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Follicle-stimulating hormone is associated with non-alcoholic fatty liver disease in Chinese women over 55 years old

Ningjian Wang,* Qin Li,* Bing Han,* Yi Chen,* Chunfang Zhu,* Yingchao Chen,* Fangzhen Xia,* Meng Lu,* Ying Meng,* Yuyu Guo,* Lin Ye,* Chunhua Sui,* Lin Kuang,† Dongping Lin* and Yingli Lu*

*Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, and †Assisted Reproduction Unit, Department of Obstetrics and Gynecology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Zhejiang, China

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Correspondence
Dr Yingli Lu, Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200011, China. Email: luyingli2008@126.com

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Abstract

Background and Aim : Obesity and diabetes are related to non-alcoholic fatty liver disease (NAFLD). A reduction in follicle-stimulating hormone (FSH) is associated with obesity and diabetes in postmenopausal women. Thus, we aim to investigate whether FSH is associated with NAFLD in women over 55 who were postmenopausal with a high probability.

Methods : Our data were obtained from the 2014 Survey on Prevalence in East China for Metabolic Diseases and Risk Factors. A total of 1635 women at the age of 55–89 years were selected. The degrees of fatty liver were categorized into mild and moderate-severe hepatic steatosis groups by ultrasonography. FSH and other sex hormones were measured by chemiluminescence.

Results : A total of 366 (22.4%) and 417 (25.5%) women had mild and moderate-severe hepatic steatosis, respectively. FSH was negatively correlated with waist circumference, homeostasis model assessment of insulin resistance (HOMA-IR), and other metabolic factors (all $P < 0.05$). After adjusting for age, estradiol, and total testosterone, increased quartiles of FSH were associated with significantly decreased odds ratios of mild and moderate-severe groups (both P for trends <0.05). After further adjustment for waist circumference and HOMA-IR, FSH was no longer associated with mild hepatic steatosis. The association of FSH with moderate-severe hepatic steatosis was attenuated by waist circumference and HOMA-IR but persisted in the fully adjusted model (P for trend <0.01).

Conclusion : Follicle-stimulating hormone was negatively associated with NAFLD in women over 55 years old. Adiposity and insulin resistance explained most of the association of mild hepatic steatosis and partially explained the association of moderate-severe hepatic steatosis with FSH.

Introduction

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of liver diseases, almost all of which involve fat accumulation in the hepatic parenchyma.[1,2] In Chinese, the prevalence of NAFLD is up to 40% in the general population and continues to increase worldwide.[3–5] NAFLD is associated with diabetes, abdominal obesity, insulin resistance, and other metabolic syndrome components.[6,7] Thus, in addition to consequences of hepatic complications, individuals with NAFLD have an increased risk of developing type 2 diabetes mellitus and mortality related to cardiovascular diseases.[8,9]

Endogenous sex hormones mainly act on the reproduction system, but their roles in NAFLD have also been gradually revealed. In postmenopausal women, higher bioavailable testosterone (T) and lower sex hormone-binding globulin are associated with NAFLD.[1,10–12] However, to date, the role of follicle-stimulating hormone (FSH) in NAFLD has not been studied. Previous studies have found that FSH was independently associated with prediabetes and diabetes in postmenopausal women.[13] Notably, the levels of FSH are lower in obese participants.[14] Two recent studies also reported that lower FSH was significantly associated with metabolic syndrome in postmenopausal women.[15,16] Therefore, we hypothesized that FSH might be associated with NAFLD in postmenopausal women.

We aimed to analyze this association between FSH and NAFLD in Chinese women over 55 who were postmenopausal with a high probability. To our knowledge, the current analyses are the first to

explore this association and focus on several possible explanatory factors, including adiposity, insulin resistance, and other common metabolic factors.

Methods

Participants. Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) is a cross-sectional survey on the prevalence of metabolic diseases and risk factors in East China (ChiCTR-ECS-14005052, www.chictr.org.cn).[17] Chinese adults who had lived in their current residence for 6 months or longer were invited to participate in this study. Those with severe communication problems or acute illness or those who were unwilling to participate were excluded from the study. Between February 2014 and June 2014, 6899 subjects who were 18–93 years of age were enrolled in the SPECT-China study from 16 sites in Shanghai, Zhejiang, and Jiangxi Provinces.[17] The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for inclusion in the study.

Women older than 55 years of age were considered to be postmenopausal with a high probability according to previous studies.[18–20] In China, at the age of 55, approximately 97% of women are postmenopausal.[21] There were 1863 women who were older than 55, were not using hormone replacement therapy, and had no history of excessive consumption (>20 g/day) of pure alcohol. Exclusion criteria included the following: FSH <25.0 IU/L ($n = 42$), missing values of FSH ($n = 6$), missing abdominal ultrasonographic results ($n = 120$), history of hysterectomy and/or oophorectomy ($n = 24$), self-reported viral hepatitis ($n = 19$), schistosome hepatic disease ($n = 1$), use of medications associated with secondary NAFLD (corticosteroids, tamoxifen, amiodarone, and methotrexate) ($n = 12$), and chronic kidney disease (stage ≥4) ($n = 4$). Finally, the current study was based on a total number of 1635 women who were older than 55 (Fig. 1).

Biochemical measurements. Participants fasted for 8 h before investigation. Fasting blood samples were drawn between 7:00 AM and 10:00 AM. The blood samples for the plasma glucose test were centrifuged 1 h after collection. Other blood samples were stored at −20 °C when collected and were shipped in dry ice within 2–4 h of collection to a central laboratory certified by the College of American Pathologists. Glycated hemoglobin (HbA1c) was assessed by high-performance liquid chromatography (MQ-2000PT, China). Plasma glucose, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured by BECKMAN COULTER AU 680 (Germany), and insulin was measured by the chemiluminescence method (Abbott i2000 SR, Chicago, IL, USA).

Total testosterone (T), estradiol (E2), FSH, and luteinizing hormone (LH) were measured by chemiluminescence (Siemens IMMULITE 2000, Munich, Germany). The minimal detectable limit for each hormone was as follows: 0.7 nmol/L (total T), 73.4 pmol/L (E2), and 0.1 IU/L (FSH and LH). Samples with values below the minimal detectable limit were given a value midway between zero and the minimal detectable limit for the analyses: total T (66.5%) and E2 (67.7%).[20] The inter-assay coefficients of variation were 6.6% (total T), 7.5% (E2), 4.5% (FSH), and 6.0% (LH). The intra-assay coefficients of variation were 5.7% (total T), 6.2% (E2), 3.8% (FSH), and 4.9% (LH).

Clinical and anthropometric measurements. In every site, the same staff collected the data. They used a questionnaire to collect information on demographic characteristics, medical history, and lifestyle risk factors. A current smoking status was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes.[22] Weight and height were measured using a balance beam and a vertical ruler with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the minimum abdominal girth, and blood pressure was measured with the use of standard methods as described previously.[22] Insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) index: (fasting insulin [mIU/L]) × (FPG [mmol/L])/22.5.[23]

Definition of variables. Two experienced ultrasonographers used an ultrasound device (MINDRAY M7, China) to perform an abdominal ultrasonographic examination of all subjects. The diagnostic criteria for fat accumulation (steatosis) by ultrasonography included increased liver echogenicity, stronger echoes in the hepatic parenchyma than in the renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins.[2,24,25] Based on the criteria by Saadeh *et al.*,[1,2,24] the degree of fat accumulation (steatosis) on ultrasonography was categorized into normal, mild, and moderate-severe groups as follows: absence of hepatic steatosis, comparable echogenicity of hepatic parenchyma with that of the renal cortex with clear visualization of the intrahepatic vessels, and the diaphragm; mild hepatic steatosis, slight diffuse increase in fine echoes in liver parenchyma with normal visualization of the intrahepatic vessels, and the diaphragm; moderate hepatic steatosis, moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels, and the diaphragm; and severe hepatic steatosis, marked increase in fine echoes in the hepatic parenchyma with poor or non-visualization of the intrahepatic vessels, the diaphragm, and the posterior right lobe.[1,2] Diabetes was defined as a previous diagnosis by healthcare professionals, an FPG of 7.0 mmol/L or higher, or a HbA1c of 6.5% or higher.

Statistical analysis. We performed survey analyses with IBM SPSS Statistics, version 22 (IBM Corporation, Armonk, NY, USA). All analyses were two-sided. A P-value <0.05 was considered to indicate a significant difference. General characteristics are summarized as the mean ± standard deviation for continuous variables or as a number with a proportion for categorical variables. To test for differences of characteristics among different degrees of hepatic steatosis and FSH quartiles, the Kruskal–Wallis test and a one-way ANOVA were used for continuous data with skewed distribution and normal distribution, and Pearson χ^2-test was used for

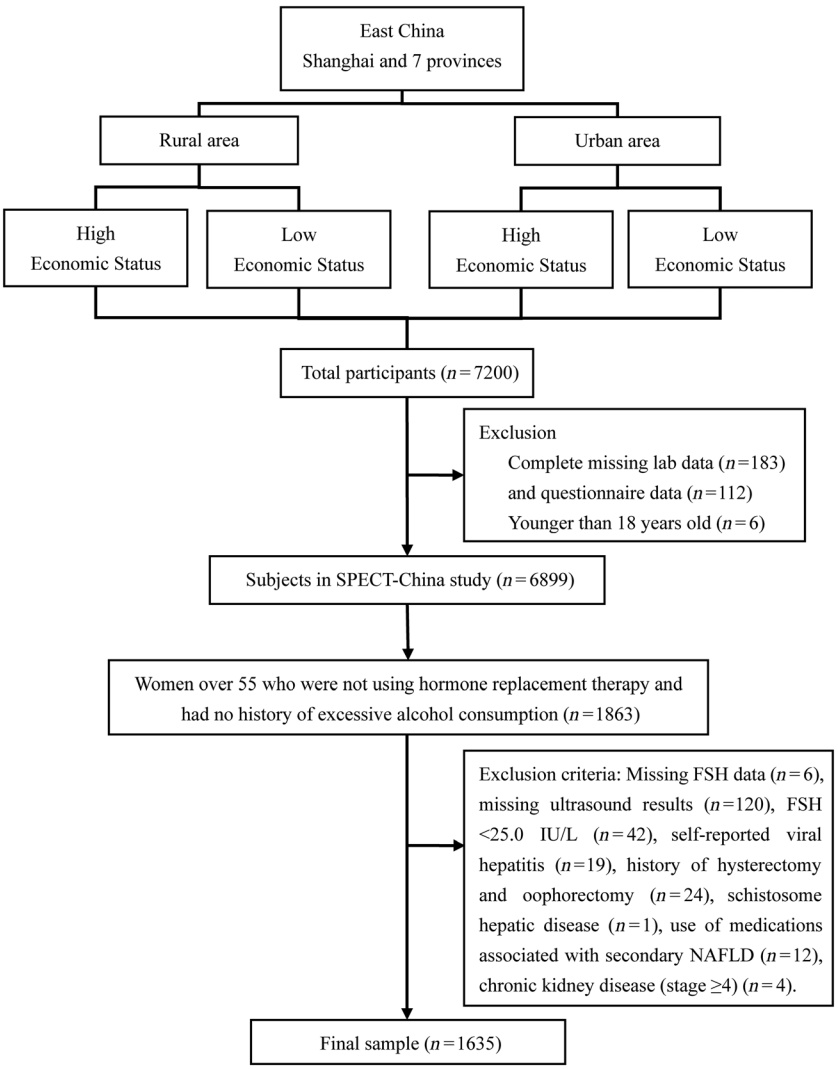

Figure 1 Flowchart of sampling frame and participants selected from SPECT-China.

categorical variables. The correlation of sex hormones with metabolic factors was assessed by Pearson correlation analysis. The results were expressed as Spearmen's rank correlation coefficient.

Follicle-stimulating hormone and LH were divided into quartiles, with the first quartile representing the lowest one and the fourth quartile representing the highest. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multinomial logistic regression to determine the risk of mild and moderate-severe hepatic steatosis for each quartile of FSH and LH, using the highest quartile as the reference. Model 1 included terms for age, total testosterone, and estradiol. Model 2 included terms for model 1, waist circumference, and HOMA-IR. Model 3 was a fully adjusted model including all covariates in model 2 and other metabolic factors (diabetes, LDL, HDL, triglycerides, and systolic blood pressure). The interaction effect was tested between FSH and waist circumference or HOMA-IR by adding a multiplicative factor in the logistic regression model.

We conducted sensitivity analyses by substituting obesity category by BMI for waist circumference and by excluding cases whose E2 was higher than the minimal detectable limit (73.4 pmol/L) in multivariable models. We also performed regression analyses in women over 60 years old. The medications for diabetes, hypertension, and dyslipidemia may affect the covariates, so we re-performed the logistical analyses after excluding subjects taking medications for diabetes, hypertension, and dyslipidemia. The area under the curve of the receiver operating characteristic was used to obtain the cutoff value of FSH for the NAFLD.

Results

Characteristics of the study population. The general characteristics of the study population are shown in Table 1. This study recruited 1635 women over 55 years old. Among them, 852 (52.1%) showed no signs of hepatic fat infiltration, 366 (22.4%) had mild hepatic steatosis, and 417 (25.5%) had moderate-severe hepatic steatosis. Compared with subjects without liver fat infiltration, women with moderate-severe hepatic steatosis were younger and had significantly greater HbA1c, fasting plasma glucose, BMI, waist circumference, HOMA-IR, LDL, triglycerides, and systolic pressure (all $P < 0.01$). Women with mild or moderate-severe hepatic steatosis had higher total T and lower E2 (both $P < 0.05$). These women also had significantly lower levels of FSH (67.2 ± 23.6 and 61.0 ± 20.9 *vs* 70.0 ± 24.2 IU/L, $P < 0.05$).

Table 1 General characteristics of subjects by severity of hepatic steatosis

	Normal	Mild	Moderate and severe	*P*
N	852	366	417	
Age (year)	65 ± 7	64 ± 7	63 ± 6	<0.001
Current smoker (%)	4.6	2.0	2.8	0.06
Diabetes (%)	12.0	17.5	26.1	<0.001
HbA1c (%)	5.4 ± 0.8	5.5 ± 0.8	5.7 ± 1.0	<0.001
Fasting glucose (mmol/L)	5.73 ± 1.21	5.88 ± 1.28	6.30 ± 1.84	<0.001
Fasting insulin (pmol/L)	36.0 ± 26.0	46.7 ± 80.4	57.2 ± 45.2	<0.001
HOMA-IR	1.4 ± 1.3	1.9 ± 4.3	2.4 ± 2.2	<0.001
LDL-cholesterol (mmol/L)	3.08 ± 0.76	3.15 ± 0.85	3.22 ± 0.70	<0.01
HDL-cholesterol (mmol/L)	1.59 ± 0.33	1.51 ± 0.34	1.43 ± 0.29	<0.001
Triglycerides (mmol/L)	1.47 ± 0.93	1.70 ± 0.95	2.14 ± 1.69	<0.001
Systolic pressure (mmHg)	137 ± 22	138 ± 21	141 ± 20	<0.01
Body mass index (kg/m^2)	23.1 ± 3.1	25.0 ± 3.0	27.4 ± 3.3	<0.001
Waist circumference (cm)	77.0 ± 9.5	80.5 ± 7.7	86.1 ± 8.2	<0.001
ALT (IU/L)	19 ± 12	20 ± 10	24 ± 12	<0.001
AST (IU/L)	26 ± 10	25 ± 8	26 ± 9	<0.01
Total T (nmol/L)	0.56 ± 0.39	0.64 ± 0.45	0.70 ± 0.55	<0.001
E2 (pmol/L)	69.0 ± 53.7	59.2 ± 44.3	58.2 ± 42.9	<0.001
FSH (IU/L)	69.8 ± 24.0	67.1 ± 23.5	60.9 ± 21.0	<0.001
LH (IU/L)	25.4 ± 10.1	25.5 ± 11.1	22.9 ± 8.9	<0.001

Data were summarized as the mean ± standard deviation for continuous variables or as a number with proportion for categorical variables. The Kruskal–Wallis test and ANOVA were used for continuous variables with a skewed or normal distribution, and the Pearson χ^2-test was used for categorical variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; E2, estradiol; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone; T, testosterone.

Characteristics of subjects by FSH quartiles are summarized in Table 2. The quartile ranges of FSH in subjects were ≤49.6, 49.7–63.7, 63.8–81.7, and ≥81.8 IU/L. Compared with women in the highest quartile, women in the lowest quartile had comparable ages but greater BMI, waist circumference, HOMA-IR, triglycerides, systolic pressure, and a higher prevalence of diabetes (all $P < 0.05$). These women had similar total T but significantly higher E2.

Correlation of FSH with potential metabolic factors. Table 3 summarizes the results of the Pearson correlation analysis between FSH and LH and potential metabolic factors in all subjects. FSH and LH were negatively correlated with HbA1c, fasting plasma glucose, HOMA-IR, triglycerides, systolic pressure, BMI, waist circumference, and alanine aminotransferase (all $P < 0.05$).

Association of FSH and LH with NAFLD. Table 4 shows the association of FSH and LH with NAFLD by multinomial logistic regression analyses. Adjusting for age in model 1, E2, and total T, compared with women in the highest quartile of FSH, the ORs of mild and moderate-severe hepatic steatosis in women in the lowest quartile of FSH were 1.84 (95% CI 1.12, 3.02) (*P* for trend <0.05) and 2.94 (95% CI 1.82, 4.77) (*P* for trend <0.001), respectively. Adjusting for waist circumference and HOMA-IR weakened the association between FSH and mild hepatic steatosis further such that the association was no longer significant (*P* for trend 0.06). Further adjustments for diabetes, LDL, HDL, triglycerides, and systolic blood pressure attenuated the association between FSH and moderate-severe hepatic steatosis further, but in Q1, there was still statistical significance (OR 2.00, 95% CI 1.15, 3.47, $P < 0.05$). Notably, LH did not show significant association with hepatic steatosis in each model. We observed no interaction between FSH and waist circumference or HOMA-IR.

Sensitivity analysis. In the sensitivity analysis, using an obesity category by BMI instead of waist circumference in the full model did not change the observed association (*P* for trend <0.05 for FSH and moderate-severe hepatic steatosis). After excluding cases whose E2 was higher than 73.4 pmol/L, the association of FSH with moderate-severe hepatic steatosis did not significantly change in the fully adjusted model (*P* for trend <0.05). When we increased the cutoff age of menopause to 60 years, a significant association still existed (*P* for trend <0.05). After excluding subjects taking medications for diabetes, hypertension, and dyslipidemia, the associations between FSH and NAFLD were still significant (*P* for trend <0.05). By receiver operating characteristic curve analysis, the cutoff value of FSH for the NAFLD was 68.9 IU/L.

Discussion

We discovered that FSH was negatively associated with NAFLD in women older than 55 who had a high probability of being postmenopausal. Abdominal obesity and insulin resistance partially

Table 2 Characteristics of subjects according to serum FSH quartiles

	Q1	Q2	Q3	Q4	*P*
N	412	409	407	407	
FSH (IU/L)	≤49.6	49.7–63.7	63.8–81.7	≥81.8	
Age (yr)	64 ± 7	65 ± 7	64 ± 7	64 ± 7	0.08
Current smoker (%)	3.8	3.1	4.7	2.7	0.46
Diabetes (%)	24.0	19.8	15.0	8.4	<0.001
Hepatic steatosis					<0.001
Mild	21.1	23.7	23.1	21.6	
Moderate-severe	33.5	28.4	21.9	18.2	
HbA1c (%)	5.7 ± 1.0	5.7 ± 1.0	5.5 ± 0.8	5.4 ± 0.7	<0.001
Fasting glucose (mmol/L)	6.11 ± 1.62	6.03 ± 1.80	5.82 ± 1.11	5.68 ± 1.01	<0.001
Fasting insulin (pmol/L)	45.3 ± 29.3	45.4 ± 45.4	47.4 ± 77.9	36.9 ± 23.2	<0.001
HOMA-IR	1.9 ± 1.7	1.8 ± 2.1	1.9 ± 4.2	1.4 ± 1.0	<0.001
LDL-cholesterol (mmol/L)	3.13 ± 0.79	3.17 ± 0.84	3.05 ± 0.73	3.17 ± 0.71	<0.05
HDL-cholesterol (mmol/L)	1.48 ± 0.30	1.50 ± 0.34	1.54 ± 0.32	1.60 ± 0.33	<0.001
Triglycerides (mmol/L)	1.87 ± 1.65	1.75 ± 1.27	1.63 ± 0.93	1.51 ± 0.74	<0.01
Systolic pressure (mmHg)	140 ± 20	139 ± 21	139 ± 22	135 ± 21	<0.01
Body mass index (kg/m^2)	25.8 ± 4.0	24.8 ± 3.3	24.1 ± 3.3	23.7 ± 3.4	<0.001
Waist circumference (cm)	83.3 ± 10.4	80.8 ± 8.7	78.8 ± 8.9	77.4 ± 9.1	<0.001
ALT (IU/L)	21 ± 12	21 ± 15	20 ± 10	19 ± 11	<0.05
AST (IU/L)	26 ± 9	26 ± 9	26 ± 9	25 ± 10	0.59
Total T (nmol/L)	0.64 ± 0.48	0.63 ± 0.49	0.59 ± 0.40	0.58 ± 0.42	0.29
E2 (pmol/L)	84.8 ± 68.4	64.2 ± 45.3	56.0 ± 37.2	50.9 ± 30.8	<0.001
LH (IU/L)	16.4 ± 5.6	21.6 ± 6.2	26.3 ± 7.2	34.9 ± 10.0	<0.001

Data were summarized as median with mean ± standard deviation for continuous variables or as a number with a proportion for categorical variables. The Kruskal–Wallis test and ANOVA were used for continuous variables with a skewed or normal distribution, and a Pearson χ^2-test was used for categorical variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; E2, estradiol; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone; T, testosterone.

Table 3 Pearson correlation of FSH and LH with metabolic factors in all subjects

	FSH	LH
Age	−0.055*	−0.117†
lg-HbA1c	−0.169†	−0.126†
lg-Fasting glucose	−0.139†	−0.098†
lg-HOMA-IR	−0.169†	−0.121†
LDL-cholesterol	0.006	0.004
HDL-cholesterol	0.158†	0.106†
lg-Triglycerides	−0.122†	−0.076†
Systolic pressure	−0.113†	−0.098†
Body mass index	−0.222†	−0.151†
Waist circumference	−0.253†	−0.206†
lg-ALT	−0.097†	−0.059*
lg-AST	−0.036	−0.016

Data are Pearson correlation coefficients.

*Indicated $P < 0.05$;

†Indicated $P < 0.01$. Pearson correlation analyses were performed. Because HbA1c, fasting glucose, HOMA-IR, triglycerides, ALT, and AST were skewed distribution, they were log transformed.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone.

explained the association of FSH with moderate-severe hepatic steatosis. To date, this is the first study to detect the association between FSH and NAFLD in a population-based study with a large sample.

Non-alcoholic fatty liver disease is closely connected with metabolic disorders[6]. There is likely to be a bidirectional relationship between the progression to non-alcoholic steatohepatitis and the development of diabetes and obesity.[9] Additionally, recent studies demonstrated that FSH is significantly associated with metabolic factors.[13–16] Every 1 standard deviation decrement of FSH is associated with a 3.83-fold increased risk of metabolic syndrome.[15] In the current study, FSH was significantly correlated with metabolic syndrome components. Thus, our finding of the association between FSH and NAFLD is reasonable and adds new evidence to the innovative role of FSH in metabolic disorders in postmenopausal women.

Compared with general obesity, abdominal obesity may pose a greater risk of NAFLD.[26] Insulin resistance is also a characteristic feature of NAFLD.[27] NAFLD could be considered to be a result of insulin resistance, as shown by studies in subjects who are genetically predisposed to NAFLD.[6] Moreover, central obesity and insulin resistance usually coexist, and in our subjects, waist circumference and HOMA-IR were significantly correlated (Spearman's correlation coefficient = 0.41; $P < 0.001$); thus, waist circumference and HOMA-IR were selected as two important covariates to be adjusted together.

Table 4 Association of circulating FSH and LH with NAFLD in all subjects

	Model 1	Model 2	Model 3
Mild hepatic steatosis			
FSH (IU/L)			
Q1 (≤49.3)	1.84 (1.12, 3.02)*	1.62 (0.97, 2.72)	1.61 (0.96, 2.71)
Q2 (49.4–63.6)	1.63 (1.08, 2.48)*	1.44 (0.93, 2.23)	1.44 (0.93, 2.23)
Q3 (63.7–81.4)	1.26 (0.87, 1.84)	1.20 (0.82, 1.78)	1.16 (0.78, 1.72)
Q4 (≥81.5)	1.00	1.00	1.00
P-value for trend	0.01	0.06	0.06
LH (IU/L)			
Q1 (≤17.4)	0.80 (0.49, 1.29)	0.72 (0.44, 1.20)	0.71 (0.43, 1.18)
Q2 (17.5–23.3)	0.91 (0.60, 1.36)	0.91 (0.60, 1.40)	0.91 (0.59, 1.41)
Q3 (23.4–30.1)	0.96 (0.66, 1.40)	1.02 (0.70, 1.51)	1.03 (0.70, 1.51)
Q4 (≥30.2)	1.00	1.00	1.00
P-value for trend	0.37	0.21	0.20
Moderate-severe hepatic steatosis			
FSH (IU/L)			
Q1 (≤49.3)	2.94 (1.82, 4.77)#	2.07 (1.21, 3.53)†	2.00 (1.15, 3.47)*
Q2 (49.4–63.6)	2.04 (1.34, 3.12)†	1.74 (1.09, 2.76)*	1.68 (1.04, 2.71)*
Q3 (63.7–81.4)	1.30 (0.88, 1.92)	1.19 (0.77, 1.83)	1.22 (0.79, 1.91)
Q4 (≥81.5)	1.00	1.00	1.00
P-value for trend	<0.001	0.004	0.008
LH (IU/L)			
Q1 (≤17.4)	1.22 (0.76, 1.97)	0.85 (0.50, 1.44)	0.76 (0.44, 1.32)
Q2 (17.5–23.3)	1.19 (0.78, 1.82)	0.86 (0.54, 1.38)	0.84 (0.52, 1.36)
Q3 (23.4–30.1)	1.33 (0.91, 1.96)	1.21 (0.79, 1.83)	1.16 (0.75, 1.77)
Q4 (≥30.2)	1.00	1.00	1.00
P-value for trend	0.59	0.35	0.21

Data were odds ratio (95% CI).

*Indicated $P < 0.05$;

†Indicated $P < 0.01$;

#Indicated $P < 0.001$. Multinomial logistic regression analyses were performed.

Model 1 included terms for age, total testosterone, and estradiol.

Model 2 included terms for model 1 in addition to waist circumference and homeostasis model assessment of insulin resistance.

Model 3 was a fully adjusted model including all covariates in model 2 and other metabolic factors (diabetes, low-density lipoprotein, high-density lipoprotein, triglycerides, and systolic blood pressure).

CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NAFLD, non-alcoholic fatty liver disease.

Follicle-stimulating hormone may be associated with NAFLD risk partly through its relationship to abdominal obesity. In a study mainly recruiting Caucasian and African-American women, obesity significantly attenuated the rise of FSH after the final menstrual period.[28] The same trend was observed in our Asian population. Another study also found that weight loss led to increases in FSH among overweight and obese postmenopausal women.[29] Some may think that E2 is involved in this association. In postmenopausal women, E2 secretion shifts from the ovary to a compensatory source in fat.[30,31] It is reasonable to deduce that FSH decreases because more E2 is secreted in obese women and E2 is positively associated with obesity.[28,31] However, in postmenopausal women after adjustment for E2, changes in FSH were still associated with changes in weight and NAFLD, which suggests that adiposity-related factors other than E2 may be associated with FSH.[29] Moreover, it is controversial whether E2 is negatively or positively associated with NAFLD in postmenopausal women.[10,12]

Our study has some strengths. First, the same trained research group completed data collection in every study site; thus, the results had strong quality control. Second, our data source is a general population as opposed to a clinic-based population, so the results may be more reflective of the general population. However, our study also has some limitations. First, we cannot draw a causal relationship between FSH and NAFLD because the nature of this study is cross-sectional. Second, we used an age proxy to define postmenopause as described in previous studies.[18–20] In China, at the age of 55, approximately 97% of women are postmenopausal.[21] Increasing the cutoff age to 60 did not change the association. Third, the use of liver ultrasonography meets certain limitations. However, the use of a liver biopsy could not be used in such a large sample. Finally, the exclusion of viral hepatitis on the basis of self-reporting may have a recall bias. Additionally, some uncommon liver diseases such as Wilson's disease and α1-antitrypsin deficiency were not recorded. Because of their uncommonness, this may not significantly affect the study results.

In conclusion, FSH was negatively associated with NAFLD in women older than 55 who had a high probability of being postmenopausal. Adiposity and insulin resistance explained most of the association of mild hepatic steatosis with FSH and partially explained the association of moderate-severe hepatic steatosis with FSH.

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