Research Article

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Age at menarche and non-alcoholic fatty liver disease

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Background & Aims: The goal of this study was to examine the association between age at menarche and non-alcoholic fatty liver disease (NAFLD) in Korean women and to explore whether any observed associations were mediated by adult adiposity.

Methods: A cross-sectional study was performed for 95,183 Korean women, aged 30 or older, who underwent a regular health screening examination between March 2011 and April 2013. Information regarding age at menarche was collected using standardized, self-administered questionnaires. The presence of fatty liver was determined using ultrasonographic findings. Poisson regression models with robust variance were used to evaluate the association between age at menarche and NAFLD.

Results: Of the 76,415 women evaluated in this study, 9601 had NAFLD. Age at menarche was inversely associated with the prevalence of NAFLD. In a multivariable-adjusted model, the prevalence ratios (95% CIs) for NAFLD comparing menarche at <12, 12, 14, 15, and 16–18 years to menarche at 13 years were 1.31 (1.18–1.45), 1.05 (0.97–1.13), 0.93 (0.87–0.99), 0.87 (0.82–0.93), and 0.78 (0.73–0.84), respectively (p for trend <0.001). Adjusting for adult BMI or percent fat mass (%) substantially reduced these associations; however, they remained statistically significant. The association between age at menarche and NAFLD was modified by age.

Conclusions: We identified an inverse association between age at menarche and NAFLD in a large sample of middle-aged women. This association was partially mediated by adiposity. The findings of this study suggest that obesity prevention strategies are needed in women who undergo early menarche to reduce the risk of NAFLD.

Keywords: Age at menarche; NAFLD; Early menarche; Obesity.

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Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; FLI, fatty liver index; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NAFLD, non-alcoholic fatty liver disease.

Introduction

Menarche represents a significant event in the reproductive life of a woman. In the last several years, age at menarche has received a great deal of attention concerning its implications for women's health [1]. Early menarche is considered an important medical and social problem, since it may result in increased morbidity and mortality in later life [2]. Indeed, a growing number of epidemiologic studies have suggested an association between early menarche and adverse outcomes including obesity, diabetes, insulin resistance, metabolic syndrome, cardiovascular disease, stroke, and mortality [1,3–8].

Non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of liver disease from simple steatosis to non-alcoholic steatohepatitis [9,10]. In addition to its potential to progress to cirrhosis or hepatocellular carcinoma [11], recent evidence from epidemiological studies have linked NAFLD to a substantial increase in risk for metabolic complications such as diabetes and cardiovascular disease [12–15]. These associations are supported by several reports that have described a close link between NAFLD and metabolic disorders such as obesity, insulin resistance, and metabolic syndrome [16,17], all of which are likely to develop in women who undergo early menarche. Therefore, it is hypothesized that the metabolic milieu in women who experience early menarche may trigger several pathophysiologic

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processes associated with NAFLD. In addition, the association between early menarche and NAFLD has implications for public health and clinical research as the average age at menarche has declined in recent years, coinciding with an increasing prevalence of obesity and NAFLD [18–20]. The association between early menarche and NAFLD remains largely unexplored and only one study has reported an inverse association between age at menarche and NAFLD among both Caucasian white and black women [21,22]. It should be noted that insulin resistance and reproductive factors such as parity, menopausal stage and use of oral contraceptives, which could influence the association with NAFLD, were not considered in the study described above.

Therefore, the goal of this study was to examine the association between age at menarche and NAFLD in a large sample of Korean women, and to explore whether any observed associations were caused by adult adiposity or insulin resistance.

Materials and methods

Study population

The Kangbuk Samsung Health Study was a cohort study comprising Korean men and women who underwent a comprehensive annual or biennial examination at the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea [23,24]. The study population for the present study consisted of women, aged 30 or older, who underwent a comprehensive health examination at the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea from March 2011 to April 2013 (n = 95,183).

We excluded 18,768 participants for various reasons, chiefly missing data for abdominal ultrasonography, alcohol intake, or age at menarche (n = 3785); a past history of a malignancy (n = 3870); alcohol intake of ⩾20 g/day (n = 4730) [25]; known liver disease or use of medications for liver disease (n = 5037); positive serologic markers for hepatitis B or C virus (n = 3086); use of medications associated with NAFLD within the past year such as valproate, amiodarone, methotrexate, tamoxifen, or corticosteroids (n = 905) [25]; and a reported age at menarche greater than 18 years, which may reflect an underlying pathological issue (n = 4839). Because some individuals met more than one exclusion criterion, the total number of patients eligible for the study was 76,415. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, and the requirement for informed consent was waived because we used non-identified retrospective data routinely collected during the health screening process.

Measurements

All examinations were conducted at Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon. Information regarding reproductive factors was collected using standardized, self-administered questionnaires that asked about regularity and frequency of menstrual periods, menopausal status, and use of oral contraceptives and hormone replacement therapy. Age at menarche was defined as the age at the first menstrual period (in years). The question asked, "At what age did your menstrual periods begin?". Response categories were "10 or younger, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 or older." The normal physiological age range at menarche was considered to be less than 19 years. Early menarche was defined as onset of menstruation occurring before the age of 12 [26]. Parity was derived from the number of reported live births and stillbirths. Data on demographic characteristics, smoking status, alcohol consumption, regular exercise, education level, medical history, and medication use were also collected by standardized, self-administered questionnaires as previously described [23,24]. Physical activity levels were assessed using the Korea-validated version of the International Physical Activity Questionnaire (IPAQ) short form and were classified into three categories: inactive, minimally active, and health-enhancing physically active (HEPA) [27,28]. Recalled body weight was self-reported via questionnaire at recruitment.

Height, weight, and body composition were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. The percentage of body fat was estimated using a multi-frequency bioimpedance analyzer with eight point tactile electrodes (InBody 720, Biospace Co., Seoul Korea), which was validated with respect to reproducibility and accuracy for body composition [29]. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2). We classified BMI according to the criteria proposed for Asian populations [30]. Measurements for serum biochemical parameters, including glucose, uric acid, hemoglobin A1c, insulin, total cholesterol, triglycerides, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) are described in detail elsewhere [23,24]. The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul (Korea) is accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL); the laboratory participates in the CAP (College of American Pathologists) Survey Proficiency Testing. Hypertension was defined as a systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg, or current use of antihypertensive medication. Diabetes was defined as a fasting serum glucose ⩾126 mg/dl, hemoglobin A1c ⩾6.5%, or current use of insulin or antidiabetic medications.

Abdominal ultrasounds were performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI, USA) by eleven experienced radiologists, all of whom were unaware of the aims of this study. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma [31]. The inter-observer reliability and intra-observer reliability for fatty liver diagnosis were substantial (kappa statistic of 0.74) and excellent (kappa statistic of 0.94), respectively [23].

Statistical analyses

Characteristics of the study participants were explored according to age at menarche, which was categorized into the following groups: <12 (early menarche), 12, 13 (the reference category), 14, 15, and 16–18 years. To test for linear trends, category numbers were used as continuous variables in regression models.

To evaluate the association of NAFLD across categories of ages at menarche, we used robust Poisson regression with robust variance to estimate prevalence ratios with 95% confidence intervals (CIs) for NAFLD. We used four models to progressively reduce confounding associations. We initially adjusted for age, and further adjusted for study center (Seoul, Suwon), year of screening exam, smoking (never, past, current, or unknown), alcohol intake (0, <10, ⩾10 g/d, or unknown), physical activity level (inactive, minimally active, HEPA, or unknown) and educational level. We next included the following reproductive factors: parity (no child, one or two children, three or more children), menopausal status (pre-menopause, late menopausal transition, early post-menopause or late post-menopause) [32], use of the oral contraceptive (ever or never), and use of hormone replacement therapy. Finally, the analysis was further adjusted for body weight at age 20. To assess whether the association between age at menarche and the prevalence of NAFLD was mediated by BMI, percent fat mass (%) or HOMA-IR, we included these variables in multivariable models.

We performed stratified analyses in pre-specified subgroups defined by menopause (yes *vs.* no), age (<50 *vs.* ⩾50 years), parity (ever *vs.* never), smoking (never smoker *vs.* ex- or current smoker), alcohol intake (<10 *vs.* ⩾10 g of alcohol per day) and physical activity (no HEPA *vs.* HEPA); interactions between subgroups were tested using likelihood ratio tests comparing models with and without multiplicative interaction terms. We also examined the association between age at menarche and fatty liver index (FLI) as a surrogate marker of NAFLD in a sensitivity analysis. The FLI was calculated according to the published formula: Fatty liver index = $(e^{0.953*\log_e(\text{triglycerides})+0.139*\text{BMI}+0.718*\log_e(\text{ggt})+0.053*\text{waist circumference}-15.745})/(1+e^{0.953*\log_e(\text{triglycerides})+0.139*\text{BMI}+0.718*\log_e(\text{ggt})+0.053*\text{waist circumference}-15.745}) \times 100$ [33]. Subjects were divided into three groups: FLI <30, 30⩽ FLI <60 and FLI ⩾60 [33].

Lastly, we examined the association of age at menarche with NAFLD and its severity. In individuals with NAFLD, serum markers of fibrosis were used to assess severity. NFS was calculated according to the published formula: NFS = $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glycemia or diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dl) [34]. The AST/platelet ratio index (APRI) was calculated as AST/ULN (upper limit of normal)/Platelets $\times$ 100 [35]. The AST/ALT ratio was calculated as ratio of AST to ALT values [36].

All *p* values were two-tailed, and values of p <0.05 were considered statistically significant. We used STATA version 13.0 (Stata Corp., College Station, TX, USA) for data analysis.

Results

The baseline characteristics of subjects by categories of ages at menarche are presented in Table 1. The mean age and BMI of