Follicle-Stimulating Hormone, Its Association with Cardiometabolic Risk Factors, and 10-Year Risk of Cardiovascular Disease in Postmenopausal Women

Ningjian Wang, MD, PhD*; Hongfang Shao, MD*; Yi Chen, MD*; Fangzhen Xia, PhD; Chen Chi, MD; Qin Li, MD, PhD; Bing Han, MD, PhD; Yincheng Teng, MD, PhD; Yingli Lu, MD, PhD

Background—Cardiovascular disease is the leading cause of mortality in postmenopausal women. Follicle-stimulating hormone (FSH) shows negative associations with obesity and diabetes mellitus in postmenopausal women. We aimed to study the associations between FSH and 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in postmenopausal women.

Methods and Results—SPECT-China (the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors) is a 22-site, population-based study conducted during 2014–2015. This study included 2658 postmenopausal women. A newly developed effective tool for 10-year ASCVD risk prediction among Chinese was adopted. Regression analyses were performed to assess the relationship among FSH, 10-year ASCVD risk, and multiple cardiometabolic risk factors. With the increase in FSH quartiles, the mean 10-year ASCVD risk in postmenopausal women decreased from 4.9% to 3.3%, and most metabolic parameters were significantly ameliorated (all P for trend <0.05). In regression analyses, a 1-SD increment in ln-FSH was negatively associated with continuous (B −0.12, 95% confidence interval, −0.16, −0.09, P<0.05) and categorical (odds ratio 0.65, 95% confidence interval, 0.49, 0.85, P<0.05) 10-year ASCVD risk. These significant associations existed in subgroups with or without medication use, obesity, diabetes mellitus, hypertension, and dyslipidemia. Body mass index and waist circumference (both B −0.35, 95% confidence interval, −0.40, −0.30, P<0.05) had the largest associations of all metabolic measures, and blood pressure had the smallest association.

Conclusions—Serum FSH levels were negatively associated with 10-year ASCVD risk in postmenopausal women. Among cardiometabolic factors, obesity indices had the largest associations with FSH. These results indicated that a low FSH might be a risk factor or a biomarker for cardiovascular disease risk in postmenopausal women. (***J Am Heart Assoc***. 2017;6:e005918. DOI: 10.1161/JAHA.117.005918.)

Key Words: cardiovascular disease risk factors • endocrinology • follicle-stimulating hormone • menopause

Cardiovascular disease (CVD) is the current leading cause of death and disease burden worldwide and in China.[1,2] More than 2150 Americans die of CVD every day, with an average of 1 death every 40 s.[3] In 2013, 3.72 million Chinese died of CVD.[2] The cost for hospitalization for acute myocardial infarction and stroke in China was ≈11 billion US dollars in 2013.[4] Thus, CVD poses a great burden on human beings.

Typically, CVD is also the leading cause of mortality in postmenopausal women.[5] Women's CVD risk significantly increases after they shift into menopause, which is not just related to aging but also, at least in part, to the decline in ovarian hormone concentrations during the menopausal transition and beyond.[6] Hence, a more sex-specific approach should be adopted for better prevention and treatment of CVD

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Clinical Perspective

What Is New?

- For the first time, this study analyzed the associations among follicle-stimulating hormone, 10-year atherosclerotic cardiovascular disease risk, various metabolic parameters, and metabolic diseases in postmenopausal women.
- A negative association of follicle-stimulating hormone with 10-year atherosclerotic cardiovascular disease risk in postmenopausal women was revealed, which was stable in subgroups with or without central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome.

What Are the Clinical Implications?

- A relatively low follicle-stimulating hormone in postmenopausal women might be a risk factor or biomarker for cardiovascular disease risk.

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in women because CVD risk is affected by hormonal status and female-specific factors.[7]

Traditionally, the main role of endogenous sex hormones is in the reproductive system, but their association with CVD and its risk factors are gradually being revealed. For example, high testosterone levels may lead to a proatherogenic profile in postmenopausal women,[8] but high sex hormone binding globulin level is associated with favorable CVD risk.[9] Follicle-stimulating hormone (FSH) is necessary for follicular growth initiation and germ cell maturation in women. Interestingly, besides their presence in reproductive tissues, FSH receptors are also expressed in blood vessels,[10] liver,[11] adipose tissue,[12] and other places, which provides the molecular basis for its extrareproductive function. Moreover, our previous studies indicated that FSH was negatively associated with obesity, fatty liver,[13] and diabetes mellitus.[14] However, we still know very little about the association between FSH and CVD risk in postmenopausal women.

Using data from an observational investigation named SPECT-China (the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors) in 2014–2015, we aimed to analyze the association between FSH and 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in postmenopausal women. It may have important implications for which cardiometabolic factors are more closely related to FSH. Therefore, we also analyzed the associations between FSH and multiple cardiometabolic factors.

## Materials and Methods

Participants

The data were from the participants in SPECT-China, a cross-sectional survey in East China (ChiCTR-ECS-14005052, www.chictr.org.cn). Recruitment and enrollment have been

previously described in detail.[15–17] Chinese citizens ≥18 years old who had lived in their current area for ≥6 months were selected. We also excluded subjects with severe communication problems, acute illness, or who were unwilling to participate. From January 2014 to December 2015, 10 441 subjects who were 18 to 93 years old were recruited into the SPECT-China study from 22 sites in Shanghai, Zhejiang, Jiangsu, Anhui, and Jiangxi provinces (Figure 1). The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong 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.

There were 3226 postmenopausal women. Postmenopausal women were defined as subjects who reported that they had stopped menstruating for a minimum of 12 months (n=1431), who were 55 years of age or older (n=2872), or who had a hysterectomy or oophorectomy at least 1 year before (n=139). Exclusion criteria included missing FSH values (n=11), FSH <25.0 IU/L (according to the 2011 Stages of Reproductive Aging Workshop +10 recommendation, late perimenopausal state is characterized as FSH level ≥25 IU/L) (n=159),[18] and history of CVD (n=398). In all, 2658 postmenopausal women were included in this study (Figure 1).

Measurements

Interviews and collection of biological specimens at each site were undertaken with a single assessment protocol. Blood samples were obtained between 7:00 AM and 10:00 AM after fasting for at least 8 hours. Blood was refrigerated immediately after phlebotomy, and it was shipped to a central laboratory certified by the College of American Pathologists within 2 to 4 hours. After immediate centrifugation, the blood, serum, and plasma were frozen in a central laboratory. Total testosterone (T), estradiol (E2), luteinizing hormone (LH), and FSH (Immulite 2000; Siemens, Erlangen, Germany) were detected using a chemiluminescence assay. Glycated hemoglobin was measured by high-performance liquid chromatography (MQ-2000PT; Medconn, Shanghai, China). Fasting plasma glucose (FPG) and lipid profiles were measured by a Beckman Coulter AU 680 (Brea, California, USA). Samples with values below the minimal detectable limit were given a value midway between zero and the minimal detectable limit for the analyses.[19] The interassay and intra-assay coefficients of variation were, respectively, 6.6% and 5.7% for total T, 7.5% and 6.2% for E2, 4.5% and 3.8% for FSH, and 6.0% and 4.9% for LH. Insulin resistance was estimated by the homeostasis
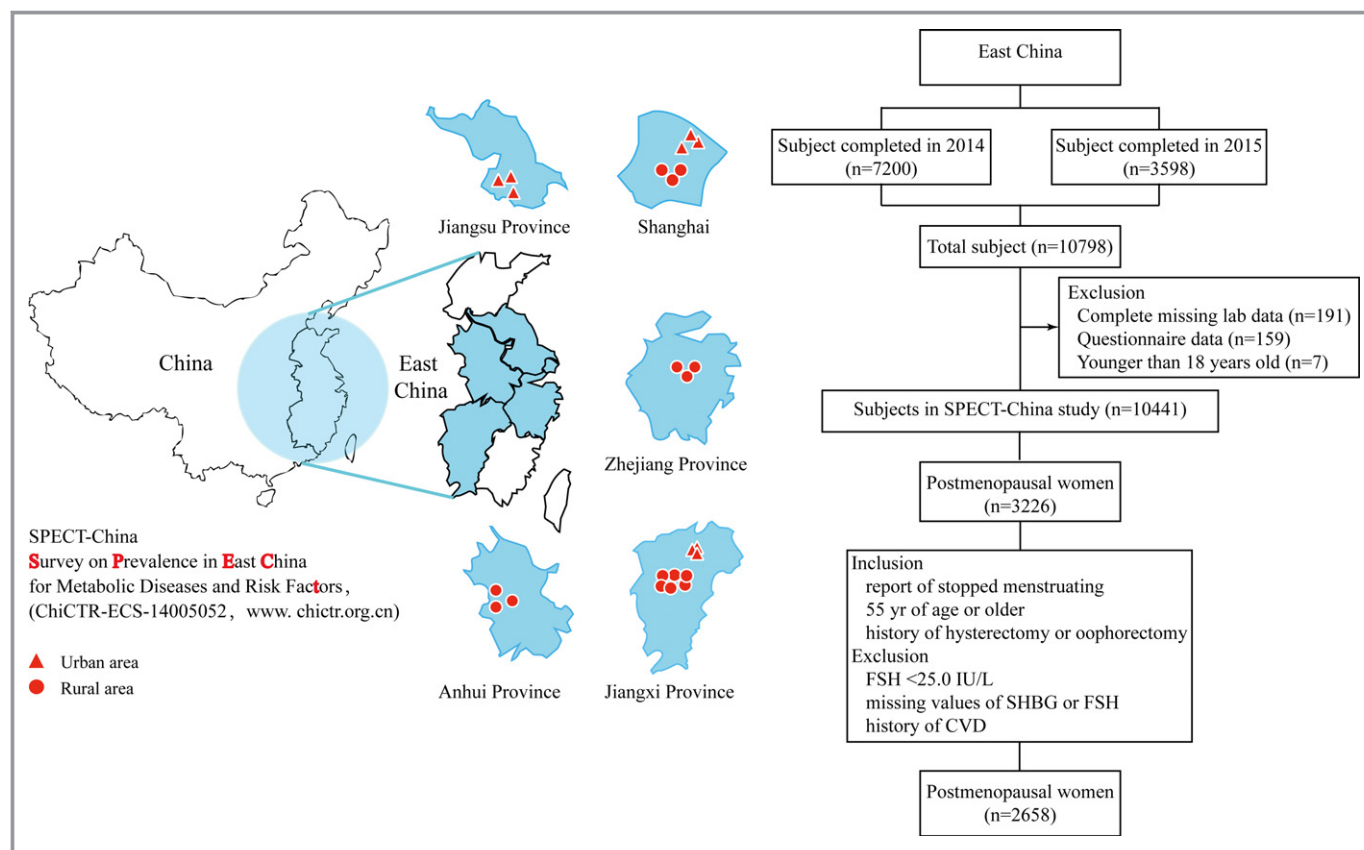
Figure 1. Flowchart of participants from East China. CVD indicates cardiovascular disease; FSH, follicle-stimulating hormone; SHBG, sex hormone binding globulin.

model assessment index of insulin resistance (HOMA-IR): (fasting insulin [mIU/L])×(FPG [mmol/L])/22.5.[20] Insulin secretion was estimated by the homeostasis model of β-cell function (HOMA-β) percentage (HOMA-β%): (20×fasting insulin [mIU/L])/(FPG [mmol/L]−3.5) (percentage).[20]

Weight (kilograms) and height (centimeters) were measured using a stadiometer and a vertical ruler when subjects wore light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at a level midway between the lowest rib and the iliac crest. Blood pressure was measured using standard methods as described previously.[21] Current smoking status was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes.[21]

Definition of Variables

A newly developed effective tool with good performance for 10-year ASCVD risk prediction among Chinese individuals was adopted.[4] This tool was developed with 21 320 Chinese participants, validated in 84 961 Chinese participants, and compared with the cohort equations reported in the American College of Cardiology/American Heart Association guidelines.[4] This equation includes age, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, waist circumference, smoking, diabetes mellitus, geographic region, and the interaction between age and systolic blood pressure. Predicted ASCVD risk higher than 10% was defined as high 10-year ASCVD risk.

Central obesity was defined as a waist circumference ≥80 cm in females.[21] Overweight and obesity were defined based upon BMI measures of 25 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively.[21] Diabetes mellitus was determined by a previous diagnosis by healthcare professionals, FPG level ≥7.0 mmol/L, or glycated hemoglobin ≥6.5%. Hypertension was identified by a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or a self-reported previous diagnosis of hypertension by a physician. According to the modified National Cholesterol Education Program-Adult Treatment Panel III, dyslipidemia was defined as total cholesterol ≥6.22 mmol/L, triglycerides ≥2.26 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L or high-density lipoprotein cholesterol <1.04 mmol/L, or treatment for hyperlipidemia by physicians.[22] Metabolic syndrome was determined based on the International Diabetes Federation criteria (2005).[23]

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, New York). All analyses were 2-sided. A *P* value <0.05 indicated significance. Continuous variables were expressed as the mean±SD, and categorical variables were expressed as a percentage (%). *P* for trend was calculated by ANOVA and χ^2 tests. There were 142 missing values for predicted 10-year ASCVD risk, 86 and 114 missing values for BMI and waist circumference, respectively, and 90 missing values for blood pressure.

Prior to regression analyses, FSH, 10-year ASCVD risk, and CVD risk factors (continuous variables) were ln-transformed and scaled to SDs. Associations among FSH, CVD risk, and risk factors were analyzed using linear regression models with each measure as the outcome and FSH as the explanatory variable. The regression models were adjusted for age, total T, E2, LH, economic status, and BMI (not included for BMI and waist circumference in regression model). To facilitate comparisons across parameters, association magnitudes are reported in SD units of CVD risk factors per 1-SD increment in ln-FSH.[24]

The associations among ln-FSH, high 10-year ASCVD risk, and metabolic diseases (categorical variables) were assessed by logistic regression. The regression models were adjusted for age, total T, E2, LH, economic status, and BMI (but not included for overweight, obesity, or central obesity in regression model). Results were expressed as odds ratios (95% confidence interval [CI]).

Subgroup analyses were conducted in those with or without medication use (including lipid, glucose and blood pressure–lowering drugs, and cortisone), central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. The regression models were adjusted for age, total T, E2, LH, economic status, and BMI. Association magnitudes are reported in SD units of 10-year ASCVD per 1-SD increment in ln-FSH. Results were expressed as unstandardized coefficients (95% CI).

We performed sensitivity analyses. First, there was concern over including women who underwent a hysterectomy, as some women who underwent a hysterectomy may not have a concurrent oophorectomy and may falsely be included in the cohort. Thus, we performed the regression analyses excluding women with previous hysterectomy or oophorectomy (n=87). We also performed the regression analyses excluding women who smoked (n=87). Second, to facilitate clinical interpretation, we used the FSH quartiles instead of ln-FSH to further reflect the association. Third, imputation could not be needed in case the missing values were <10%. However, we wanted to know whether the results were solid, so we imputed the missing values by the means of the observed values.

Results

Characteristics of the Study Population by Quartiles of FSH

General demographic and laboratory characteristics of the study population are summarized in Table 1. The quartile ranges were ≤47.47, 47.48–61.19, 61.20–78.18, and ≥78.19 nmol/L. The FSH of postmenopausal women with previous CVD (n=398) was 63.0 (23.1) IU/L, slightly lower than that of postmenopausal women without previous CVD (n=2658) (64.5 [23.6] IU/L), though there was no significant difference.

According to trend analysis, with the increase in FSH quartiles, 10-year ASCVD risk in postmenopausal women decreased from 4.9 (3.2)% to 3.3 (2.5)% (*P* for trend <0.001), and similarly, most metabolic parameters were significantly ameliorated including BMI, waist circumference, triglycerides, high-density lipoprotein, FPG, glycated hemoglobin, HOMA-IR, and diastolic blood pressure (all *P* for trend <0.05). The prevalence of being overweight, obesity, dyslipidemia, hypertension, diabetes mellitus, and metabolic syndrome also decreased with increasing quartiles of FSH (all *P* for trend <0.05).

No women recruited were using hormone replacement therapy in this study, mainly because subjects with FSH lower than 25.0 IU/L were excluded. The proportions of subjects taking lipid-, glucose-, or blood pressure–lowering drugs were 0.9%, 5.8%, and 16.4%, respectively. Five women were taking cortisone, and 4 women were taking levothyroxine.

Association of FSH With 10-Year ASCVD Risk and CVD Risk Factors

Figure 2 summarizes the results of SD units of 10-year ASCVD risk and metabolic parameters per 1-SD increment in ln-FSH expressed with unstandardized coefficients (B) (95% CI). Ln-FSH (B −0.12, 95% CI, −0.16, −0.09, *P*<0.05) was negatively associated with 10-year ASCVD risk. Various metabolic measures were also associated with FSH. Overall, higher FSH was associated with metabolic biomarkers linked with lower cardiometabolic risk. Ln-BMI and ln-waist circumference (B −0.35, 95% CI, −0.40, −0.30) had the largest association magnitudes of all metabolic measures. In lipid profile, ln-high-density lipoprotein (B 0.26, 95% CI, 0.20, 0.31) had the largest association strength, and ln-total cholesterol (B 0.03, 95% CI, −0.02, 0.09) had the smallest. Regarding glycemic indices, ln-glycated hemoglobin (B −0.20, 95% CI, −0.26, −0.15) had stronger associations with ln-FSH than ln-FPG (B −0.07, 95% CI, −0.12, −0.01) and ln-HOMA-IR (B −0.09, 95% CI, −0.15, −0.04). Moreover, there was a significant association with ln- systolic blood pressure

Table 1. Characteristics of the Participants by Quartiles of Follicle Stimulating Hormone

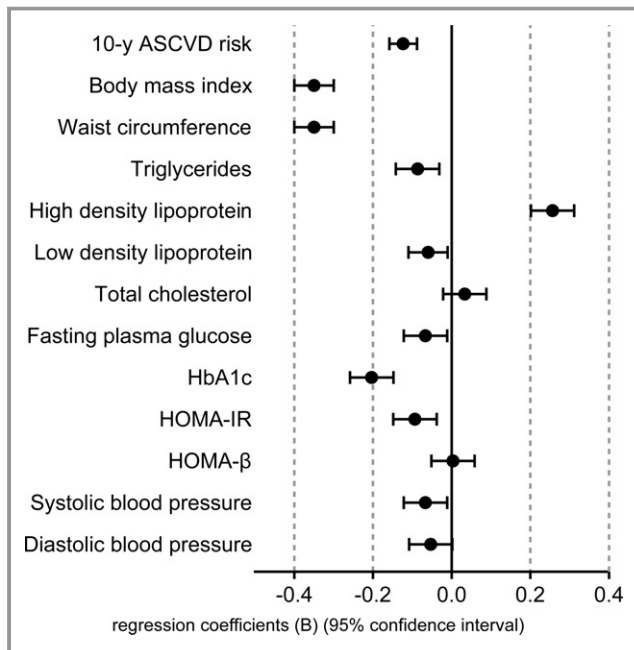| | Follicle Stimulating Hormone, IU/L | | | | |
| | Q1 | Q2 | Q3 | Q4 | |
	≤47.47	47.48 to 61.19	61.20 to 78.18	≥78.19	P for Trend
N	664	664	666	664	
Age, y	63 (7)	63 (7)	63 (8)	62 (8)	<0.01
10-y ASCVD risk predicted, %	4.9 (3.2)	4.4 (3.0)	4.2 (3.2)	3.3 (2.5)	<0.001
Total T, nmol/L	0.71 (1.31)	0.64 (0.46)	0.60 (0.42)	0.56 (0.39)	<0.001
E2, pmol/L	82.3 (89.3)	61.6 (65.3)	55.9 (88.1)	44.0 (34.0)	<0.001
LH, IU/L	17.4 (6.3)	23.2 (7.2)	27.8 (7.8)	37.7 (12.6)	<0.001
Body mass index, kg/m^2	26.2 (3.9)	25.2 (3.3)	24.3 (3.3)	23.7 (3.3)	<0.001
Waist circumference, cm	84.7 (10.2)	82.2 (9.2)	80.0 (9.0)	77.6 (8.9)	<0.001
Triglycerides, mmol/L	1.84 (1.39)	1.69 (1.00)	1.63 (0.96)	1.53 (0.80)	<0.001
HDL, mmol/L	1.40 (0.33)	1.46 (0.31)	1.52 (0.32)	1.57 (0.32)	<0.001
LDL, mmol/L	3.31 (0.85)	3.36 (0.84)	3.26 (0.80)	3.34 (0.80)	0.90
Total cholesterol, mmol/L	5.49 (1.44)	5.49 (1.10)	5.44 (1.00)	5.56 (1.00)	0.44
Fasting plasma glucose, mmol/L	6.00 (1.75)	5.84 (1.51)	5.72 (1.41)	5.59 (1.19)	<0.001
HbA1c, mmol/L	5.90 (1.14)	5.78 (0.96)	5.62 (0.82)	5.51 (0.82)	<0.001
HOMA-IR	1.96 (1.77)	1.82 (2.89)	1.72 (3.13)	1.38 (1.18)	<0.001
HOMA-β	64.6 (41.7)	62.5 (48.5)	60.7 (44.1)	57.4 (38.2)	<0.01
Systolic blood pressure, mm Hg	142 (21)	140 (22)	140 (22)	135 (22)	<0.001
Diastolic blood pressure, mm Hg	81 (13)	80 (13)	80 (12)	79 (12)	<0.01
Current smoker, %	3.6	2.6	4.8	2.1	0.46
Overweight, %	47.4	44.0	33.0	26.1	<0.001
Obesity, %	15.7	6.8	4.8	4.2	<0.001
Central obesity, %	70.4	63.1	51.3	41.2	<0.001
Diabetes mellitus, %	25.3	18.5	15.3	9.9	<0.001
Hypertension, %	64.7	61.5	58.9	52.2	<0.05
Dyslipidemia, %	46.8	39.8	35.3	34.5	<0.001
Metabolic syndrome, %	66.0	58.0	48.0	36.7	<0.001
Lipid-lowering drugs, %	1.2	0.5	1.4	0.8	0.79
Glucose-lowering drugs, %	8.9	6.0	4.5	3.6	<0.001
Blood pressure–lowering drugs, %	21.4	15.7	14.9	13.6	<0.001

The data are summarized as the mean (SD) for continuous variables or as a numerical proportion for categorical variables. *P* for trend was calculated by ANOVA and χ^2 tests. There were 142 missing values for predicted 10-y ASCVD risk, 86 and 114 missing values for body mass index and waist circumference, respectively, and 90 missing values for blood pressure. ASCVD indicates atherosclerotic cardiovascular disease; E2, estradiol; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model of β-cell function; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone; T, testosterone.

(B −0.07, 95% CI, −0.12, −0.01) and a marginal association with ln–diastolic blood pressure (B −0.05, 95% CI, −0.11, 0.00).

In Figure 3, according to the stratified analyses, the significant associations between each 1-SD increment in ln-FSH and 10-year ASCVD risk existed in subgroups with or without medication use, central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome (all *P*<0.05).

Association of FSH With High 10-Year ASCVD Risk and Metabolic Diseases

The associations between ln-FSH and high 10-year ASCVD risk and metabolic diseases by logistic regression are listed in Figure 4. The odds ratio between each 1-SD increment of ln-FSH and high 10-year ASCVD risk was 0.65 (95% CI, 0.49, 0.85). All the associations of ln-FSH with high 10-year ASCVD risk, obesity, diabetes mellitus, hypertension, dyslipidemia,
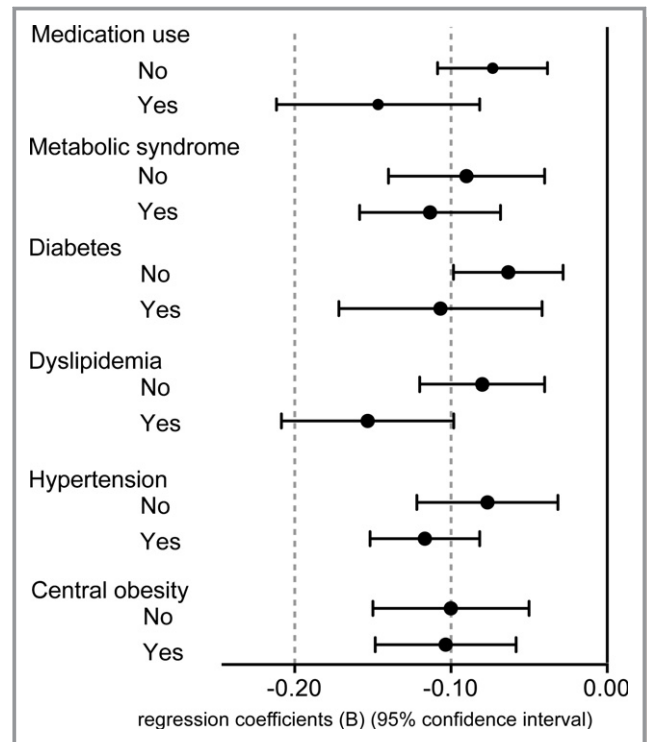
Figure 2. Associations of follicle-stimulating hormone with 10-y ASCVD risk and cardiometabolic measures in postmenopausal women. They were analyzed using linear regression models with each measure as the outcome and follicle-stimulating hormone as the explanatory variable. To facilitate comparisons across parameters, association magnitudes are reported in SD units of parameters per 1-SD increment in ln-follicle-stimulating hormone. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index (but not included for body mass index and waist circumference in regression model). The results are expressed as unstandardized coefficients (95% confidence interval). ASCVD indicates atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment index of insulin resistance.

and metabolic syndrome were in the same direction. Obesity defined by BMI (odds ratio [OR] 0.35, 95% CI, 0.28, 0.44) still had the largest association strength with each 1-SD increment of ln-FSH, and hypertension (OR 0.89, 95% CI, 0.79, 0.99) had the smallest association strength.

Sensitivity Analyses

We performed a sensitivity analysis that excluded women with a previous hysterectomy or oophorectomy (n=139). The results were not changed. Ln-FSH (B -0.12, 95% CI, -0.15, -0.08, $P<0.001$) was still negatively associated with 10-year ASCVD risk. The OR between each 1-SD increment in ln-FSH and high 10-year ASCVD risk was 0.65 (95% CI, 0.49, 0.86). In women who did not currently smoke, the results were similar (B -0.12, 95% CI, -0.15, -0.08, $P<0.001$; OR 0.65, 95% CI, 0.49, 0.88).


Figure 3. Subgroup analyses of associations between follicle-stimulating hormone and 10-y atherosclerotic cardiovascular disease (ASCVD) risk in postmenopausal women. Medication use included lipid-, glucose-, and blood pressure–lowering drugs and cortisone (n=552). Association magnitudes are reported in SD units of 10-y ASCVD risk per 1-SD increment in follicle-stimulating hormone. Linear regression analysis was used. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status and body mass index. The results are expressed as unstandardized coefficients (95% confidence interval).

In Table 2, when using the FSH quartiles instead of ln-FSH, compared with women in the highest quartile of FSH, we found B and OR of 10-year ASCVD risk in women in the lowest quartile of FSH were 0.22 (95% CI, 0.15, 0.29) and 4.22 (95% CI, 1.90, 9.36), respectively. The Bs and ORs of 10-year ASCVD risk decreased across FSH quartiles (both P for trend <0.05).

Finally, we imputed the missing values of BMI, waist circumference, and blood pressure. The association did not change. Ln-FSH (B -0.13, 95% CI, -0.17, -0.10, $P<0.001$) was still negatively associated with 10-year ASCVD risk.

Discussion

Overall, this study analyzed the associations among FSH, 10-year ASCVD risk, various metabolic parameters, and metabolic diseases in postmenopausal women. For the first time, our study revealed a negative association of FSH with 10-year ASCVD risk in postmenopausal women. This
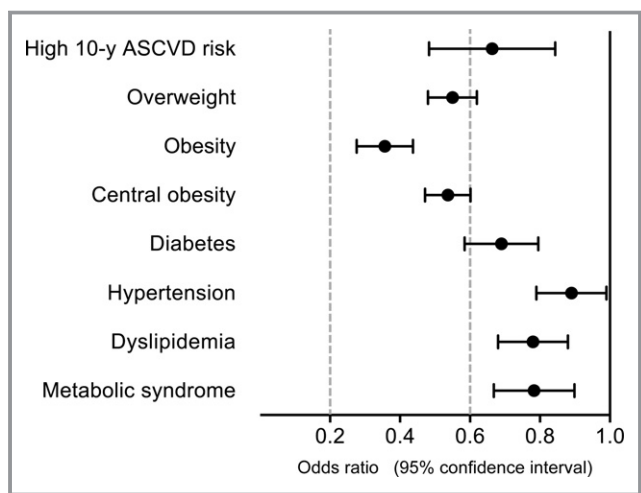
Figure 4. Associations of follicle-stimulating hormone with high 10-y ASCVD risk and metabolic diseases in postmenopausal women. They were analyzed using logistic regression models with each disease as the outcome and follicle-stimulating hormone as the explanatory variable. Adjusted ORs for each 1-SD increment of ln-follicle-stimulating hormone associated with corresponding diseases are shown. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index (but not included for overweight, obesity, and central obesity in regression model). The results were expressed as odds ratios (95% confidence interval). ASCVD indicates atherosclerotic cardiovascular disease; OR, odds ratio.

association was stable in subgroups with or without central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. Additionally, among cardiometabolic factors, BMI and waist circumference had the largest magnitude of significant association, and blood pressure had the smallest association. These results indicated that a relatively low FSH in postmenopausal women might be a risk factor or biomarker for CVD risk and needs further exploration.

Because the predicted 10-year ASCVD risk is an algorithm based on several cardiometabolic risk factors including waist circumference, blood pressure, lipid profile, diabetes mellitus, and others, the association between FSH and CVD risk, as expected, partly relied on the link between FSH and CVD risk

factors. Adiposity indices had the largest association strength in this study. Each 1-SD higher FSH level (0.36 natural-log IU/L) in postmenopausal women was associated with ≈1.3 kg/m^2 lower BMI and a 3.4-cm-smaller waist circumference. Previous studies found that in white and black women, obesity could obviously decrease the rise in FSH in the period after the final menstrual period,[25] and women with a normal weight tended to have a slow decline in E2 and the high/medium FSH trajectories.[26] Moreover, weight loss could elevate FSH levels in overweight subjects.[27] This finding may exist because increased BMI could inhibit gonadotropin secretion.[28] The odds of diabetes mellitus in postmenopausal women in the lowest quartile of FSH increased ≈300%, which has been reported and discussed in a previous article.[14] Two recent studies also found that FSH was a good marker to assess the probability of metabolic syndrome, even better than C-reactive protein, leptin, and sex hormone binding globulin in postmenopausal women.[29,30] The above information lends credibility to the findings on FSH and lipid profile. However, interestingly, a recent study showed FSH interacted with FSH receptors in hepatocytes and reduced low-density lipoprotein receptor levels, which subsequently attenuated the endocytosis of low-density lipoprotein cholesterol in a mouse model.[11] Studies have also found that FSH promoted lipid biosynthesis in adipose tissue and visceral fat accumulation by upregulating FSH receptor mRNA expression and the Gai/Ca^{2+}/cAMP-response-element-binding protein pathway in animal models.[12,31] These results seem to be contradictory to previous epidemiological studies and require further longitudinal investigations to confirm.

Notably, the cardiometabolic factor associations with FSH remained significant after adjustment for BMI. This finding indicated that the associations between FSH and numerous metabolic risk perturbations were independent of the measure of adiposity. Though previous studies found obesity had an inhibitory effect on FSH levels,[25,28] this effect may not be enough to explain the strong associations observed between FSH and other metabolic parameters. The underlying mechanism still needs to be clarified.

We also noticed that the association between FSH and 10-year ASCVD risk persisted in subjects with or without

Table 2. Associations Between FSH Quartiles and 10-Year ASCVD Risk in Postmenopausal Women

	FSH				
	Q1	Q2	Q3	Q4	P for Trend
ln-(10-y ASCVD risk)	0.22 (0.15, 0.29)	0.11 (0.05, 0.17)	0.10 (0.04, 0.15)	0.00 (Ref)	<0.001
High 10-y ASCVD risk	4.22 (1.90, 9.36)	2.09 (1.00, 4.37)	2.42 (1.22, 4.80)	1.00 (Ref.)	<0.01

Data are unstandardized coefficients (95% confidence interval) for ln-(10-y ASCVD risk) and odds ratio (95% confidence interval) for high 10-y ASCVD risk. Linear and logistic regression analyses were used. The model controls for age, total testosterone, estradiol, luteinizing hormone, economic status, and body mass index. ASCVD indicates atherosclerotic cardiovascular disease; FSH, follicle-stimulating hormone.

central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. Thus, they may have some intrinsic relationship. Recently, we found that FSH was positively associated with sex hormone binding globulin in men and postmenopausal women, and we further performed an in vitro study using HepG2 cells pretreated with FSH at different concentrations. Dose-dependent sex hormone binding globulin expression was found.[32] Low plasma sex hormone binding globulin is a risk factor for the development of CVD.[33,34] Hence, sex hormone binding globulin may be one of the association mediators. Second, recent studies have indicated that FSH has an angiogenesis effect through stimulating vascular endothelial growth factor (VEGF) expression in some tumors[35] and the umbilical vein.[36] Previous study found VEGF levels were negatively associated with 10-year coronary heart disease and stroke risk,[37] and another showed an inverted U-shaped relation was found in VEGF levels with the risk of developing CVD events, with the lowest risk at the lower and upper ends.[38] Whether postmenopausal women with higher FSH have higher VEGF and whether VEGF really mediates the association between FSH and CVD risk remain to be elucidated.

Readers may have concerns that estrogens protect women from CVD, but participants with higher FSH had lower estradiol in Table 1. It is possible that participants with higher FSH also had better metabolic parameters. The associations between FSH and metabolic parameters were independent of estradiol as shown in Figure 2, which led to a negative association between FSH and calculated 10-year CVD risk. The equations calculating the 10-year ASCVD risk did not contain estradiol, which also indicates that estradiol fluctuates at such a low level in postmenopausal women that it may not influence 10-year ASCVD risk. Some studies found that estradiol levels were not associated with risk of CVD in hormone replacement nonusers after menopause.[39,40]

Our study had some strengths. First, it presented a novel association between FSH and 10-year ASCVD risk for the first time in a large sample. Second, the study was performed in a general population as opposed to a clinic-based population, providing better external validity of the results.

However, our study also had some limitations. First, we cannot address the temporality of the observed associations because of the cross-sectional design. Thus, the causal relationship between FSH and multiple cardiometabolic risk factors cannot be drawn. Second, some of the postmenopausal women were defined based on the age proxy similar to previous studies.[41,42] We have considered why we chose 55 years old. In China, the overall median age at natural menopause is 50 years old, and at the age of 55 years old, ≈97% of women are postmenopausal.[43] Third, it is unfortunate that we had no information on family history of CVD. However, in this newly developed effective tool for 10-year ASCVD risk prediction among the Chinese, family history of ASCVD was not included in the model for women. Thus, a family history of ASCVD might not be a strong confounder in women in this equation. Fourth, 1-time measurement of FSH may be a limitation. For consistency, all the women here were sampled in the morning and in a fasting state. Multiple samples for individuals may not be feasible in a large epidemiological study.[25] Moreover, FSH was relatively stable 2 years after the final menstrual period. Finally, we have some missing values of waist circumference, blood pressure, and thus predicted 10-year ASCVD risk. Though imputation could not be needed when the missing values were far less than 10%, they were imputed by the means to prove the results were solid.[44] The imputation did not change the association between ln-FSH and 10-year ASCVD.

In conclusion, serum FSH levels were negatively associated with 10-year ASCVD risk in postmenopausal women regardless of central obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. Among cardiometabolic factors, obesity indices had the largest association strength with FSH, and blood pressure had the smallest association strength. These results indicated that a low FSH might be a risk factor or biomarker for CVD risk in postmenopausal women. Whether there is causal relationship needs further investigation.

Disclosures

None.

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