Follicle-stimulating Hormone and Lipid Profile in Women Older than 55

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Abstract

Purpose. Follicle stimulating hormone (FSH) is associated with higher risks of metabolic syndrome and diabetes in menopausal women. We aimed to investigate whether FSH was associated with lipid profile in women older than 55 who were postmenopausal with a high probability.

Methods. Our data were from Survey on Prevalence in East China for Metabolic Diseases and Risk Factors. 1795 women at the age of 55-89 were selected. Sex hormones and lipid profile were measured from morning serum. Linear and logistic regression analyses were used.

Results. Lower FSH was associated with lower HDL-C, higher TG, TC/HDL-C ratio and LDL-C/HDL-C ratio (all P for trend <0.05), after adjusting for age and other sex hormones. Further adjustment for body mass index, diabetes and hypertension, the associations of FSH with lipid profile weakened, but the association of FSH quartiles with HDL-C and TC/HDL-C ratio was still significant (both P for trend <0.05). Compared with women in the highest FSH quartile, odds of low HDL-C (HDL-C <1.04 mmol/L) in women in the lowest FSH quartile were 5.25 (95% confidence interval 1.60, 17.26) (P for trend <0.05) in fully adjusted model, and odds of $TC \geq 6.22$ mmol/L, $TG \geq 2.26$ mmol/L and $LDL-C \geq 4.14$ mmol/L were not significant. LH did not show significant association with dyslipidemia.

Conclusion. Lower FSH was associated with worse lipid profile in women older than 55. Diabetes, adiposity and hypertension mostly explained the association of FSH with TG and LDL-C/HDL-C ratio but only partially explained the associations of FSH with HDL-C and TC/HDL-C ratio.

1 Introduction

Atherosclerotic cardiovascular disease (CVD) rank highest among the leading cause of death and disability-adjusted life years lost in developed and most of developing countries as well as in China.^{1,2} It is known that elevated serum concentrations of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and decreased concentrations of high-density lipoprotein cholesterol (HDL-C) are major risk factors for CVD.³⁻⁵ The overall prevalence of dyslipidemia reached 53% and 34.0% in US⁶ and China.² Also postmenopausal female has a higher prevalence than male.² Thus, abnormal lipid profile is a big concern globally, especially in postmenopausal women, who were considered as a special population in Europe and America dyslipidemia management guidelines.^{7,8}

Endogenous sex hormones mainly act on the reproduction system but their association with lipid metabolism are being revealed. In postmenopausal women, endogenous testosterone (T) levels in postmenopausal women may be part of a proatherogenic profile.^{9,10} Sex hormone binding globulin level is associated with favorable lipid profiles.^{11,12} However, until now, the association between follicle stimulating hormone (FSH), the sex hormone released from pituitary, and lipid profile has not been fully studied in population-based research. A recent study reported in 400 Chinese postmenopausal women, subjects with higher serum FSH had higher TC and LDL-C levels.¹³ Whereas our previous studies have

found in postmenopausal women lower FSH was independently associated with diabetes and non-alcoholic fatty liver disease which were closely related to abnormal lipid profile.^{14,15} Therefore, the relationship between FSH and lipid profile is controversial in postmenopausal women and should be further analyzed.

Using data from an observational investigation named **Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China)** in 2014, we aimed to analyze the association between FSH and lipid profile in Chinese women older than 55 who were postmenopausal with a high probability.

2 Materials And Methods

2.1 Study population

SPECT-China was a cross-sectional investigation (ChiCTR-ECS-14005052, www.chictr.org.cn). "A stratified cluster sampling method was used to select a sample from the general population. The sampling process was stratified according to rural/urban area and economic development status in Shanghai, Jiangxi Province and Zhejiang Province".¹⁶ Detailed sampling information was described in previous study.¹⁷ Totally, 6899 subjects were recruited. In consistence with previous studies,^{18,19} women older than 55 years of age were considered postmenopausal with a high probability. Also, about 97% of Chinese women above 55 are postmenopausal.²⁰ In our sample, there were 1863 women who were older than 55 and were not using hormone replacement therapy. Women with FSH < 25.0IU/L (n = 42), with missing values of FSH (n = 6), having lipid lowering drugs (n = 20) were excluded. Finally, the current study was based on a total number of 1795 women older than 55.

The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine. All procedures followed 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 included in the study.

2.2 Clinical, anthropometric, and laboratory measurements

All subjects were interviewed about their demographic characteristics, medical history and lifestyle risk factors. Body weight and height were measured height with a Seca scale (Hamburg, Germany) and a fixed stadiometer. Body mass index (BMI) was calculated using the measured height and fasting body weight. Blood pressure were measured with the use of standard methods described previously.²¹

After fasting for at least 8 h, blood samples were collected from 7AM to 10AM. They were stored at -20°C when collected and shipped within 2 to 4 hours of collection by air on dry ice to a central laboratory, which was certified by the College of American Pathologists. Glycated hemoglobin (HbA1c) was assessed by high-performance liquid chromatography (MQ-2000PT, China). Fasting plasma glucose, TC,

TG, HDL-C and LDL-C were measured by hexokinase method, CHOD-PAP method, GPO-POD assay, homogeneous methods, respectively (AU 680 analyzer, Beckman Coulter, USA).

Total T, estradiol (E2), FSH and luteinizing hormone (LH) were measured by chemiluminescence (SIEMENS immulite 2000, Germany). The minimal detectable limit for total T, E2, FSH and LH was 0.7nmol/L, 73.4pmol/L and 0.1IU/L, respectively. Samples with values below the minimal detectable limit were given a value midway between zero and the minimal detectable limit for the analyses²². Both the inter-assay and intra-assay coefficients of variation for each hormone were less than 10%.

2.3 Definition of Variables

According to the National Cholesterol Education Program-Adult Treatment Panel III, it defined elevated TC (TC $\geq$ 6.22 mmol/L), elevated TG (TG $\geq$ 2.26 mmol/L), elevated LDL-C (LDL-C $\geq$ 4.14 mmol/L), and low HDL-C (HDL-C $<$ 1.04 mmol/L).²³

Diabetes was defined as a previous diagnosis by health care professionals, fasting plasma glucose 7.0mmol/L or higher, or HbA1c 6.5% or higher. Hypertension was identified by systolic blood pressure $\geq$ 140 mmHg, or diastolic blood pressure $\geq$ 90 mmHg, or a self-reported previous diagnosis of hypertension by a physician.

2.4 Statistical Analysis

All the statistical analyses were performed with IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, NY, USA). All analyses were two-sided. A *P* value $<$ 0.05 indicated a significant difference unless otherwise noted. Continuous variables were expressed as the mean (SD), and categorical variables were described as a percentage (%).

The association of FSH (independent variable) with LDL-C, HDL-C, non-HDL-C, TC, TG, TC/HDL-C ratio and LDL-C/HDL-C ratio (dependent variables) was assessed by linear regression. The base model (model 1) included terms for age, T, E2 and LH. Model 2 included terms for model 1, BMI, hypertension and diabetes. Since TG was non-normally distributed, they were log transformed. Results were expressed as unstandardized coefficients (standard errors).

FSH and LH was divided into quartiles, with the first quartile representing the lowest one and the fourth quartile the highest. Odds ratio (OR) and 95% confidence intervals (CI) were calculated using multinomial logistic regression to determine the risk of elevated TC, TG and LDL-C, and low HDL-C for each quartile of FSH and LH, using highest quartile as the reference. Models were the same as those in linear regression.

3 Results

3.1 Characteristics of the study population

Characteristics of subjects by FSH quartiles are summarized in Table 1. The quartile ranges of FSH were ≤ 49.3 , 49.4–63.4, 63.5–81.2 and ≥ 81.3 IU/L. Through FSH quartiles, women in the lower quartile had significant increasing or decreasing trend of HDL-C, Non-HDL-C, TG, TC/HDL-C ratio, LDL-C/HDL-C ratio, BMI, LH and prevalence of diabetes and hypertension (P for trend < 0.05). LDL-C and TC did not show significant trend (P for trend > 0.05).

Table 1
Characteristics of subjects according to serum FSH quartiles

	Q1	Q2	Q3	Q4	<i>P for trend</i>
<i>N</i>	450	449	449	447	
FSH, IU/L	≤ 49.3	49.4–63.4	63.5–81.2	≥ 81.3	
Age, yr	64(7)	65(7)	64(7)	64(7)	0.088
Diabetes, %	24.4	19.2	14.7	8.3	< 0.001
Hypertension, %	58.7	52.8	54.5	46.3	0.866
LDL-C, mmol/L	3.15(0.79)	3.18(0.83)	3.04(0.71)	3.18(0.71)	0.749
HDL-C, mmol/L	1.49(0.30)	1.50(0.34)	1.55(0.32)	1.61(0.33)	< 0.001
Non-HDL-C, mmol/L	4.01(0.99)	3.99(1.05)	3.79(0.90)	3.92(0.86)	< 0.05
TC, mmol/L	5.50(1.08)	5.48(1.16)	5.34(0.97)	5.52(0.95)	0.731
TG, mmol/L	1.84(1.59)	1.74(1.24)	1.60(0.90)	1.51(0.74)	< 0.001
TC/HDL-C ratio	3.78(0.81)	3.78(0.89)	3.54(0.75)	3.52(0.71)	< 0.001
LDL-C/HDL-C ratio	2.17(0.57)	2.19(0.58)	2.02(0.54)	2.04(0.53)	< 0.001
Body mass index, kg/m ²	25.7(4.0)	24.9(3.3)	24.0(3.3)	23.7(3.4)	< 0.001
Total T, nmol/L	0.71(1.57)	0.63(0.48)	0.59(0.41)	0.58(0.42)	< 0.05
E2, pmol/L	84.9(68.0)	66.8(47.3)	57.0(37.7)	51.2(31.0)	< 0.001
LH, IU/L	16.0(5.5)	21.6(6.3)	26.1(7.3)	35.0(10.5)	< 0.001
Data were summarized as mean (standard deviation) for continuous variables or as number with a proportion for categorical variables.					
T, testosterone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.					

3.2 Association of FSH with lipid profile (continuous variables)

Table 2 summarizes the results of the linear regression models studying the association of FSH with LDL-C, HDL-C, non-HDL-C, TC, TG, TC/HDL-C ratio and LDL-C/HDL-C ratio. In base model (Table 2, model 1), higher FSH quartiles were associated with higher HDL-C, lower log-TG, TC/HDL-C ratio and LDL-C/HDL-C ratio (all P for trend < 0.05). LDL-C, non-HDL-C and TC did not show significant association with FSH quartiles. After further adjustment for metabolic factors (BMI, diabetes and hypertension), the associations of FSH with log TG and LDL-C/HDL-C ratio weakened such further that no significant relationship was observed (Table 2, model 2). The association of FSH quartiles with HDL-C and TC/HDL-C ratio was still significant (both P for trend < 0.05) (Table 2, model 2). Moreover, LH quartiles did not show significant association with these lipid indices in both models (Table 3).

Table 2
Association of circulating FSH with lipid profile (continuous variables)

FSH, IU/L					
	Q1 (≤ 49.3)	Q2 (49.4–63.4)	Q3 (63.5–81.2)	Q4 (≥ 81.3)	<i>P</i> for trend
LDL-C					
Model 1	-0.058(0.069)	-0.021(0.060)	-0.156(0.055)*	Ref.	0.934
Model 2	-0.112(0.071)	-0.067(0.062)	-0.157(0.056)*	Ref.	0.373
HDL-C					
Model 1	-0.139(0.029)*	-0.121(0.025)*	-0.061(0.023)*	Ref.	< 0.001
Model 2	-0.091(0.030)*	-0.095(0.026)*	-0.059(0.023)*	Ref.	< 0.01
Non-HDL-C					
Model 1	0.018(0.087)	0.009(0.075)	-0.168(0.069)*	Ref.	0.276
Model 2	-0.061(0.089)	-0.064(0.077)	-0.184(0.070)*	Ref.	0.972
log-TG					
Model 1	0.066(0.019)*	0.041(0.016)*	0.015(0.015)	Ref.	< 0.001
Model 2	0.025(0.019)	0.015(0.016)	0.004(0.015)	Ref.	0.154
TC/HDL-C ratio					
Model 1	0.241(0.071)*	0.227(0.062)*	-0.009(0.057)	Ref.	< 0.001
Model 2	0.109(0.072)	0.138(0.063)*	-0.027(0.057)	Ref.	< 0.05
LDL-C/HDL-C ratio					
Model 1	0.145(0.050)*	0.155(0.044)*	-0.020(0.040)	Ref.	< 0.001
Model 2	0.051(0.051)	0.095(0.044)*	-0.026(0.040)	Ref.	0.073
TC					
Model 1	-0.121(0.095)	-0.112(0.083)	-0.229(0.076)*	Ref.	0.577

Data were unstandardized coefficients (standard errors). * indicated $P < 0.05$. Linear regression analyses were performed. FSH, follicle-stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

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

Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.

FSH, IU/L					
Model 2	-0.152(0.098)	-0.159(0.085)	-0.244(0.077)*	Ref.	0.326
Data were unstandardized coefficients (standard errors). * indicated $P < 0.05$. Linear regression analyses were performed. FSH, follicle-stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.					
Model 1 included terms for age, total testosterone, estradiol and luteinizing hormone.					
Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.					

Table 3
Association of circulating LH with lipid profile (continuous variables)

LH, IU/L					
	Q1 (≤ 17.4)	Q2 (17.5–23.2)	Q3 (23.4–30.0)	Q4 (≥ 30.1)	<i>P</i> for trend
LDL-C					
Model 1	0.021(0.073)	0.015(0.063)	-0.035(0.056)	Ref.	0.589
Model 2	0.019(0.072)	0.003(0.063)	-0.039(0.056)	Ref.	0.625
HDL-C					
Model 1	0.004(0.031)	-0.021(0.027)	-0.024(0.024)	Ref.	0.830
Model 2	0.008(0.030)	-0.014(0.026)	-0.020(0.023)	Ref.	0.697
Non-HDL-C					
Model 1	0.055(0.091)	-0.007(0.079)	-0.054(0.070)	Ref.	0.423
Model 2	0.048(0.090)	-0.020(0.078)	-0.061(0.070)	Ref.	0.473
log-TG					
Model 1	0.004(0.020)	-0.009(0.017)	0.004(0.015)	Ref.	0.986
Model 2	-0.002(0.019)	-0.014(0.017)	-0.001(0.015)	Ref.	0.767
TC/HDL-C ratio					
Model 1	0.043(0.075)	0.046(0.065)	-0.016(0.058)	Ref.	0.410
Model 2	0.028(0.073)	0.028(0.064)	-0.028(0.056)	Ref.	0.517
LDL-C/HDL-C ratio					
Model 1	0.012(0.053)	0.044(0.046)	-0.004(0.041)	Ref.	0.609
Model 2	0.004(0.052)	0.029(0.045)	-0.012(0.040)	Ref.	0.728
TC					
Model 1	0.059(0.100)	-0.028(0.086)	-0.077(0.077)	Ref.	0.425

Data were unstandardized coefficients (standard errors). * indicated $P < 0.05$. Linear regression analyses were performed. LH, luteinizing hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Model 1 included terms for age, total testosterone, estradiol and follicle-stimulating hormone.

Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.

LH, IU/L					
Model 2	0.057(0.100)	-0.035(0.086)	-0.081(0.077)	Ref.	0.443
Data were unstandardized coefficients (standard errors). * indicated $P < 0.05$. Linear regression analyses were performed. LH, luteinizing hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.					
Model 1 included terms for age, total testosterone, estradiol and follicle-stimulating hormone.					
Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.					

3.3 Prevalence of dyslipidemia (Fig. 1)

The prevalence of low HDL-C through FSH quartiles was 4.7%, 6.2%, 2.9% and 1.3%, respectively, and that of elevated TG was 20.0%, 19.6%, 15.6% and 13.2%. Both of these two kinds of dyslipidemia showed significant trend (P for trend < 0.05).

The prevalence of elevated LDL-C through FSH quartiles was 10.9%, 10.0%, 7.8% and 8.3%, respectively, and that of elevated TC was 23.1%, 20.9%, 17.4% and 21.3%. Prevalence of elevated LDL-C and TC did not have significant trend through FSH quartiles.

3.4 Association of FSH with dyslipidemia (categorical variables)

Table 4 shows the association of FSH with elevated TC ($TC \geq 6.22$ mmol/L), elevated TG ($TG \geq 2.26$ mmol/L), elevated LDL-C ($LDL-C \geq 4.14$ mmol/L), and low HDL-C ($HDL-C < 1.04$ mmol/L) by logistic regression analyses. In model 1 adjusted for age and other sex hormones, compared with women in the highest quartile of FSH, ORs of elevated LDL-C, low HDL-C, elevated TG and elevated TC in women in the lowest FSH quartile were 1.00 (95% CI 0.53, 1.88), 6.41 (95% CI 1.97, 20.92), 1.37 (95% CI 0.83, 2.26), and 0.92 (95% CI 0.59, 1.44) respectively. Only low HDL-C showed significant association with FSH quartiles (P for trend < 0.05). Further adjusting for other metabolic factors (BMI, diabetes and hypertension) weakened the association between FSH and low HDL-C, but it still has significance (OR 5.25, 95%CI 1.60, 17.26) (Table 4, model 2). LH quartiles did not show significant association with dyslipidemia in both models (Table 5). Previous study found the significant association between FSH and diabetes,¹⁵ we further did diabetes and non-diabetes subgroup analysis. The results showed the associations between FSH and HDL-C were significant in non-diabetic subjects (P for trend < 0.05) and marginal in diabetic subjects (P for trend 0.063).

Table 4
Association of circulating FSH with lipid profile (dichotomous variables)

FSH, IU/L					
	Q1 (≤ 49.3)	Q2 (49.4–63.4)	Q3 (63.5–81.2)	Q4 (≥ 81.3)	<i>P</i> for trend
LDL-C ≥ 4.14 mmol/L					
Model 1	1.00(0.53, 1.88)	0.97(0.56, 1.70)	0.79(0.47, 1.34)	Ref.	0.773
Model 2	0.94(0.50, 1.79)	0.94(0.54, 1.65)	0.79(0.46, 1.33)	Ref.	0.934
HDL-C < 1.04 mmol/L					
Model 1	6.41(1.97, 20.92)	7.35(2.60, 20.77)	2.82(1.00, 7.98)	Ref.	0.001
Model 2	5.25(1.60, 17.26)	6.54(2.31, 18.50)	2.70(0.96, 7.63)	Ref.	0.003
TG ≥ 2.26 mmol/L					
Model 1	1.37(0.83, 2.26)	1.34(0.87, 2.07)	1.06(0.71, 1.60)	Ref.	0.137
Model 2	1.01(0.61, 1.69)	1.13(0.72, 1.76)	0.99(0.66, 1.50)	Ref.	0.852
TC ≥ 6.22 mmol/L					
Model 1	0.92(0.59, 1.44)	0.76(0.51, 1.13)	0.69(0.47, 1.00)	Ref.	0.964
Model 2	0.91(0.58, 1.44)	0.75(0.50, 1.13)	0.68(0.47, 0.99)	Ref.	0.922
Data were odds ratio (95% CI). Logistic regression analyses were performed. FSH, follicle-stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.					
Model 1 included terms for age, total testosterone, estradiol and luteinizing hormone.					
Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.					

Table 5
Association of circulating LH with lipid profile (dichotomous variables)

LH, IU/L					
	Q1 (≤ 17.4)	Q2 (17.5–23.2)	Q3 (23.4–30.0)	Q4 (≥ 30.1)	<i>P</i> for trend
LDL-C ≥ 4.14 mmol/L					
Model 1	0.83(0.45, 1.53)	0.55(0.31, 0.97)	0.79(0.48, 1.28)	Ref.	0.465
Model 2	0.89(0.47, 1.66)	0.59(0.33, 1.06)	0.81(0.49, 1.33)	Ref.	0.615
HDL-C < 1.04 mmol/L					
Model 1	0.62(0.23, 1.66)	0.80(0.34, 1.90)	0.91(0.41, 2.03)	Ref.	0.302
Model 2	0.66(0.24, 1.81)	0.75(0.31, 1.84)	0.90(0.40, 2.02)	Ref.	0.376
TG ≥ 2.26 mmol/L					
Model 1	1.31(0.79, 2.15)	1.00(0.64, 1.56)	1.20(0.81, 1.78)	Ref.	0.453
Model 2	1.28(0.76, 2.15)	0.99(0.62, 1.57)	1.14(0.76, 1.71)	Ref.	0.482
TC ≥ 6.22 mmol/L					
Model 1	1.13(0.73, 1.77)	0.75(0.51, 1.12)	0.85(0.60, 1.22)	Ref.	0.622
Model 2	1.03(0.65, 1.63)	0.77(0.51, 1.16)	0.82(0.57, 1.18)	Ref.	0.990
Data were odds ratio (95% CI). Logistic regression analyses were performed. LH, luteinizing hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.					
Model 1 included terms for age, total testosterone, estradiol and follicle-stimulating hormone.					
Model 2 included terms for model 1 in addition to body mass index, diabetes and hypertension.					

4 Discussion

In women older than 55 with a high probability of postmenopause, we discovered that subjects with lower FSH had lower HDL-C, higher TG, TC/HDL-C ratio and LDL-C/HDL-C ratio. Metabolic factors including

diabetes, BMI and hypertension mostly explained the association of FSH with TG and LDL-C/HDL-C ratio but only partially explained the associations of FSH with HDL-C and TC/HDL-C ratio. As far as we know, this is the first study to detect the association between FSH and lipid profile in detail in a large population sample.

Dyslipidemia is a well-known independent risk factor for CVD and cerebral ischemic stroke.²⁴ With rapid socioeconomic development, urbanization, and lifestyle and diet changes, the prevalence of dyslipidemia has also been rapidly increasing.²⁵ Dyslipidemia is closely related to other metabolic comorbidities such as diabetes, obesity and fatty liver. For example, the features of diabetic dyslipidemia are elevated TG concentration, reduced HDL-C concentration, and increased LDL-C concentration.²⁶ NAFLD is also characterized by atherogenic dyslipidemia and HDL dysfunction.²⁷ According to recent studies, FSH was found to be significantly associated with metabolic diseases.^{13–15, 28} Our previous studies showed, compared with postmenopausal women in the highest quartile of FSH, the odds of diabetes and non-alcoholic fatty liver disease in postmenopausal women in the lowest quartile of FSH increased 96% and 84–194%, respectively.^{14,15} In this study, we further demonstrated lower FSH was significantly associated with lower HDL-C, and higher TG, TC/HDL-C ratio and LDL-C/HDL-C ratio after adjusting for age, total T, E2 and LH. These results accord with recent studies about the association of FSH with metabolic syndrome.^{28,29} The above information lends credibility to the findings on FSH and lipid profile.

FSH is mainly secreted by the pituitary gland and it regulates development and function of reproductive organ after being released into the blood, therefore it is not surprising that FSH receptor (FSHR) is mainly expressed in the reproductive system.³⁰ However, FSHR has also been found to be expressed in non-reproductive organs and tissues such as mouse osteoclasts,³¹ human blood vessel,³² chicken adipose tissue³³ and human liver,¹³ exerting extra-reproduction function. Interestingly, a recent study showed FSH interacted with FSHR in hepatocytes and reduced LDL receptors levels, which subsequently attenuated the endocytosis of LDL-C in mouse model. This might lead to an elevated circulating LDL-C level in postmenopausal women with a mean age of 48.6 years.¹³ In chicken and mouse model, studies also found FSH promoted lipid biosynthesis in adipose tissue and visceral fat accumulation through upregulating FSHR mRNA expression and the *Gai*/Ca²⁺/cAMP-response-element-binding protein pathway.^{33,34} These results seem to be contradictory to previous epidemiological studies. A negative correlation between FSH concentration and BMI was observed.^{22,35–37} Also, every 1 standard deviation decrement of FSH is associated with a 3.83-fold increased risk of metabolic syndrome, in which adiposity is the core element.²⁸ Moreover, in observational cohort studies, in obese women the rise of FSH was significantly attenuated, especially after the final menstrual period., and weight loss would increase FSH among overweight and obese postmenopausal women.³⁸ In regard of opposite study results, here is one explanation: FSH may induce fat accumulation and lipid biosynthesis in early stage of postmenopause, but the development of metabolic diseases especially obesity would conversely suppress the release of FSH and LH. This hypothesis needs further investigations to confirm.

It is not surprising that common metabolic factors including diabetes, BMI and hypertension largely mediated the association between FSH and lipid profile. Other endogenous sex hormones may also have a role in this association. For example, total testosterone may induce rise of TC, LDL-C or TG, and fall of HDL-C,^{10,39} though some studies found no such effect.^{11,40} Estrogen hormone replacement therapy usually ameliorated lipid profile.^{41,42} However, it is worth mentioning that in our study, even after adjustment for total T, E2 and LH, FSH was still significantly associated with some elements of lipid profile. Also, considering the independent association of FSH and HDL-C, some internal relationship might exist which needs further exploration.

Our study had some strengths. First, the novelty, it presented in detail the association between FSH and lipid profile for the first time in a large sample, and focus on several possible explanatory factors. Second, the study was performed in a general population as opposed to a clinic-based population. However, our study also has some limitations. Because the nature of this study is cross-sectional, causal relationship could not be confirmed. Moreover, final menstruation information was not obtained, so based on previous studies^{18,19} and natural menopause age in Chinese women,²⁰ we used an age proxy 55 years to define postmenopause.

In conclusion, lower FSH was associated with lower HDL-C, higher TG, TC/HDL-C ratio and LDL-C/HDL-C ratio in women older than 55 with a high probability of postmenopause. Diabetes, BMI and hypertension mostly explained the association of FSH with TG and LDL-C/HDL-C ratio but only partially explained the associations of FSH with HDL-C and TC/HDL-C ratio. Further prospective trials and animal studies are needed to clarify this association.

Declarations

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Author contributions

YL, NW, and HZ conceived and designed the research; WZ, YC, and XZ analysed the data and drafted the manuscript. All authors contributed to data interpretation and the editing of the manuscript. YL, NW, and HZ critically revised the manuscript for important intellectual content. All authors have approved the final version to be published. YL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with Ethical Standards

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Disclosure statement

No potential conflicts of interest relevant to this article were reported.

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Figures

Figure 1

Prevalence of abnormal lipid profile according to FSH quartiles. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.