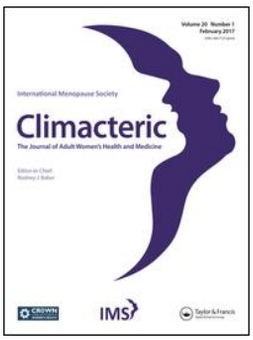

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ORIGINAL ARTICLE

Lack of association between early menopause and non-alcoholic fatty liver disease in postmenopausal women

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ABSTRACT

Background: The possibility of an association between early menopause and the risk of non-alcoholic fatty liver disease (NAFLD) is as yet unclear.

Methods: The subjects consisted of 4354 postmenopausal women who participated in the 2010–2012 Korea National Health and Nutrition Examination Survey. Early, normal, and late menopause were defined as age at menopause <45 years, 45–54 years, and ≥55 years, respectively. NAFLD was defined by a hepatic steatosis index of >36.

Results: When compared with normal menopausal women, early or late menopausal women had no significant differences in the odds ratios (ORs) of NAFLD: OR = 1.05, 95% confidence interval (CI), 0.83–1.32 and OR = 1.02, 95% CI, 0.75–1.39, respectively. These results remained similar after adjustment for known risk factors for NAFLD, reproductive factors, and comorbidities. The OR for NAFLD per 1-year increase in age at menopause was 1.01 (95% CI, 0.99–1.03; $p = 0.329$). The prevalence of advanced fibrosis was 2.1% (95% CI, 0.7–6.4%), 2.2% (95% CI, 1.3–3.8%), and 3.9% (95% CI, 1.2–12.2%) in early, normal, and late menopausal women, respectively.

Conclusions: This study provides no evidence for an association of early menopause with NAFLD risk. However, NAFLD-related advanced fibrosis is highly prevalent in postmenopausal women.

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Age at menopause; early menopause; non-alcoholic fatty liver disease

Introduction

As life expectancy increases, women live two-fifths of their life in the postmenopausal state. Menopause is a major transition point in the physical and psychological health of women, and the related health problems have been of interest to the scientific and medical community. Assorted changes in endogenous hormones, lipid profiles, and body composition predispose postmenopausal women to a risk of developing cardiovascular disease[1] and diabetes[2]. The age at menopause is also a key clinical determinant of longevity and future risk of morbidity and mortality[3]. Accumulating evidence indicates that early menopause is positively associated with coronary heart disease and stroke[4], diabetes[5], and all-cause mortality[6].

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common chronic liver disease, with an estimated prevalence of 25% in the global adult population[7]. NAFLD has been well established to be closely linked to cardiometabolic abnormalities, including obesity, diabetes, and dyslipidemia[8–11], that together contribute to cardiovascular disease. The protective effect of estrogen on liver fibrogenesis has been reported in an animal model[12] and in an observational study of patients with NAFLD[13], providing evidence for early menopausal women to be at higher risk of developing NAFLD fibrosis. These findings are further supported by a recent study of histologically proven NAFLD, which showed a strong association between duration of estrogen deficiency and fibrosis risk in postmenopausal women with NAFLD[14]. Nonetheless, whether early menopause is associated with the risk of NAFLD, which is a fundamental question for developing the disease, remains uncertain. In addition, whether the relationship between early menopause and the severity of NAFLD fibrosis extends to the general population, beyond the highly selected patient cohort, has not been explored.

This study aimed to examine the association of early menopause with the risk of NAFLD and NAFLD-related advanced fibrosis in a representative Korean adult population of the Korea National Health and Nutrition Examination Survey (KNHANES).

Methods

Sample population

The KNHANES is a series of cross-sectional national health and nutrition surveys designed to provide representative

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prevalence estimates for a variety of health measures and conditions. The KNHANES is conducted by the Korean Centers for Disease Control. The survey design is a complex, stratified, multistage probability sampling of the civilian, non-institutionalized Korean population. The procedures used to select the sample and to conduct the interviews and examinations have been previously specified[15]. This survey included an interview to obtain information concerning an individual's health history, health behaviors, and risk factors. A subsequent health examination was performed at a mobile examination center.

Our analyses included data from the KNHANES 2010–2012, in which 31,596 individuals were sampled as subjects, and of these, 25,534 individuals participated in the survey: the response rate was 81%. Of this number, the subjects who met the following criteria were excluded based on our protocol: male ($n = 11,616$); premenopausal women ($n = 7659$); menopausal status not known ($n = 190$); and missing data on menopausal status ($n = 881$). At baseline, a total of 5188 postmenopausal women were selected for this analysis. Of these, 834 women were excluded from the analysis because of unknown age at menopause ($n = 71$), alcohol consumption >70 g/week ($n = 222$), hepatitis B ($n = 145$), and incomplete data for components in the NAFLD prediction model ($n = 396$), thereby leaving 4354 women to be included in the final analysis. Informed consent was obtained from all participants, and the protocol was approved by the Institutional Review Board of the Korean Centers for Disease Control.

Definition of early menopause

The health interview was performed by trained interviewers at the mobile examination center. Information on menopausal status was obtained and assessed through open questions addressed to the participants. Age at menopause was defined as the self-reported age at menopause. Women were considered of postmenopausal status based on self-reporting of their last menstrual episode >1 year. Early menopause was defined as age at menopause <45 years. Surgical menopause was also regarded as menopause. Normal and late menopause were defined as age at menopause 45–54 years and ≥55 years, respectively.

Definition of NAFLD

NAFLD was defined using a validated hepatic steatosis index calculated as follows: 8 × [alanine aminotransferase/aspartate aminotransferase (AST) ratio] + body mass index (+2, if diabetes; +2, if female)[16]. The optimal cut-off value for NAFLD was set at >36. Diabetes mellitus was defined based on use of insulin or oral hypoglycemic agents or fasting plasma glucose of ≥126 mg/dl. In the subpopulation with NAFLD, the AST-to-platelet ratio index (APRI)[17] and the fibrosis-4 index (FIB-4)[18] were used to evaluate liver fibrosis. Their formula were as follows: APRI = [AST (upper limit of normal) / platelet count (10^9/l)] × 100, where the upper limit of normal AST level was set at 29 IU/l for women[19]; and FIB-4 = [age × AST] / [platelets (10^9/l) × (alanine aminotransferase)$^{1/2}$]. The cut-off values for advanced fibrosis (≥F3) were set at 1 and 2.67 for APRI and FIB-4, respectively.

Covariates and potential confounders

Sociodemographic variables, smoking, alcohol intake, physical activity, self-reported comorbidities (e.g. diabetes, hypertension, hypercholesterolemia, and cardiovascular disease), and reproductive factors (age at menarche, parity, oral contraceptive use, and hormone replacement therapy use) were considered covariates. Participants were diagnosed as hypertensive if systolic pressure was ≥140 mmHg, diastolic pressure was ≥90 mmHg, or consuming antihypertensive medication. Dyslipidemia was defined as a cholesterol level of ≥240 mg/dl or by the intake of cholesterol-lowering medication. Physical activity was assessed weekly by means of metabolic equivalent unit (MET)-hours, which was calculated using the following formula: MET level of each activity × hours × frequency per week, where MET levels of walking, moderate activity, and rigorous activity are 3.3 METs, 4 METs, and 8 METs, respectively. Personal income was calculated by household income / $\sqrt{}$number of household members and equalized to four groups based on sex and age.

Statistical analysis

A formal sample size should have been calculated a priori; however, as the data were readily available from the KNHANES, sample size calculations were not performed. Sample weights were included in the estimation process for all of the analyses to reflect the differential probabilities for selection, non-response, and non-coverage[15]. All analyses were performed using Complex Samples in SPSS statistics (version 25.0; IBM Corp., Armonk, NY, USA), which provides the specialized statistics for complex sample designs, such as stratified, clustered, or multistage sampling. The data were presented as weighted means or weighted proportions with standard errors for continuous or categorical variables, respectively. Differences between menopausal age groups were examined with an *F*-test in a general linear model for continuous variables and the Rao–Scott adjusted chi-square test for categorical variables. Because the distribution of MET-hours per week data was skewed, analysis of this variable was based on natural log transformations.

Analyses were adjusted for potential confounders in consecutive models, with the normal menopausal group as a reference. The first model was adjusted for age. Subsequently, we added known NAFLD risk factors to the model, including smoking status (ever vs. never), alcohol consumption (yes vs. no), physical activity (continuous), and personal income (low, mid-low, mid-high, and high). The third model included all covariates from the previous model, along with reproductive factors: age at menarche (continuous); parity (continuous); and duration (by months) of oral contraceptive consumption and hormone replacement therapy (continuous). In the final multivariable model, we further adjusted the analyses for the

following self-reported comorbidities: diabetes, hypertension, dyslipidemia, and cardiovascular disease.

We also performed a couple of alternative analyses to investigate whether the result of main analysis is altered in the subgroup analyses. Because hormone replacement therapy and smoking are significant factors of age at menopause, we restricted the analysis to subjects who did not report ever smoking and the use of hormone replacement therapy. We restricted the analysis also to women who had no history of hysterectomy and/or oophorectomy.

Results

The demographic, clinical, and health-related behavioral characteristics of the participants are presented in Table 1. The mean age of the study population was 62.5 years (95% confidence interval [CI], 62–63 years) and age at menopause was 48.8 years (95% CI, 48.6–49.0 years), respectively. Health-related behavioral and comorbidity factors were comparable among menopausal age groups. NAFLD was present in 26.7% (95% CI, 22.6–31.4%) of early menopausal women, 25.8% (95% CI, 23.9–27.8%) of normal menopausal women, and 26.2% (95% CI, 20.9–32.3%) of late menopausal women.

The odds ratios (ORs) for the association between menopausal age groups and NAFLD are presented in Table 2. Compared with normal menopausal women, the ORs of NAFLD in the early or late menopausal groups were not significantly different (OR = 1.05, 95% CI, 0.83–1.32; OR = 1.02, 95% CI, 0.75–1.39, respectively). The results remained similar after adjustment for known risk factors for NAFLD, reproductive factors, and comorbidities. The OR for NAFLD per 1-year increase in age at menopause was 1.01 (95% CI 0.99–1.03; $p = 0.329$). When the analyses were stratified by type of menopause, the results did not change either. After restricting the population to the subjects who had never smoked and never used hormone replacement therapy, the association between early menopause and NAFLD was similar to that shown in model 4 of Table 2.

Among 1104 women with NAFLD, the prevalence of advanced fibrosis, defined by APRI >1 or FIB-4 > 2.67, was not significantly different among menopausal age groups ($p = 0.643$): 2.1% (95% CI, 0.7–6.4%), 2.2% (95% CI, 1.3–3.8%), and 3.9% (95% CI, 1.2–12.2%) in early, normal, and late menopausal women, respectively.

Discussion

In this population-based study, we found no evidence of an association between early menopause and NAFLD. This lack of association was solid even after adjustment for a wide range of potential intermediate risk factors for NAFLD including health-related behavioral, reproductive, and comorbidity factors. The effect estimates were of similar magnitude after excluding participants who had experienced surgical menopause, ever been smokers, and ever used hormone replacement therapy. Although several studies have investigated the impact of menopause on NAFLD, reporting an increased susceptibility to development of NAFLD[20,21], no study has explored an association between age at menopause onset and the risk of NAFLD. Until results contrary to our findings are obtained, this study provides no evidence for an association between age at menopause and NAFLD risk.

The prevalence of NAFLD seems to be higher in postmenopausal women compared with premenopausal subjects[9]. Conceptually, early onset of menopause is more predisposed to the risk of NAFLD due to early cessation of the protective effects of endogenous estrogen[21]. Animal studies have shown that estradiol suppresses the induction of hepatic

Table 1. Demographic, behavioral, and clinical characteristics of the study sample ($n = 4354$).

Characteristic	*Early menopause*	*Normal menopause*	*Late menopause*	*p-Value*
n	672	3225	457	
Age (years)	63.4 (0.7)	61.7 (0.2)	66.7 (0.5)	<0.001
Menopausal age (years)	39.7 (0.2)	49.7 (0.1)	56.4 (0.1)	<0.001
Time since menopause (years)	23.7 (0.7)	12.0 (0.2)	10.3 (0.4)	<0.001
Age at menarche (years)	15.9 (0.1)	16.0 (0.1)	16.6 (0.1)	<0.001
Parity (*n*)	3.4 (0.1)	3.0 (0.0)	3.5 (0.1)	<0.001
OCP use, duration (months)	3.5 (0.6)	5.4 (0.4)	6.5 (1.3)	0.015
HRT use, duration (months)	6.9 (1.1)	4.3 (0.4)	4.3 (0.9)	0.067
Ever HRT use (%)	14.9 (1.7)	15.3 (0.8)	11.8 (1.8)	0.279
Hysterectomy or oophorectomy (%)	39.2 (2.5)	9.1 (0.7)	1.0 (0.4)	<0.001
Personal income[a], high class (%)	20.6 (2.0)	23.3 (0.9)	24.1 (2.5)	0.798
Ever smoking (%)	9.6 (1.5)	7.6 (0.7)	7.5 (1.7)	0.403
Alcohol consumption[b] (%)	45.1 (2.6)	50.1 (1.2)	43.3 (2.6)	0.023
Body mass index (kg/m^2)	24.4 (0.2)	24.2 (0.1)	24.6 (0.2)	0.084
Waist circumference (cm)	82.5 (0.6)	81.9 (0.2)	83.7 (0.5)	0.003
Physical activity (MET-hours)[c,d]	6.4 (0.6)	5.7 (0.3)	3.8 (0.5)	0.001
Diabetes (%)	17.2 (1.7)	13.7 (0.8)	15.6 (2.2)	0.119
Hypertension (%)	49.0 (2.7)	44.6 (1.1)	61.4 (3.1)	<0.001
Dyslipidemia (%)	26.3 (2.1)	26.2 (1.0)	31.1 (2.8)	0.211
Cardiovascular disease (%)	5.7 (0.9)	4.8 (0.5)	8.4 (1.7)	0.048
Hepatic steatosis index >36 (%)	26.7 (2.2)	25.8 (1.0)	26.2 (2.9)	0.917

Data reported as weighted percentage or mean (standard error). HRT, hormone replacement therapy; OCP, oral contraceptive pill.
[a]Monthly personal income was calculated by household income / √number of household members, and equalized to four groups according to gender and age.
[b]Alcohol consumption defined as any reported alcohol intake but <70 g per week.
[c]Physical activity is recorded in metabolic equivalent unit (MET)-hours per week.
[d]Log-transformed.

Table 2. Associations of age at menopause with the risk of non-alcoholic fatty liver disease in postmenopausal women ($n = 4354$).

Type of menopause	*Unadjusted*	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Natural or surgical					
Early	1.05 (0.83–1.32)	1.07 (0.85–1.36)	1.08 (0.85–1.37)	1.04 (0.82–1.33)	0.97 (0.76–1.25)
Normal	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
Late	1.02 (0.75–1.39)	1.11 (0.81–1.51)	1.11 (0.81–1.52)	1.15 (0.83–1.57)	1.08 (0.76–1.53)
Natural ($n = 3821$)					
Early	1.08 (0.82–1.41)	1.18 (0.89–1.57)	1.19 (0.89–1.59)	1.13 (0.84–1.51)	1.05 (0.79–1.41)
Normal	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
Late	1.08 (0.79–1.47)	1.15 (0.84–1.58)	1.16 (0.84–1.59)	1.21 (0.88–1.67)	1.12 (0.79–1.58)
Surgical ($n = 533$)					
Early	0.67 (0.43–1.06)	0.65 (0.41–1.02)	0.68 (0.43–1.08)	0.71 (0.44–1.14)	0.73 (0.43–1.25)
Normal	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)	Reference (1.00)
Late	0.80 (0.16–4.13)	0.92 (0.18–4.65)	0.84 (0.16–4.43)	0.83 (0.16–4.44)	0.90 (0.05–18.1)

Data reported as odds ratio (95% confidence interval). Model 1, adjusted for age; model 2, same as model 1 + smoking, alcohol consumption, physical activity, and personal income; Model 3, same as model 2 + age at menarche, parity, and duration of oral contraceptive use and hormone replacement therapy use; Model 4, same as model 3 + diabetes, hypertension, dyslipidemia, and cardiovascular disease.

fibrosis and estradiol metabolism is an important determinant for protective effects against fibrosis[12,22]. Estradiol deficiency is also associated with the severity of NAFLD fibrosis in postmenopausal women[13,14]. In accordance with the aforementioned effects of estrogen, a previous study reported a protective potential of hormone replacement therapy against NAFLD[23]. However, the present study neither supports these findings nor extends the unfavorable effect of estrogen loss on NAFLD to the general population. Our results did not indicate any beneficial effect of hormone replacement therapy on NAFLD risk (OR for use = 0.9; 95% CI, 0.7–1.2).

Our findings shed some light on NAFLD fibrosis in the general population and showed that the prevalence of advanced fibrosis (≥F3) was approximately 2.5% (95% CI, 1.5–3.7%) among postmenopausal women with NAFLD. This prevalence is about 1.5 times the estimate reported in the US population[24], indicating highly prevalent advanced fibrosis in postmenopausal women with NAFLD. Considering the fact that age is an important factor in the prediction model for NAFLD fibrosis, the observed higher prevalence of NAFLD-related advanced fibrosis might be partially attributable to differences in mean age of the participants in the two study groups (62.5 vs. 47.3 years). This finding emphasizes that reproductive information on menopausal status may be important to assess the severity of NAFLD to prevent disease progression to cirrhosis in postmenopausal women.

A health-related behavioral factor, such as smoking, is closely linked to age at menopause onset. A previous study has reported that smokers reach menopause 2 years earlier on average than non-smokers[25]. Early menopause has also been linked to increased risk of cardiovascular diseases, and its risk factors are also correlated with NAFLD. Consequently, the link between early menopause and NAFLD is plausibly confounded by these factors. However, in our analysis, adjusting for these variables had no influence on the results, making it less likely that these factors explained the association in question.

The strengths of the present study are that the data were representative of the Korean population and collected using standardized measurements. Although this study makes important contributions to the literature, several limitations exist. Age at menopause is reliant on retrospective self-reporting, which is subject to faulty memory and reporting bias and may be affected by reporting inaccuracy. However, menopause is considered an important event by most women, and the validity and reproducibility of self-reported age at menopause is fairly good[26]. Because of the absence of imaging or histological diagnosis of NAFLD, we adopted operational criteria for defining NAFLD based on a predictive model that has been widely validated. The cross-sectional nature of the study limited our ability to draw causal inferences from the relationships observed. Finally, the survey participants were sampled only from the non-institutionalized Korean population, and we may have underestimated the prevalence of NAFLD because participants who were physically unable to attend the mobile examination center were excluded in our analysis.

In conclusion, this large population-based study found that early menopause was not associated with NAFLD. This association remained unchanged after adjustment for socio-demographic, health-related behavioral, reproductive, and comorbidity factors. Early menopause was also not linked to NAFLD-related advanced fibrosis, despite its high prevalence in postmenopausal women. Our results emphasize the need for further study, in a preferred prospective fashion, to explore the precise relationship between age at menopause onset and the risk of NAFLD.

Potential conflict of interest No potential conflict of interest was reported by the authors.

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