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Circulating Estradiol as an Independent Risk Factor for Metabolic Dysfunction–Associated Steatotic Liver Disease and Fibrosis Risk in Women: Evidence From a Multicenter Health-Checkup Cohort

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ABSTRACT

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) shows marked sexual dimorphism, with estrogen believed to be liver-protective. This study investigated the independent association between circulating estradiol levels, MASLD, and advanced fibrosis (defined by fibrosis index-4 [FIB-4] ≥ 1.3) in Korean women, utilizing stratified analyses by age and body mass index (BMI) to identify context-dependent effects.
Methods: We analyzed cross-sectional data from the Korean Health Screening-Based Metabolic Dysfunction-Associated Steatotic Liver Disease Registry, including 995 women (352 with MASLD). Multivariable logistic regression was used to evaluate the association of log2-transformed estradiol with MASLD and high-risk fibrosis, stratified by age (proxy for menopausal status, ≥ 50 vs. < 50 years) and BMI (≥ 25 vs. < 25 kg/m^2).
Results: In multivariable analysis of the entire cohort, lower estradiol levels were independently associated with MASLD (adjusted odds ratio [aOR], 0.88; 95% confidence interval [CI], 0.79–0.98; $P = 0.025$). This association was particularly evident in women with lower BMI (aOR, 0.84; 95% CI, 0.71–0.98), but not in high BMI women, suggesting attenuation of estrogen's metabolic protection in the presence of obesity. Estradiol demonstrated a strong and consistent inverse association with FIB-4 ≥ 1.3 (aOR, 0.65; 95% CI, 0.56–0.75; $P < 0.001$). This protective antifibrotic effect remained robust across

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The authors have no potential conflicts of interest to disclose.

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Data sharing statement is provided in Supplementary Material 1.

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BMI strata and was also significant in women aged ≥ 50 years (aOR, 0.70; 95% CI, 0.59–0.82; $P < 0.001$).

Conclusion: Low circulating estradiol independently increases the risk of MASLD and high-risk fibrosis in women. While its protective effect against steatosis weakens with obesity, its antifibrotic effect remains strong across all subgroups. Estradiol may serve as an important hormonal marker for risk stratification in female MASLD patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT06843421

Keywords: Metabolic Dysfunction–associated Steatotic Liver Disease; Estradiol; Liver Fibrosis; Women; Risk Stratification

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, affecting nearly one in three adults.[1,2] Its prevalence continues to rise in parallel with obesity, diabetes, and other metabolic disorders, and MASLD has become a major contributor to cirrhosis, hepatocellular carcinoma, and cardiovascular disease.[3,4] A notable feature of MASLD is its marked sexual dimorphism.[5] Despite higher rates of obesity, women are relatively protected against MASLD and metabolic complications until menopause, whereas men and postmenopausal women experience a substantially higher disease burden.[6,7]

Estrogen is thought to play a central role in this disparity. Preclinical studies consistently demonstrate that estrogen protects the liver by reducing lipid accumulation, improving insulin sensitivity, and attenuating inflammation and oxidative stress.[7] Epidemiological evidence also supports this protective effect: MASLD prevalence and severity rise sharply after menopause, and early or premature menopause is associated with a disproportionately higher risk of steatosis and fibrosis.[8] These findings reinforce the concept of an "ovary–liver axis," linking ovarian function to hepatic health.[9]

Fibrosis progression represents the strongest predictor of adverse outcomes in MASLD, and noninvasive indices such as the fibrosis index-4 (FIB-4) score are widely applied in clinical practice.[2] While experimental and epidemiological data suggest that estrogen is a key regulator of fibrosis, clinical studies on hormone replacement therapy have reported conflicting results, with outcomes varying according to hormone formulation, route of administration, and duration of use.[10] A key limitation in many of these studies is the failure to adequately account for confounding factors such as BMI and menopausal status, which could significantly modulate the effect of estrogen.

Against this background, we investigated the association between circulating estrogen levels, MASLD, and fibrosis in a large, health screening–based Korean cohort. To address the critical knowledge gap identified above, we conducted stratified analyses by both body mass index (BMI) and age to examine whether the association between estradiol and MASLD-related outcomes varied across metabolic and age-related contexts.

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METHODS

Study population

This study was conducted using data from the Korean Health Screening-Based Metabolic Dysfunction-Associated Steatotic Liver Disease Registry (K-MASLD Registry; ClinicalTrials.gov identifier NCT06843421). The registry was designed as a multicenter retrospective cohort to evaluate the association of hepatic steatosis with cardiovascular disease incidence and other chronic metabolic diseases. Study participants were recruited from university-affiliated health screening centers. Although data collection was initially planned across six hospitals, complete data were ultimately obtained from four centers, yielding a total of 3,466 participants between January 2020 and December 2023. Recruitment was based on abdominal ultrasonography: 1) individuals with hepatic steatosis and metabolic dysfunction were classified as the MASLD group, and 2) those without steatosis were classified as controls. To enhance statistical power for group comparisons, MASLD and non-MASLD participants were enrolled in approximately a 1:1 ratio; therefore, the prevalence of MASLD in this registry does not reflect its true prevalence in the general population. According to the ClinicalTrials.gov registration (NCT06843421), eligible participants were adults undergoing routine health screening with available abdominal ultrasonography and metabolic laboratory data, and without known chronic liver diseases other than MASLD. The present study represents a predefined sub-analysis of this registry, focusing specifically on women with available serum estradiol measurements to address sex-specific hormonal associations with MASLD and fibrosis risk.

For the present analysis, men (n = 2,065) and participants with missing serum estradiol data (n = 403) were excluded from the total registry population.

Among women classified as having MASLD, individuals with moderate-to-severe alcohol consumption (n = 3) were additionally excluded to avoid inclusion of alcohol-related liver disease or metabolic dysfunction–associated alcohol-related liver disease. The final analytic cohort consisted of 995 women and is summarized in the study flowchart (**Supplementary Fig. 1**).

Although the overall registry includes both men and women, the inclusion and exclusion criteria applied in the current analysis are consistent with the original registry design and were further refined to address the specific research question of this study.

Data collection and definitions

Baseline demographic and clinical variables, including age, BMI, hypertension, diabetes mellitus, hyperlipidemia, liver function tests, lipid profile, platelet count, hemoglobin A1c, thyroid function, and sex hormones, were obtained from the health screening database.

MASLD was defined according to current international consensus criteria, based on evidence of hepatic steatosis on ultrasonography in the presence of metabolic dysfunction, and after exclusion of moderate-to-severe alcohol intake.[11] Moderate alcohol use was defined as an average alcohol consumption of ≥ 20 g/day in women, based on self-reported questionnaires that assessed both drinking frequency and amount; weekly intake was calculated by multiplying frequency and quantity and converted into grams of ethanol.

The FIB-4 was calculated as an estimate of fibrosis risk, with a cutoff of 1.3 used to stratify groups.[12] Serum estradiol levels exhibited a highly right-skewed distribution, with substantial

clustering at the lower detection limit (5 pg/mL) and a long upper tail (**Supplementary Fig. 2A**). To reduce the influence of extreme values, stabilize variance, and improve model robustness, estradiol levels were $\log_2$-transformed prior to regression analyses. This transformation also allows effect estimates to be interpreted per doubling of estradiol concentration. Although some residual right-skewness persisted after transformation, this approach was considered the most appropriate given the distributional characteristics of the data (**Supplementary Fig. 2B**).

BMI was categorized using a cutoff of 25 kg/m^2, in line with Asian population–specific recommendations, where both 23 and 25 kg/m^2 are used, and 25 kg/m^2 is commonly applied to define a high-risk group in clinical and epidemiological practice.

Age was stratified at 50 years, a commonly used epidemiological proxy for menopausal status in the absence of direct menopause data, based on evidence that the mean and median ages at natural menopause among Korean women are approximately 49–50 years.[13]

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and percentages. Differences between groups were compared using the Student's *t*-test or χ^2 test, as appropriate. Univariable logistic regression analyses were performed to evaluate associations between clinical variables and outcomes (MASLD and FIB-4 ≥ 1.3).

For models with FIB-4 ≥ 1.3 as the outcome, age, aspartate aminotransferase (AST), alanine transaminase (ALT), and platelet count were not included in the multivariable analyses because they are components of the FIB-4 formula, which would otherwise result in multicollinearity. To reduce further multicollinearity, only the most representative or statistically significant variables from overlapping domains were retained (e.g., ALT among liver enzymes, HbA1c instead of diabetes status).

To evaluate the incremental predictive value of estradiol for MASLD, receiver operating characteristic (ROC) curve analyses were performed. A base clinical model was defined a priori, incorporating age, BMI, hypertension, alanine aminotransferase, HbA1c, triglycerides, and other metabolic covariates. Model discrimination was assessed using the area under the ROC curve (AUC). Sequential models were compared, including the base model alone, the base model with HDL-C, and the base model with HDL-C and $\log_2$-transformed estradiol. Pairwise comparisons of AUCs were conducted using DeLong's test for correlated ROC curves.

All analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and a two-tailed *P* value < 0.05 was considered statistically significant.

Ethics statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of Ajou University Hospital (IRB No. AJOUIRB-DB-2024-310) and by the respective IRBs of the participating centers. The requirement for written informed consent was waived due to the retrospective nature of the study and the use of de-identified health screening data.

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RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics of the study population. A total of 995 women with available serum estradiol data were included, of whom 352 (35.4%) had MASLD and 643 (64.6%) did not. Women with MASLD were significantly older (60.1 ± 8.3 vs. 57.3 ± 10.0 years, $P < 0.001$) and had higher BMI (26.1 ± 3.1 vs. 22.7 ± 2.9 kg/m^2, $P < 0.001$) compared to those without MASLD. The prevalence of hypertension (41.5% vs. 21.0%), diabetes mellitus (21.0% vs. 8.6%), and dyslipidemia (47.4% vs. 26.4%) was also markedly higher in the MASLD group (all $P < 0.001$). Alcohol consumption patterns differed modestly across groups ($P = 0.019$).

Regarding laboratory parameters, women with MASLD had significantly higher levels of AST, ALT, GGT, ALP, HbA1c, and triglycerides, as well as lower HDL-C (all $P < 0.001$). Serum albumin and platelet count were modestly higher in the MASLD group, while total bilirubin, low-density lipoprotein cholesterol (LDL-C), total cholesterol, thyroid-stimulating hormone, and free T4 did not differ significantly.

Notably, serum estradiol levels were significantly lower in women with MASLD compared to those without (28.7 ± 62.4 vs. 55.9 ± 98.0 pg/mL, $P < 0.001$) (**Supplementary Fig. 3A**).

Overall, women with MASLD exhibited a more adverse metabolic and biochemical profile, along with markedly lower circulating estradiol levels.

Table 1. Baseline characteristics of female patients with available estradiol data

Variables	All (N = 995)	No MASLD (n = 643)	MASLD (n = 352)	*P* value
Age, yr	58.27 ± 9.54	57.29 ± 10.04	60.07 ± 8.27	< 0.001
BMI, kg/m^2	23.91 ± 3.38	22.72 ± 2.88	26.08 ± 3.13	< 0.001
HTN	281 (28)	135 (21)	146 (41)	< 0.001
DM	129 (13)	55 (8.6)	74 (21)	< 0.001
Dyslipidemia	337 (34)	170 (26)	167 (47)	< 0.001
Alcohol				0.019
No	570 (57)	356 (55)	214 (61)	
Mild	414 (42)	276 (43)	138 (39)	
Moderate-severe	11 (1.1)	11 (1.7)	0 (0)	
AST, U/L	30.28 ± 27.81	27.74 ± 11.87	34.94 ± 43.58	< 0.001
ALT, U/L	25.27 ± 17.80	20.93 ± 11.03	33.20 ± 24.03	< 0.001
GGT, U/L	24.91 ± 24.87	20.74 ± 17.63	32.51 ± 33.06	< 0.001
ALP, U/L	71.69 ± 21.06	68.53 ± 21.23	77.45 ± 19.49	< 0.001
Total bilirubin, mg/dL	0.70 ± 0.31	0.69 ± 0.31	0.70 ± 0.32	0.498
Albumin, g/dL	4.70 ± 0.29	4.68 ± 0.28	4.74 ± 0.28	0.002
Platelet count, ×10^9/L	260.47 ± 59.79	257.26 ± 60.51	266.34 ± 58.06	0.011
HbA1c, %	5.78 ± 0.79	5.60 ± 0.64	6.11 ± 0.91	< 0.001
Triglyceride, mg/dL	101.30 ± 64.45	83.56 ± 43.40	133.70 ± 81.79	< 0.001
HDL-C, mg/dL	63.75 ± 16.74	68.38 ± 16.51	55.30 ± 13.57	< 0.001
LDL-C, mg/dL	124.68 ± 41.31	123.52 ± 39.62	126.79 ± 44.21	0.296
Estradiol, pg/mL	46.29 ± 88.02	55.91 ± 98.03	28.72 ± 62.35	< 0.001
TSH, μIU/mL	3.01 ± 3.64	3.06 ± 4.30	2.92 ± 1.92	0.697
Free T4, ng/dL	1.27 ± 0.26	1.27 ± 0.28	1.26 ± 0.20	0.197

Values are presented as number (%) or mean ± standard deviation.
MASLD = metabolic dysfunction–associated steatotic liver disease, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, Free T4 = free thyroxine.

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Risk factors associated with MASLD

In the overall female cohort (n = 995), multivariable logistic regression analysis demonstrated that higher BMI (adjusted odds ratio [aOR], 1.34; 95% confidence interval [CI], 1.26–1.42; $P < 0.001$), higher ALT (aOR, 1.04; 95% CI, 1.03–1.06; $P < 0.001$), dyslipidemia (aOR, 1.65; 95% CI, 1.11–2.45; $P = 0.014$), and higher HbA1c (aOR, 1.64; 95% CI, 1.27–2.16; $P < 0.001$) were independently associated with MASLD (**Table 2**). Conversely, higher HDL-C (aOR, 0.97; 95% CI, 0.96–0.99; $P < 0.001$) and serum estradiol (log_2-transformed; hereafter referred to as log_2E2) (aOR, 0.88; 95% CI, 0.79–0.98; $P = 0.025$) were associated with lower MASLD risk (**Supplementary Fig. 4A**).

Baseline characteristics stratified by BMI category are additionally presented in **Supplementary Table 1** to provide detailed contextual information for the subgroup analyses. When stratified by BMI (**Table 3**), different patterns emerged. Among women with BMI < 25 kg/m^2, MASLD was significantly associated with increasing BMI within this range (aOR, 1.65; 95% CI, 1.41–1.95; $P < 0.001$), ALT (aOR, 1.03; 95% CI, 1.02–1.05; $P < 0.001$), hypertension (aOR, 2.04; 95% CI, 1.21–3.44; $P = 0.007$), and HbA1c (aOR, 1.73; 95% CI, 1.24–2.47; $P = 0.002$). In this subgroup, log_2E2 remained an independent protective factor (aOR, 0.84; 95% CI, 0.71–0.98; $P = 0.027$) (**Supplementary Fig. 4B**).

In contrast, in women with high BMI (≥ 25 kg/m^2), log_2E2 was not significantly associated with MASLD (aOR, 0.90; 95% CI, 0.75–1.08; $P = 0.262$). Instead, MASLD risk was mainly associated with higher BMI (aOR, 1.18; 95% CI, 1.04–1.35; $P = 0.014$), higher ALT (aOR, 1.07; 95% CI, 1.04–1.11; $P < 0.001$), and higher HbA1c (aOR, 1.68; 95% CI, 1.09–2.75; $P = 0.028$) (**Supplementary Fig. 4C**).

In exploratory age-stratified analyses (**Supplementary Table 2**), the association between estradiol and MASLD did not reach statistical significance in either age group.

To assess whether estradiol adds predictive value beyond established clinical risk factors, we next evaluated the incremental predictive value of estradiol beyond established clinical risk

Table 2. Risk factors associated with metabolic dysfunction–associated steatotic liver disease: univariable and multivariable logistic regression (N = 995)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
Age, yr	1.03	1.02–1.05	< 0.001	0.99	0.96–1.01	0.246
BMI, kg/m^2	1.45	1.37–1.53	< 0.001	1.34	1.26–1.42	< 0.001
HTN, yes	2.65	1.99–3.54	< 0.001	1.44	0.98–2.11	0.063
DM, yes	2.86	1.95–4.20	< 0.001			
Dyslipidemia, yes	2.52	1.91–3.32	< 0.001	1.65	1.11–2.45	0.014
AST, U/L	1.03	1.01–1.04	< 0.001			
ALT, U/L	1.06	1.05–1.07	< 0.001	1.04	1.03–1.06	< 0.001
GGT, U/L	1.02	1.02–1.03	< 0.001			
ALP, U/L	1.02	1.01–1.03	< 0.001			
HbA1c, %	2.95	2.32–3.81	< 0.001	1.64	1.27–2.16	< 0.001
Triglyceride, mg/dL	1.02	1.01–1.02	< 0.001	1.01	1.01–1.01	< 0.001
HDL-C, mg/dL	0.94	0.93–0.95	< 0.001	0.97	0.96–0.99	< 0.001
LDL-C, mg/dL	1.00	1.00–1.01	0.209			
Estradiol (log_2-transformed)	0.82	0.76–0.88	< 0.001	0.88	0.79–0.98	0.025
TSH, mIU/L	0.99	0.94–1.03	0.632			
FreeT4, ng/dL	0.70	0.36–1.23	0.271			

OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, Free T4 = free thyroxine.

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Table 3. Risk factors associated with metabolic dysfunction–associated steatotic liver disease by BMI subgroup (BMI < 25 vs. ≥ 25 kg/m²): univariable and multivariable logistic regression

Variables	Low BMI (n = 654)						High BMI (n = 341)					
	Univariable			Multivariable			Univariable			Multivariable		
	OR	95% CI	*P* value	aOR	95% CI	*P* value	OR	95% CI	*P* value	aOR	95% CI	*P* value
Age	1.05	1.03–1.08	< 0.001	1.00	0.97–1.03	0.974	0.98	0.96–1.01	0.181	0.97	0.93–1.00	0.069
BMI	1.74	1.53–2.02	< 0.001	1.65	1.41–1.95	< 0.001	1.23	1.10–1.39	< 0.001	1.18	1.04–1.35	0.014
HTN, yes	2.92	1.91–4.44	< 0.001	2.04	1.21–3.44	0.007	1.22	0.78–1.93	0.380			
DM, yes	4.12	2.46–6.88	< 0.001				1.52	0.82–2.92	0.196			
Dyslipidemia, yes	3.50	2.36–5.19	< 0.001				1.25	0.80–1.97	0.336			
AST	1.02	1.00–1.03	0.021				1.05	1.03–1.08	< 0.001			
ALT	1.04	1.03–1.06	< 0.001	1.03	1.02–1.05	< 0.001	1.09	1.06–1.12	< 0.001	1.07	1.04–1.11	< 0.001
GGT	1.02	1.01–1.03	< 0.001				1.02	1.01–1.04	0.001			
ALP	1.02	1.01–1.03	< 0.001				1.02	1.00–1.03	0.010			
Total bilirubin	1.12	0.61–1.99	0.697				1.71	0.80–3.87	0.180			
HbA1c	2.73	2.03–3.79	< 0.001	1.73	1.24–2.47	0.002	2.06	1.42–3.15	< 0.001	1.68	1.09–2.75	0.028
Triglyceride	1.01	1.01–1.02	< 0.001	1.01	1.00–1.01	0.010	1.02	1.01–1.02	< 0.001	1.01	1.01–1.02	< 0.001
HDL-C	0.94	0.93–0.96	< 0.001	0.97	0.95–0.99	< 0.001	0.96	0.94–0.98	< 0.001	0.98	0.97–1.00	0.128
LDL-C	1.00	1.00–1.01	0.819				1.00	1.00–1.01	0.077	1.00	1.00–1.01	0.177
Estradiol	0.76	0.68–0.85	< 0.001	0.84	0.71–0.98	0.027	0.97	0.86–1.10	0.625	0.90	0.75–1.08	0.262
TSH	0.99	0.91–1.03	0.7				1.03	0.91–1.18	0.615			
FreeT4	0.67	0.23–1.43	0.4				0.74	0.25–2.18	0.585			

BMI = body mass index, OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, HTN = hypertension, DM = diabetes mellitus, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, Free T4 = free thyroxine.

factors. A base clinical model was first defined a priori, incorporating age, BMI, hypertension, ALT, HbA1c, triglycerides, and HDL-C, which are well-recognized determinants of MASLD in women. We then sequentially assessed model performance by comparing the base model alone, the base model plus HDL-C, and the base model plus HDL-C and $\log_2$-transformed estradiol. While the addition of HDL-C modestly improved model discrimination, inclusion of $\log_2$E2 resulted in a small but statistically significant improvement in discrimination compared with the base model alone (AUC 0.876 vs. 0.883; DeLong $P = 0.044$) (**Supplementary Fig. 5**). These findings suggest that estradiol provides complementary information beyond conventional metabolic risk factors, albeit with a modest effect size.

Risk factors for FIB-4 ≥ 1.3 in MASLD females

We next evaluated clinical and biochemical factors associated with higher fibrosis risk, defined by FIB-4 ≥ 1.3, among women with MASLD. Among the 352 women with MASLD, 172 (48.9%) had a FIB-4 score ≥ 1.3. In the multivariate analysis, log2-transformed estradiol was strongly and independently associated with lower odds of FIB-4 ≥ 1.3 (aOR, 0.65; 95% CI, 0.56–0.75; $P < 0.001$). In addition, lower LDL-C showed a modest inverse association (aOR, 0.99; 95% CI, 0.99–1.00; $P = 0.014$), and lower Free T4 was also identified as an independent risk factor (aOR, 0.19; 95% CI, 0.05–0.61; $P = 0.007$) (**Table 4**, **Supplementary Fig. 6A**).

When stratified by BMI (**Table 5**), $\log_2$E2 remained a consistent protective factor in both subgroups: low BMI (< 25 kg/m²) (aOR, 0.71; 95% CI, 0.56–0.89; $P = 0.003$) (**Supplementary Fig. 6B**) and high BMI (≥ 25 kg/m²) (aOR, 0.61; 95% CI, 0.49–0.74; $P < 0.001$) (**Supplementary Fig. 6C**). In the high-BMI group, additional significant predictors included LDL-C (aOR, 0.99; 95% CI, 0.98–1.00; $P = 0.013$), and Free T4 (aOR, 0.06; 95% CI, 0.01–0.30; $P = 0.001$).

In women aged ≥ 50 years (n = 325, **Table 6**), $\log_2$E2 again demonstrated a robust protective association with FIB-4 ≥ 1.3 (aOR, 0.70; 95% CI, 0.59–0.82; $P < 0.001$). Additional significant predictor included LDL-C (aOR, 0.99; 95% CI, 0.99–1.00; $P = 0.021$), and Free T4 (aOR, 0.21;

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Table 4. Risk factors associated with FIB-4 ≥ 1.3 in metabolic dysfunction–associated steatotic liver disease females: univariable and multivariable logistic regression (N = 352)

Variables	Univariable			Multivariable		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
BMI	0.96	0.89–1.02	0.184			
HTN, yes	1.30	0.85–2.00	0.221			
DM, yes	0.92	0.55–1.54	0.762			
Dyslipidemia, yes	1.17	0.77–1.78	0.468			
GGT	1.00	0.99–1.01	0.877			
ALP	1.01	1.00–1.02	0.150			
Total bilirubin	1.63	0.84–3.24	0.152			
Albumin	0.58	0.27–1.21	0.150			
HbA1c	1.09	0.86–1.38	0.487			
Triglyceride	1.00	1.00–1.00	0.165			
HDL-C	1.00	0.98–1.01	0.870			
LDL-C	0.99	0.99–1.00	0.005	0.99	0.99–1.00	0.014
Estradiol	0.66	0.57–0.76	< 0.001	0.65	0.56–0.75	< 0.001
TSH	0.97	0.87–1.09	0.647			
Free T4	0.34	0.11–1.00	0.051	0.19	0.05–0.61	0.007

OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, GGT = gamma-glutamyl transferase, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, Free T4 = free thyroxine.

Table 5. Risk factors associated with FIB-4 ≥ 1.3 by BMI subgroup (BMI < 25 vs. ≥ 25 kg/m²): univariable and multivariable logistic regression

Variables	Low BMI (n = 139)						High BMI (n = 213)					
	Univariable			Multivariable			Univariable			Multivariable		
	OR	95% CI	*P* value	aOR	95% CI	*P* value	OR (Univ)	95% CI (Univ)	*P* value (Univ)	aOR	95% CI	*P* value
BMI	0.97	0.75–1.24	0.792				0.95	0.84–1.06	0.328			
HTN, yes	1.08	0.54–2.15	0.837				1.51	0.88–2.61	0.137			
DM, yes	0.53	0.24–1.14	0.109				1.40	0.70–2.84	0.341			
Dyslipidemia, yes	0.81	0.42–1.59	0.546				1.46	0.85–2.51	0.174			
GGT	1.00	0.99–1.02	0.535				1.00	0.99–1.01	0.662			
ALP	1.00	0.98–1.02	0.964				1.01	1.00–1.03	0.054			
Total bilirubin	1.04	0.37–2.93	0.943				2.26	0.94–5.70	0.074			
Albumin	0.37	0.11–1.14	0.093	0.39	0.11–1.25	0.124	0.74	0.26–2.05	0.566			
HbA1c	0.91	0.61–1.30	0.598				1.24	0.91–1.74	0.195			
Triglyceride	1.00	0.99–1.00	0.475				1.00	0.99–1.00	0.244			
HDL-C	0.99	0.96–1.01	0.350				1.00	0.99–1.03	0.637			
LDL-C	1.00	0.99–1.00	0.228				0.99	0.98–1.00	0.009	0.99	0.98–1.00	0.013
Estradiol	0.71	0.56–0.88	0.003	0.71	0.56–0.89	0.003	0.63	0.51–0.76	< 0.001	0.61	0.49–0.74	< 0.001
TSH	0.99	0.85–1.17	0.951				0.96	0.82–1.11	0.573			
FreeT4	2.30	0.34–16.57	0.400				0.12	0.03–0.50	0.005	0.06	0.01–0.30	0.001

BMI = body mass index, OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, HTN = hypertension, DM = diabetes mellitus, GGT = gamma-glutamyl transferase, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid-stimulating hormone, Free T4 = free thyroxine.

95% CI, 0.06–0.69; *P* = 0.012) (**Supplementary Fig. 6D**). Subgroup analyses for women aged < 50 years could not be performed due to the limited number of MASLD cases (n = 27).

DISCUSSION

MASLD is characterized by prominent sexual dimorphism, and estrogen has long been considered a key biological factor underlying the relative hepatic protection observed in women. This study provides robust, quantified clinical evidence from a multicenter Korean female cohort. Our core finding is that lower circulating estradiol is an independent and significant risk factor for both MASLD development and advanced fibrosis (FIB-4 ≥ 1.3).

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Table 6. Uni- and multivariate logistic regression analysis for FIB-4 ≥ 1.3 in age ≥ 50 (N = 325)

Variables	Univariate			Multivariate		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
BMI	0.98	0.91–1.05	0.563			
HTN, yes	1.07	0.69–1.66	0.773			
DM, yes	0.88	0.51–1.49	0.621			
Dyslipidemia, yes	0.99	0.64–1.53	0.958			
ALP	1.00	0.99–1.02	0.388			
Albumin	0.62	0.28–1.33	0.224			
HbA1c	1.02	0.80–1.30	0.876			
Triglyceride	1.00	1.00–1.00	0.364			
LDL-C	0.99	0.99–1.00	0.013	0.99	0.99–1.00	0.021
HDL-C	0.99	0.98–1.01	0.431			
Estradiol	0.71	0.61–0.83	< 0.001	0.70	0.59–0.82	< 0.001
FreeT4	0.35	0.11–1.05	0.066	0.21	0.06–0.69	0.012

OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, ALP = alkaline phosphatase, HbA1c = hemoglobin A1c, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, Free T4 = free thyroxine.

In addition to low serum estradiol, our multivariable analysis confirmed that higher BMI, elevated ALT, higher HbA1c, higher triglyceride levels, and lower HDL-C were significant risk factors for MASLD in the overall cohort, consistent with global epidemiological data.[14] The protective effect of estradiol observed in women with BMI < 25 kg/m^2 suggests that, in the context of lower metabolic burden, the influence of estradiol on hepatic metabolism may be more readily detectable.[15,16] The findings align with the mechanistic understanding derived from other studies, which proposes that estradiol improves mitochondrial function and reduces oxidative stress in hepatocytes, thereby potentially counteracting lipotoxicity.[17,18] Therefore, the loss of this hormonal protection may contribute significantly to MASLD development in metabolically healthier women. In stark contrast, the loss of protection in obese women (BMI ≥ 25 kg/m^2) may indicate a threshold or 'point of metabolic dominance,' where the beneficial effects of estrogen are likely overwhelmed by the substantial metabolic dysfunction and chronic inflammation characteristic of visceral obesity. Systemic low-grade chronic inflammation (e.g., elevated tumor necrosis factor-α, interleukin-6) induced by obesity is hypothesized to interfere with ER signaling pathways or simply accelerate liver damage beyond the hormone's capacity to compensate.[19]

In contrast, age-stratified analyses using a dichotomous cutoff (< 50 vs. ≥ 50 years) did not demonstrate significant effect modification. This finding should be interpreted with caution, as age-based categorization is an imperfect surrogate for menopausal status and does not fully capture inter-individual variability in circulating estradiol levels. Accordingly, age was included as a continuous covariate in the primary multivariable models (**Table 2**) to account for potential confounding, rather than being used as a categorical surrogate for menopausal status. Notably, under this adjustment strategy, $\log_2$E2 remained independently and significantly associated with MASLD.

Perhaps the most significant clinical insight from our study is the strong and consistent inverse relationship between circulating estradiol levels and the risk of significant fibrosis (FIB−4 ≥ 1.3). This protective effect was observed across all metabolic strata, remaining significant in both the low BMI (< 25 kg/m^2) and high BMI (≥ 25 kg/m^2) groups. Unlike the context-dependent association with simple steatosis, this consistency suggests that estradiol may play a more fundamental role in inhibiting the progression to fibrosis—the most critical stage of liver injury.[20,21] Mechanistically, estradiol has been reported to suppress hepatic stellate cell activation through estrogen receptor-β receptors and to downregulate major

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pro-fibrotic mediators such as transforming growth factor-β, pathways that are likely relevant regardless of metabolic load.[22-25] The robustness of this finding implies that estradiol level may serve as a potential prognostic marker. For postmenopausal women, a low estradiol level may serve as an indicator that liver injury is progressing beyond simple steatosis toward fibrosis, suggesting the need for more intensive monitoring and management.

Interestingly, in the present study, lower LDL-C and free T4 levels, together with lower circulating estradiol, were inversely associated with fibrosis risk as defined by FIB-4 ≥ 1.3. These findings suggest that the metabolic and hormonal milieu accompanying fibrosis progression may differ from that underlying simple steatosis. In particular, lower LDL-C levels may reflect reduced hepatic lipid synthesis in more advanced liver disease or may be confounded by the use of lipid-lowering therapy, which reduces LDL-C while potentially modifying fibrosis risk. Although medication data, including statin use, were not available in this study, statins can substantially lower LDL-C and have been associated with improved liver-related outcomes and potential antifibrotic effects; therefore, residual confounding by statin exposure cannot be excluded.[26,27] In addition, the inverse association between free T4 and fibrosis risk is biologically plausible given the established role of thyroid hormones in hepatic lipid handling and fibrogenic pathways; however, the cross-sectional nature of this study precludes determination of whether lower free T4 levels contribute to fibrosis progression or represent a consequence of advanced liver disease.[28]

Our study is limited by its cross-sectional design, which prevents us from establishing a causal relationship; prospective studies are required to determine whether declining estradiol levels drive MASLD progression or whether MASLD influences hormone clearance. A further limitation is the reliance on a single estradiol measurement, as well as the use of FIB-4 as a surrogate marker of fibrosis rather than a direct histologic assessment. In this context, FIB-4 should be interpreted as an indirect indicator of fibrosis risk rather than a definitive measure of fibrotic burden. Nevertheless, the FIB-4 cutoff of 1.3 has been widely validated as a rule-out threshold for advanced fibrosis in metabolic liver disease and population-based cohorts, supporting its use for risk stratification in large epidemiologic studies.

In conclusion, this study demonstrates that lower circulating estradiol is an independent risk factor for MASLD in women, with its association being modified by metabolic context, particularly BMI. The protective effect of estradiol was evident in women with low-BMI but not in those with high-BMI, suggesting that metabolic burden plays a dominant role in determining susceptibility to steatosis. In contrast, estradiol showed a strong and consistent inverse association with fibrosis risk (FIB-4 ≥ 1.3) across all subgroups, indicating a potentially fundamental role in limiting fibrotic progression. These findings highlight the value of circulating estradiol as a potential biomarker for risk stratification in female MASLD patients and underscore the need for future prospective studies.

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SUPPLEMENTARY MATERIALS

Supplementary Material 1

Supplementary Table 1
Baseline characteristics stratified by BMI category and MASLD status

Supplementary Table 2
Uni- and multivariate logistic regression analysis by age group, MASLD

Supplementary Fig. 1
Flowchart of study population selection.

Supplementary Fig. 2
Distribution of serum estradiol levels in the study cohort. **(A)** Histogram showing the raw distribution of serum estradiol levels. **(B)** Distribution of $\log_2$-transformed estradiol values.

Supplementary Fig. 3
Distribution of serum estradiol by MASLD status (**A**) and FIB-4 category (**B**) in women.

Supplementary Fig. 4
Forest plots of factors associated with MASLD in the overall cohort and stratified subgroups. Forest plots display adjusted odds ratios (aOR) from multivariable logistic regression with 95% confidence intervals (log scale). (**A**) Overall cohort: HbA1c, hyperlipidemia, BMI, ALT, triglycerides, HDL cholesterol, and estradiol. (**B**) Low BMI (< 25 kg/m^2): hyperlipidemia, BMI, ALT, triglycerides, and estradiol. (**C**) High BMI (≥ 25 kg/m^2): HbA1c, BMI, ALT, triglycerides (estradiol not significant).

Supplementary Fig. 5
Incremental predictive value of HDL-C and estradiol for MASLD.

Supplementary Fig. 6
Forest plots of factors associated with fibrosis risk (FIB-4 ≥ 1.3) among women with MASLD. Adjusted odds ratios (aOR) with 95% confidence intervals are shown from multivariable logistic regression analyses. (**A**) Overall MASLD female cohort: total bilirubin, LDL cholesterol, estradiol, and free T4. (**B**) Low BMI subgroup (< 25 kg/m^2): estradiol. (**C**) High BMI subgroup (≥ 25 kg/m^2): LDL cholesterol, free T4, and estradiol. (**D**) Age ≥ 50 subgroup: LDL cholesterol, BMI, estradiol, albumin, and free T4. Squares indicate point estimates; horizontal lines represent 95% confidence intervals on a log scale.

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