0, 2, and 25 (CT measures) across study centers using standard protocols[14] were used in the current analyses.

Main Exposure—Age at menarche was defined as the age in whole years at the first menstrual period. At both year 0 and 2 exams females were asked the open-ended question, "How old where you when you began menstruating?" The Pearson correlation between year 0 and year 2 self-report of age at menarche was 0.89. If both reports of age at menarche were available (and within 2 years of age), the average was taken.

Control Variables—Anthropometric assessment was made after women changed into light clothing and removed shoes. Trained and certified technicians took all measurements. Quality control checks were made at regular intervals throughout each exam cycle. Standing height was measured to the nearest 0.5 cm with the participant standing erect on the floor with her back against a vertical-mounted centimeter ruler. Body weight was measured to the nearest 0.2 kg with a calibrated balance-beam scale. BMI was calculated as weight (kg)/ height squared (m^2). Year 2 BMI was used for those missing year 0 BMI (*n*=7). Sociodemographic characteristics were assessed by standard questionnaires. Participants reported their mothers' and fathers' educational attainment at year 0. Participant educational attainment was based on self-reported years of schooling and was updated at each exam. Level of pre-high school physical activity was measured using an activity scale of 1 (physically active) to 5 (very active) and assessed by selfreport at year 0. Dietary history (focused on past month and based on modified Burke method[16]), alcohol consumption, cigarette smoking history, and medical history were obtained from interviewer-administered

questionnaires at year 0. Medication use was self-reported and participants were asked to bring their medications for verification. Birth weight was able to be ascertained through birth records in a subsample of participants. Self-reported number of pregnancies was updated at each exam.

Dependent Variable Measurements

CT images were acquired at year 25 at each CARDIA field center and then electronically transmitted to the central CT reading center at Wake Forest University School of Medicine, Winston-Salem, NC. The protocol entailed a non-contrast CT scan of the abdomen and was performed using multidetector CT scanners [GE 750HD and GE LightSpeed VCT Birmingham and Oakland Centers, respectively; GE Healthcare, Waukesha, WI; Siemens Sensation, both Chicago and Minneapolis Centers; Siemens Medical Solutions, Erlangen, Germany]. Image analysis and quality control were performed at the central reading center (Wake Forest University Health Sciences, Winston-Salem, NC). The protocol included scout images through the lower abdomen.

Liver attenuation, measured in Hounsfield units, was acquired from non-contrast CT (in axial scan mode) images of the upper abdomen. It was based on the mean of 3 separate CT slices at the T12-L1 intervertebral space, measuring 100 mm^2 in the parenchyma of the right lobe of the liver. Analysts performing the measurements were trained to avoid placing regions of interest that included large hepatic vessels or common hepatic lesions (cysts and hemangiomas).[17, 18] The intraclass correlation coefficient between 2 different readers on a randomly selected sample of 156 participants was 0.98 for liver attenuation, indicating high reproducibility. Liver attenuation is inversely correlated with hepatic steatosis measured by liver biopsy.[17, 19] A literature-supported < 51 Hounsfield units (comparable to a liver-to-spleen ratio of 1.0) was used to diagnose fatty liver.[20]

CT scans of the abdomen were reconstructed into 5 mm slices with the maximum 50 cm field-of-view to include the whole abdomen for body composition. The abdominal muscular wall was first manually traced and the adipose tissue in different compartments was measured by a semiautomatic segmentation technique. Adipose tissue depots were measured volumetrically from 2 contiguous 5 mm slices located at the level of the lumbar disk between the 4^{th} and 5^{th} (L4-L5) vertebra. Volume analysis software (Advantage Windows, GE Healthcare, Waukesha, WI) was used to segment and characterize each individual voxel as a tissue attenuation of fat. Tissue with attenuation between −190 to −30 Hounsfield units was defined as adipose tissue. Analysts used the Medical Image Processing, Analysis, and Visualization (http://mipav.cit.nih.gov/index.php) application to segment the images based on anatomic boundaries (skin, subcutaneous fat-muscle interface, and peritoneum) into the entire abdomen, abdominal wall and intra-abdominal compartments. In each compartment visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and inter-muscular adipose tissue (IMAT) were quantified. The intraclass correlation coefficient for inter-reader comparisons was 0.99 for VAT, and intra- and inter-reader error were 2.4% and 6.7%, respectively, in 156 scans that were blinded and reevaluated.

Statistics

All analyses were performed using SAS 9.2 (SAS institute, Cary, NC). We summarized the characteristics of the cohort using mean (SD) for continuous variables and % for categorical variables across age at menarche categories (8–<12, 12–<14, 14–18 years).

We used multivariable linear regression to assess the association between continuous measures of liver attenuation, VAT, SAT, IMAT, and age at menarche. Poisson regression with robust variances[21] was used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for NAFLD by menarche age. Covariates included in our models were chosen *a priori* based on their association with age at menarche and our outcome variables. Model 1 included variables considered potential confounders: birthdate, race, study center, parental educational attainment, maternal diabetes, paternal diabetes, year 0 diet score, year 0 smoking status (never, former, current), and pre-high school physical activity. Model 2 included additional adjustment for the earliest BMI measure in CARDIA assessed (at exam year 0) when participants were 18–30 years old. We then further adjusted a third model for weight gain (kg) between year 0 and year 25 exam—the exam at which CT was measured—to determine if this mediated associations. Further inclusion of participant education level (less than high school, completed high school but not college, completed college but no graduate school, graduate school plus), year 0 alcohol use (yes/no), year 25 postmenopausal status (yes/no), and year 25 parity (0, 1–2, 3–4, 5+) did not alter results and thus these variables were not included in the final models.

We evaluated effect measure modification by including cross-product terms in the models for our exposures and race (black vs. white), smoking (ever vs. never), education (<high school vs. ≥high school), and BMI at year 0 exam (25kg/m^2 vs. ≥25 kg/m^2). We used the F-test *p*-value, with menarche age as a continuous variable, to test for linear trend. All statistical tests were two-sided and significance was defined at $p < 0.05$.

Results

The mean (±SD) age at menarche for the 1,214 eligible women was 12.6±1.5 years. Participants were 18–30 years old at baseline exam and 43–55 years old at year 25. Baseline participant characteristics according to categories of age at menarche are presented in Table 1. Compared to mid-to-late menarche, early menarche (8–<12 y) was associated with black race, lower maternal and paternal education, higher maternal and paternal diabetes, shorter legs, greater BMI, and lower pre-high school physical activity. Early and late maturing females were more likely to smoke tobacco at year 0. There were no marked differences in birth weight, parity, postmenopausal status, or baseline diet score across menarche categories.

Age at menarche in relation to continuous measures of liver attenuation, VAT, SAT, and IMAT are presented in Table 2. Earlier menarche onset was associated with lower liver attenuation (consistent with higher hepatic steatosis), and higher abdominal VAT, IMAT, and SAT (*p* for trend <0.05; model 1). These associations were slightly attenuated but still significant (*p* for trend <0.05) after further adjustment for BMI measured (at year 0) when participants were 18–30 years of age (model 2). They were further attenuated toward the

null (all p for trend > 0.05 except for VAT, $p = 0.047$) after adjustment for weight change between exam year 0 and year 25 when participants were 43–55 years old (model 3).

Of the 1,214 women eligible for analyses, 235 (19.3%) had CT-diagnosed NAFLD. The association between age at menarche and NAFLD is shown in Table 3. After adjusting for multiple potential confounders, earlier age at menarche was associated with greater risk of NAFLD (model 1, RR for 1 year earlier menarche=1.15; 95% CI: 1.07, 1.24). This association was substantively unchanged after adjustment for BMI at year 0 (model 2, RR for 1 year earlier menarche=1.10; 95% CI: 1.02, 1.19), or weight change between year 0 and year 25 (model 3, RR for 1 year earlier menarche =1.06; 95% CI: 0.98, 1.15). There were no substantive differences when using alternative CT-diagnosed NAFLD definitions of <40 or <48 HU.[17, 19, 20]

In evaluation of effect modification on the multiplicative scale, we observed evidence (Table 4) that the association between age at menarche and VAT was stronger among white women (p for interaction=0.002). Yet, there was no evidence of race interaction for liver attenuation (p for interaction=0.66), SAT (p for interaction=0.18), or IMAT (p for interaction=0.18). We also found no evidence of multiplicative interaction by enrollment age, BMI at year 0 exam, or education (p for interaction >0.05).

Discussion

Our findings suggest that a one year earlier age at menarche onset is associated with 10% increased risk of NAFLD in middle adulthood (43–55 years of age) after adjusting for socio-demographic and lifestyle confounding factors and BMI measured at 18 to 30 years of age. Earlier menarche was also associated with visceral and subcutaneous abdominal ectopic fat depots in middle adulthood. These associations were somewhat attenuated after adjustment for weight change between young and middle adulthood.

This is the first study to report the association between a marker of pubertal timing and NAFLD. In previous research, we found earlier menarche was associated with higher alanine aminotransferase,[12] C-reactive protein,[12] triglyceride levels,[12] BMI,[12] waist circumference,[12] adult diabetes,[12] in addition to cardiovascular disease mortality.[8] These findings are largely consistent with research on age at menarche and cardiometabolic diseases from other settings.[4–10, 22, 23] Moreover, earlier menarche has also been positively associated with development of advanced liver disease and carcinoma.[24]

There are several potential biologic mechanisms that may explain the observed association between timing of menarche and hepatic steatosis. The foremost involves adiposity and related hormones, such as leptin, which are associated with steatosis and pubertal timing.[25–28] In our study age at menarche was associated with hepatic steatosis after adjusting for BMI measured when the participants were 18–30 years old. Yet this association was no longer significant after adjustment for weight change between young and middle adulthood, when liver attenuation was measured. Thus, from our data it does not appear that general adiposity confounds so much as it mediates the association between age at menarche and NAFLD.

Evidence on alternative, but related, mechanisms comes from a series of experimental trials by Ibanez *et al.* in precocious-pubarche[22, 29, 30] and advanced-puberty[31] females. In the trial of precocious-pubarche girls, early vs. late metformin—an insulin-sensitizing medication commonly used to treat type 2 diabetes—was shown to delay puberty and menarche,[30] as well as reduce leptin levels,[30] pro-inflammatory markers,[22] and visceral and central fat.[22] In advanced puberty girls, metformin (vs. no metformin) therapy during puberty delayed menarche onset, increased height, and reduced % body fat, insulin resistance, leptin, sex-hormone binding globulin (SHBG), insulin-like growth factor-1 (IGF-1) and IGF binding protein-1 levels.[31] These trials provide strong evidence that modulating insulin sensitivity before and/or during puberty can delay pubertal transition and improve cardiometabolic parameters. We did not have a measure of insulin resistance before puberty to test whether this pathologic parameter was driving the age at menarche and NAFLD association.

As insulin concentrations increase, serum SHBG and IGF binding protein-1 levels decrease. These may alter unbound estrogen and IGF-1, respectively, which may then act upon the endometrium and epiphyseal growth plate. Higher insulin concentrations and IGF-1 may also increase aromatase activity and ovarian estrogen synthesis.[32] Yet, many of these mechanisms also relate to general, as opposed to liver-specific, adiposity. Continued basic science in cell, animal, and human models seems warranted to help shed etiologic light on the interplay of growth factors, hormones and their binding proteins, as well as other biologic intermediaries as they relate to pubertal timing, adiposity, and hepatic steatosis.

Only one previous investigation, the Framingham Heart Study, has reported on the association between age at menarche and visceral and subcutaneous adipose tissue. In this study, as in ours, earlier age at menarche was associated with greater midlife VAT and SAT. These associations were attenuated toward the null when the authors adjusted for midlife BMI, measured at the same time as fat depots.[13] In our study, we were interested in whether age at menarche was associated with abdominal fat depots and NAFLD independent of young adult BMI, and, if so, whether weight maintenance between young and middle adulthood could mitigate this risk. When we adjusted for young adult BMI—measured 25 years prior to CT when women were 18 to 30 years old—there was an independent association between age at menarche and all midlife abdominal adipose depots. But, when we adjusted for weight change between young and middle adulthood, these associations were attenuated, with only the association between age at menarche and VAT remaining marginally significant.

The composition of the Framingham Heart Study is primarily white, and thus was also not able to determine if the associations between age at menarche and abdominal adipose depots differed by race. In our study, the inverse association between age at menarche and VAT was stronger in white women than in black women. Compared to white women, black women accumulate less visceral and more subcutaneous fat.[33] It is possible that early-life determinants associated with menarcheal timing and fat depositions vary by race. Another possibility is that black women experience less variation in exposure to factors that predispose women to early maturation and accretion of VAT. This may also explain, at least in part, the stronger menarcheal age-diabetes association that has been found in white compared to black women.[9]

The strengths of the current study include the large, well-characterized community-based sample of whites and blacks, the highly sensitive measurement of body composition and liver attenuation by computed tomography, and a wide array of demographic, lifestyle, and physiologic measures to assess cofounding and effect modification. Another strength was the collection of age at menarche at two consecutive exams soon after puberty. While menarche age was self-reported, leaving potential for misclassification, the correlation was high in our data between self-report of age at menarche in year 0 and year 2 exams (Pearson correlation=0.89) and in data from others.[34] Our definition of NAFLD, which we obtained by CT liver attenuation after excluding participants with known chronic liver disease or those with secondary causes of liver dysfunction, could also be considered a strength. But this was an epidemiologic definition that should be validated in future studies by using alternative measures of NAFLD and follow-up for hard clinical endpoints.

There were also limitations to the current study. One limitation is the absence of a baseline or earlier measure of liver attenuation or fat depots, limiting inference about temporality of the associations. We also cannot rule out residual confounding by unmeasured early-life socioeconomic, lifestyle, or physiologic measures, such as prepubertal diet and adiposity. Weight change between young and middle adulthood is likely on the causal pathway between menarcheal timing and midlife abdominal fat measures. Obtaining unbiased estimates from this mediation model relies on the additional assumptions that 1) there is no interaction between age at menarche and year 25 BMI on risk of NAFLD, and 2) that there is no unmeasured confounding between year 25 BMI and hepatic steatosis. Because these assumptions may not hold, the parameter estimate from this final model should be interpreted cautiously. Another limitation is that our definition of NAFLD—measured by CT—is less sensitive than liver biopsy and does not capture hepatic fibrosis.[19, 35] However, liver biopsy is an invasive procedure, not practical in a population-based study. We accounted for the lack of data on liver function or viral hepatitis serologies in the present study by excluding participants with a history of HIV, intravenous drug use, medication use, or excessive alcohol intake known to contribute to steatosis. We acknowledge that individuals identified with NAFLD by our definition may not progress to steatohepatitis or more severe liver disease. More work, using adjunct measures of liver dysfunction, inflammation, and follow-up for liver-related events, is needed to test the validity of NAFLD diagnosed by liver attenuation. Finally, although comparisons were specified *a priori*, there is a chance that one or more of the statistically significant results are false positives.

Conclusion

In sum, our findings provide evidence that age at menarche is associated with risk of CT-diagnosed NAFLD and developing abdominal ectopic fat more than 25 years after puberty, independent of socio-demographic and lifestyle confounding factors and young adult BMI. Weight maintenance between young and middle adulthood may partially mitigate this risk. As such, age at menarche may serve as a harbinger for diverging trajectories of adiposity and NAFLD later in life, and collecting this information in women early in life may help facilitate primordial prevention of these conditions.

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NTM and MAP designed the analytic strategy, undertook analyses, interpreted results, and wrote, reviewed and edited the manuscript. DRJ, JJC, and JGT contributed to the study design, data collection, results interpretation, and manuscript revision. EWD, JGD, and RFM contributed to analytic strategy, results interpretation, and manuscript revision. All authors were involved in writing the paper and provided final approval of the manuscript.

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What is already known about this subject?

- Earlier age at menarche has been linked to higher risk for obesity and cardiometabolic disease risk later in life.
- However, it is unclear whether, independent of young-adult general adiposity, having information on age at menarche can help identify women at higher risk for developing non-alcoholic fatty liver disease (NAFLD) and ectopic adiposity.

What this study adds?

- Earlier age at menarche is associated with higher risk of NAFLD and ectopic fat, independent of confounders and BMI measured in young adulthood.
- Associations were slightly attenuated upon adjustment for weight gain between young and middle adulthood.
- Collecting information on age at menarche in early adulthood may help identify women at future risk developing liver and ectopic fat. Preventing weight gain between young and middle adulthood may help prevent midlife NAFLD and ectopic fat associated with earlier menarche.

Table 1

Characteristics of Women by Age at Menarche Categories: CARDIA study.

	Age at menarche (years)		
	8–<12 (*n*=293)	**12–<14 (*n*=692)**	**14–18 (*n*=229)**
Age at year 0 exam	24.7 (3.7)	25.1 (3.6)	24.8 (3.8)
Black race (%)	62.1	50.4	52.4
Participant education > high school (%)	77.8	79.8	76.9
Maternal education > high school (%)	35.3	42.7	43.8
Paternal education > high school (%)	37.2	44.4	48.6
Maternal diabetes (%)	13.0	10.7	9.6
Paternal diabetes (%)	13.3	11.6	8.3
Birth weight (g) (*n*=38/93/33)	3031.9 (708.3)	3072.7 (548.0)	3078.9 (678.1)
Parity at year 25 exam	2.6 (2.0)	2.7 (2.0)	2.5 (1.9)
Postmenopausal at year 25 exam (%)	49.7	47.0	46.1
Early-life lifestyle variables			
Highest level of pre-high school PA (%)	28.3	30.2	32.8
Diet score at year 0 exam	62.6 (12.4)	63.9 (13.1)	63.2 (13.6)
Ever smoker at year 0 exam (%)	23.6	19.9	25.8
Year 0 anthropometric fat indicators			
BMI at year 0 exam (kg/m^2)	26.3 (5.8)	24.6 (5.5)	23.2 (4.9)
Obese* at year 0 exam (%)	23.2	14.2	10.5
Weight gain (kg) between year 0 and 25	19.7 (17.6)	18.5 (16.2)	15.1 (14.9)

Values presented are unadjusted means (and standard deviations) unless otherwise indicated.

*Obesity is defined as BMI ≥ 30 kg/m^2

Correlations between menarcheal age and: year 0 BMI = 0.18; year 25 BMI = 0.20; year 25 liver attenuation = 0.11.
Correlations between year 0 BMI and: year 25 BMI = 0.68; year 25 liver attenuation = 0.30.
Correlations between year 25 BMI and liver attenuation = 0.41.

Table 2

Adjusted Means (and 95% CI) for Liver Attenuation and Abdominal Ectopic Fat Depots by Age at Menarche in Women from CARDIA.

	Age at menarche (years)			
	8–<12 (*n*=293)	**12–<14 (*n*=692)**	**14–18 (*n*=229)**	**1-yr earlier menarche**
Liver attenuation[a]				
Model 1	55.0 (53.7, 56.2)	57.2 (56.4, 58.0)[c]	59.1 (57.7, 60.5)[c]	−0.8 (−1.2, −0.4)[c]
Model 2	55.8 (54.6, 57.0)	57.1 (56.3, 57.8)	58.4 (57.0, 59.7)[c]	−0.5 (−0.9, −0.1)[c]
Model 3	56.1 (54.9, 57.2)	57.2 (56.5, 57.9)	57.6 (56.3, 58.9)	−0.2 (−0.6, 0.1)
Abdominal visceral adipose tissue[b]				
Model 1	124.4 (117.3, 131.5)	116.6 (112.0, 121.2)	97.4 (89.4, 105.4)	6.7 (4.3, 9.0)[c]
Model 2	118.4 (111.7, 125.0)	117.0 (112.7, 121.3)	103.9 (96.4, 111.4)	4.0 (1.8, 6.2)[c]
Model 3	115.1 (109.9, 120.3)	115.8 (112.5, 119.2)	111.2 (105.3, 117.1)	1.8 (0.02, 3.50)[c]
Abdominal intermuscular adipose tissue[b]				
Model 1	19.9 (18.6, 21.1)	18.4 (17.7, 19.2)c	15.9 (14.5, 17.2)	1.0 (0.6, 1.4)[c]
Model 2	18.6 (17.6, 19.7)	18.5 (17.8, 19.2)	17.2 (16.0, 18.4)	0.5 (0.1, 0.8)[c]
Model 3	18.3 (17.3, 19.2)	18.3 (17.7, 18.9)	18.1 (17.0, 19.1)	0.2 (−0.1, 0.5)
Abdominal subcutaneous adipose tissue[b]				
Model 1	427.8 (408.5, 447.2)	397.4 (384.9, 410.0)[c]	337.3 (315.5, 359.1)	19.6 (13.2, 26.0)[c]
Model 2	402.9 (386.8, 419.1)	399.0 (388.6, 409.4)	364.3 (346.1, 382.5)	8.4 (3.0, 13.8)[c]
Model 3	393.7 (384.4, 403.0)	395.0 (389.0, 401.0)	386.2 (375.6, 396.7)	1.5 (−1.6, 4.6)

Model 1: Adjusted for birthdate, race, study center, parental education, maternal diabetes, paternal diabetes, pre-high school physical activity, year 0 smoking status (never, former, current), and year 0 diet score.
Model 2: Model 1 + year 0 BMI
Model 3: Model 1 + weight change between year 0 and year 25

[a] Liver attenuation measured in Hounsfield units.

[b] Abdominal adipose depots measured in cubic centimeters.

[c] $p < 0.05$; 8–<12 year category is referent except in 1-year earlier menarche models

Table 3

Risk Ratios (and 95% CI) for Nonalcoholic Fatty Liver Disease[a] by Age at Menarche in Women from CARDIA.

	Age at menarche (years)			
	8–<12 (*n*=293)	**12–<14 (*n*=692)**	**14–18 (*n*=230)**	**1-yr earlier menarche**
Cases	74	132	29	
Model 1	1 (referent)	0.77 (0.61, 0.99)	0.49 (0.33, 0.72)	1.15 (1.07, 1.24)
Model 2	1 (referent)	0.83 (0.65, 1.06)	0.59 (0.40, 0.87)	1.10 (1.02, 1.19)
Model 3	1 (referent)	0.87 (0.68, 1.12)	0.71 (0.49, 1.04)	1.06 (0.98, 1.15)

Model 1: Adjusted for birthdate, race, study center, parental education, maternal diabetes, paternal diabetes, pre-high school physical activity, year 0 smoking status (never, former, current), and year 0 diet score.
Model 2: Model 1 + adjustment for BMI at year 0 exam.
Model 3: Model 2 + adjustment for weight change between year 0 and year 25.

[a] Nonalcoholic fatty liver disease is defined by liver attenuation < 51 Hounsfield units.

Table 4

Adjusted Means (and 95% CI) for Liver Attenuation and Abdominal Ectopic Fat Depots by Age at Menarche and Stratified by Race in Females from CARDIA.

	Age at menarche (years)			
	8–<12	**12–<14**	**14–18**	**1-yr earlier menarche**
	White females			
n	111	343	109	
LA[a]	56.2 (54.4, 58.1)	57.4 (56.3, 58.4)	58.2 (56.3, 60.1)	−0.5 (−1.1, 0.1)
VAT[b]	122.1 (111.0, 133.1)	119.3 (113.0, 125.5)	99.2 (87.9, 110.4)	6.9 (3.3, 10.4)[c]
IMAT[b]	20.3 (18.5, 22.1)	20.5 (19.4, 21.5)	17.9 (16.0, 19.7)	0.8 (0.2, 1.4)[c]
SAT[b]	351.0 (327.2, 374.9)	342.5 (329.1, 356.0)	296.1 (271.9, 320.4)	13.2 (5.5, 20.9)[c]
	Black females			
n	182	349	120	
LA[a]	55.3 (53.8, 56.9)	56.8 (55.7, 57.9)	58.7 (56.8, 60.6)	−0.5 (−1.0, 0.1)
VAT[b]	116.5 (108.4, 124.6)	114.7 (108.9, 120.4)	108.0 (98.0, 118.0)	2.0 (−0.8, 4.8)
IMAT[b]	17.3 (16.0, 18.6)	16.8 (15.9, 17.7)	16.5 (14.9, 18.1)	0.3 (−0.2, 0.7)
SAT[b]	450.0 (428.1, 471.8)	448.0 (432.4, 463.6)	421.8 (394.7, 448.8)	4.8 (−2.7, 12.4)

Abbreviations: LA, liver attenuation; VAT, visceral adipose tissue; IMAT, intermuscular adipose tissue; SAT, subcutaneous adipose tissue.

All models adjusted for birthdate, race, study center, parental education, maternal diabetes, paternal diabetes, pre-high school physical activity, year 0 smoking status (never, former, current), year 0 diet score, and year 0 BMI.

[a] Liver attenuation measured in Hounsfield units.

[b] Abdominal adipose depots measured in cubic centimeters.

[c] $p < 0.05$; 8–<12 year category is referent except in 1-year earlier menarche models