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ORIGINAL ARTICLE

Non-Linear Association of Serum Sex Hormone Binding Globulin Concentration with Female Infertility

Jian Zhuang [1], Kaiqiang Xi [2], Luhu Yu [2], Xiaoyu Li [2]

[1] *Department of Clinical Laboratory, Ganzhou Maternal and Child Health Hospital, Ganzhou, Jiangxi Province, China*
[2] *Department of Clinical Laboratory, Ganzhou People's Hospital, Ganzhou, Jiangxi Province, China*

SUMMARY

Background: **Accumulating proofs suggested that disturbance of serum sex hormone-binding globulin (SHBG) concentration can affect the reproductive system. However, the effect of serum SHBG on female infertility remains to be clarified.**
Methods: **Data from 1,787 adults from the National Health and Nutrition Examination Survey (NHANES) was applied to examine the correlation between serum SHBG and female infertility. Multivariate logistic regression was used to evaluate the independent association between serum SHBG and female infertility. Furthermore, generalized additive model (GAM) and two-piecewise linear regression model were applied to assess the underlying non-linear association in our participants.**
Results: **We observed a reverse association between serum SHBG and infertility based on a fully-adjusted model (OR = 0.99, 95% CI: 0.99-1, p = 0.002), and the results were stable in several sensitive analyses. Furthermore, we detected a non-linear link by GAM and two-piecewise linear regression model. A protective association was observed at < 58.84 nmol/L serum SHGB; in contrast, no statistical link was found at > 58.84 nmol/L serum SHGB.**
Conclusions: **Our results provide evidence for a non-linear association with serum SHBG and female infertility. This finding needs to be further confirmed in future large-scale prospective cohort studies.**
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Correspondence:
Xiaoyu Li
Department of Clinical Laboratory
Ganzhou People's Hospital
Meiguan Avenue
Ganzhou, Jiangxi Province, 341000
China
Phone: +86 18979776793
Email: 394639734@qq.com

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KEYWORDS

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INTRODUCTION

Sex hormone-binding globulin (SHBG) is a protein synthesized by the liver that binds androgens and estrogens [1]. It is also known as testosterone-estrogen binding globulin or steroid-binding protein [2]. The expression of the SHBG is under the control of hepatocyte nuclear factor 4 alpha (HNF4A) and constitutive androstane receptor [3]. Meanwhile, it is regulated by many factors such as insulin, thyroxine, and endogenous sex hormones. Its main physiological function is to specifically bind and transport sex hormones, regulate the concentration of biologically active sex hormones in the blood, and affect the bio-availability [2]. It has a close relation-

ship with the pathological and physiological state of a variety of diseases in the body. In males, SHBG is associated with spermatogenic function, sperm maturation, and male fertility [4]. In females, this disorder is closely related to many gynecological diseases such as polycystic ovary syndrome (POCS) [5], female hirsutism [6] and masculinization, and endometrial cancer [7]. Researches also pointed out that SHBG imbalance had impacts on many diseases like metabolic syndrome (including metabolic complex central obesity, insulin resistance, hypertension, hypertriglyceridemia, type 2 diabetes [8]), liver diseases [9], and malignant tumor [10]. Therefore, SHBG plays a vital role in human health, especially in the reproductive system.

In recent years, the relationship between sex hormone binding globulin (SHBG) and reproductive health has attracted much attention by many researchers. The literature on the relationship between serum SHBG and the human reproductive system are mainly concentrated in polycystic ovary syndrome (POCS) [11], male adiposity, and sperm parameters [12]. To the best of our knowledge, the large-scale population-based epidemiology studies that have already evaluated the independent associations between serum SHGB level and female infertility are few. So, in the present cross-sectional study, we selected women of childbearing age with complete variable information in the National Health and Nutrition Examination Survey (NHANES) from 2013 to 2018 and explored the potential linear and non-linear relationship between serum SHGB and infertility.

MATERIALS AND METHODS

Study population

NHANES, a national population-based representative survey, was designed to further estimate the fitness of participants in America. The survey was conducted by the National Center for Health Statistics (NCHS), part of the U.S. Centers for Disease Control and Prevention (CDC). The informed written consent of all participants was obtained prior to the questionnaire. The protocols of the study were approved by the Research Ethics Review Committee of NCHS.

In our study, data from three continuous cycles of NHANES (2013 - 2014, 2015 - 2016, 2017 - 2018). Because only these three cycles contained the reproductive health questionnaire about infertility. A total of 29,401 individuals completed the interview. Participants with missing data for infertility (n = 23,969) or those who were younger than 20 years old or older than 45 years (n = 1,337) were excluded. We excluded participants with missing data for serum SHGB, testosterone, estradiol, and other key covariates (n = 2,308). The final study left 1,787 participants (Figure 1).

Measurement of serum sex hormone

Sex hormones, including testosterone (TT), estradiol (E2), and sex hormone-binding globulin (SHBG), were tested in serum samples. Isotope dilution liquid phase chromatography tandem mass spectrometry (ID-LC-MS/MS) was utilized to assess the concentration of serum TT and E2, while SHBG was evaluated based on its reaction with immune antibodies and chemiluminescence measurements (NHANES). If analysis results are below the detection limit (LOD), the testing result was the LOD divided by the square root of 2. Detailed instructions are available on the NHANES website.

Determination of female infertility

Self-reported infertility was obtained from the reproductive health questionnaire. Participants were asked: “Have you ever tried to get pregnant for a period of time? Pre-certified not to be pregnant for at least a year?” If the answer is "yes", it is defined as "sterile"; if the answer is "no", it is defined as "fertile"; otherwise, it is considered that the data is missing.

Covariates

We collect age, sex, race/ethnicity, education level, poverty income ratio (PIR), smoking status, dietary consumption, smoking status, and physical activity, because they may potentially affect the link between sex hormones and fertility. Researchers have proposed that body mass index (BMI) may affect both the distribution of sex hormones and a woman's ovulation [13]. We further divided BMI into three levels: normal weight (< 25 kg/m^2), overweight (25 kg/m^2 - 30 kg/m^2) and obesity (≥ 30 kg/m^2). Individuals’ age was categorized into two groups: 20 - 34 years and 35 - 45 years, while PIR was classified into two levels: < 3 and ≥ 3. Race/ethnicity was categorized as Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic, and other race. Educational attainment was classified as less than high school, high school graduate, and a college degree or more. Self-reported smoking status include current smokers, former smokers, and never smokers. Dietary data, including alcohol consumption, folate, fiber, vitamin D, calcium and magnesium intakes, were obtained through a 24-hours dietary recall. We also took the regularity of menstrual cycle into account. The regularity of the menstrual cycle was determined based on the responses in the reproductive health questionnaire.

Statistical analysis

In line with NHANES recommendations, all analyses were performed using a sophisticated design and appropriate sub-sample weights. First, we used logistic regression to estimate the association between serum SHBG and infertility prevalence. In order to measure the stability of the results, serum SHBG was divided into quartiles. The quartile of serum SHBG was included in the model as a continuous variable, and the linear trend was tested. Considering the possible nonlinear correlations, we used a generalized additive model with penalty splines. We gradually adjusted for potential confounding factors in a multi-factor model. Model 1 did not adjust any variables. Model 2 adjusted for age

and race/ethnicity. Model 3 adjusted for age, race, PIR, education attainment, BMI, magnesium, fiber, folate, calcium, vitamin D, alcohol consumption, menstrual regularity, work activity, and smoking status. We also examined the possible effect of age on the relationship between serum SHBG and risk of infertility.

To ensure the robustness of the results, we performed some sensitivity analyses. First, continuous variable blood calcium was converted into categorical variable quartile. Second, the penalty curve method and generalized additive model (GAM) were used to analyze the possible nonlinear relationship between serum SHBG and infertility risk. The recursive method of inflection point was calculated, and then a weighted two-stage linear model was built on both sides of the inflection point. Finally, the optimal model was established according to the p-value of likelihood comparison number.

Software packages that were involved in this study contained statistics R (http://www.R-project.org, The R Foundation) and empower statistics (http://www. empowerstats.com, X&Y Solutions, Inc., Boston, MA). $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the participants

The characteristics of the participants are displayed in Table 1 (n = 1,787). Participants with self-reported infertility were generally older, had lower household income, more likely be obesity, had lower serum SHBG, and consumed less fiber daily. Chi-squared tests indicated no significant variances in race, educational attainment, status of regular periods, smoking status, physical activity, dietary factors like magnesium, calcium, and folate intake.

Multiple-factor regression model and sensitivity tests

We observed a significant association between serum SHBG and infertility in all models (Model 1, Model 2, and Model 3) (Table 2). All covariates listed in Table 1 including age, race, PIR, education attainment, serum TT, E2, daily magnesium, fiber, folate, calcium, vitamin D, alcohol consumption, regular periods, smoking status, and physical activity were adjusted in Model 3. Model 1 was a crude model that adjusted for none. Model 2 just adjusted for age and race. We converted the continuous variable SHBG into a quartile for categorical variable and assessed its association with serum SHBG and infertility via multivariate logistic regression. The p for trends were robust in three different models (p for trend < 0.05).

Next, the association between SHBG and female infertility was further evaluated by age stratification (Table 3). Multiple logistic regression analysis showed that even after adjusting for possible confounding factors, there was a protective association between serum SHBG and infertility in the younger group ($p < 0.001$), whereas this association was not significant in older group ($p = 0.149$).

Assessment of the potential non-linear relationship

A non-linear association between serum SHGB and female infertility was observed by performing the GAM with penalty splines in the full adjustment model (Figure 2). The two-piecewise linear regression model and recursive algorithm are used to calculate the inflection point. A protective association was observed at < 58.84 nmol/L serum SHGB; in contrast, no statistical link was found at > 58.84 nmol/L serum SHGB. Log-likelihood ratio test was conducted comparing the one-line regression model with a two-piecewise model ($p = 0.012$) (Table 4).

DISCUSSION

The main conclusion of this study is that there is a reverse association of serum SHBG with female infertility prevalence in the U.S. Furthermore, a non-linear correlation was identified after conducting a smooth curve fitting and a weighted two-piecewise linear model. The turning point of serum SHGB was at 58.84 nmol/L. Below 58.84 nmol/L, we have statistical evidence suggesting protective association with serum SHBG and prevalence of female infertility. To our knowledge, this is the first epidemiological study to display a non-linear relationship between serum SHGB and female fertility which indicated a protective effect of SHBG on female infertility.

Human sex hormone-binding globulin (SHBG) is a glycoprotein produced by the liver with a high affinity and specific binding steroid. Emerging evidence from both *in vitro* and *in vivo* studies have indicated that SHBG is closely related to reproductive system diseases. Ruth et al. conducted a Mendelian randomization study to assess the association of serum SHBG with several complex diseases, including PCOS [14]. Data from a meta-analysis of sixteen studies have shown that serum SHBG levels are reduced in women with PCOS, especially in obese adolescents [15]. Low levels of SHBG are often associated with hyperandrogenemia. Weinberg et al. reported that elevated SHBG levels are associated with lower risk of metabolic syndrome [16,17]. In the current study, we also found an inverse association between serum SHBG and risk of female infertility at a serum SHBG concentration of below 58.84 mmol/L. The reference values for serum SHBG were 20.9 - 50.6 nmol/L for men and 33.8 - 71.1 nmol/L for women by immunodiagnostic systems (IDS) [18]. It is worth noting that the inflection point is within the normal value range for female. Therefore, our findings may provide a reference for the SHBG status or possible safe lower limit of risk of female infertility. However, our results still require more dose-response studies, especially prospective cohort studies in different populations, or clinical trials, to confirm our findings.

At present, evidence about exact pathogenesis of the

Table 1. The characteristics of the study grouped by infertility.

Variables	Total (n = 1,787)	Non-infertility (n = 1,573)	Infertility (n = 214)	p-value
Age, n (%)				
20 - 34	984 (55.1)	900 (57.2)	84 (39.3)	< 0.001
35 - 45	803 (44.9)	673 (42.8)	130 (60.7)	
Race, n (%)				
Mexican American	338 (18.9)	297 (18.9)	41 (19.2)	0.267
Non-Hispanic Black	361 (20.2)	312 (19.8)	49 (22.9)	
Non-Hispanic White	611 (34.2)	531 (33.8)	80 (37.4)	
Other Hispanic	200 (11.2)	183 (11.6)	17 (7.9)	
Other Race	277 (15.5)	250 (15.9)	27 (12.6)	
PIR, n (%)				
PIR < 3	1,130 (67.9)	1,004 (68.8)	126 (61.5)	0.036
PIR ≥ 3	535 (32.1)	456 (31.2)	79 (38.5)	
Education level, n (%)				
< High school	291 (16.3)	265 (16.8)	26 (12.1)	0.315
Graduated from high school	342 (19.1)	299 (19)	43 (20.1)	
College education or above	1,153 (64.5)	1,008 (64.1)	145 (67.8)	
NA	1 (0.1)	1 (0.1)	0 (0)	
BMI, (kg/m^2) n (%)				
BMI < 25	599 (33.7)	539 (34.4)	60 (28.3)	< 0.001
BMI 25 - 30	441 (24.8)	410 (26.2)	31 (14.6)	
BMI ≥ 30	737 (41.5)	616 (39.4)	121 (57.1)	
Regular menstrual cycle, n (%)				
No	191 (10.7)	171 (10.9)	20 (9.3)	0.498
Yes	1,596 (89.3)	1,402 (89.1)	194 (90.7)	
Smoking status, n (%)				
Never smoker	1,275 (71.4)	1,125 (71.6)	150 (70.1)	0.899
Former smoker	184 (10.3)	161 (10.2)	23 (10.7)	
Current smoker	326 (18.3)	285 (18.1)	41 (19.2)	
Physical activity, n (%)				
Light work activity	1,036 (58.0)	912 (58)	124 (57.9)	0.996
Moderate work activity	462 (25.9)	407 (25.9)	55 (25.7)	
Vigorous work activity	289 (16.2)	254 (16.1)	35 (16.4)	
Dietary Factor				
Magnesium (mg), Median (IQR)	249.0 (180.5, 336.0)	249.0 (182.0, 336.0)	243.5 (170.2, 327.5)	0.356
Folate (μg), Median (IQR)	314.0 (205.0, 455.0)	314.0 (205.0, 459.0)	290.0 (186.8, 434.5)	0.09
Fiber (gm), Median (IQR)	13.6 (8.9, 19.9)	13.9 (9.0, 19.9)	12.5 (8.2, 19.0)	0.012
Calcium (mg), Median (IQR)	786.0 (510.0 - 1,108.0)	788.0 (506.0 - 1,107.0)	774.5 (515.2 - 1,116.0)	0.857
Vitamin D (mg), Median (IQR)	2.7 (1.0, 5.3)	2.7 (1.0, 5.4)	2.6 (1.0, 5.1)	0.06
Alcohol (gm), Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	< 0.001
SHBG (nmol/L), Median (IQR)	58.8 (39.3, 92.0)	59.9 (40.2, 94.2)	46.9 (34.4, 83.5)	< 0.001
Testosterone (nmol/L), Median (IQR)	23.3 (16.4, 32.3)	23.1 (16.3, 31.9)	24.7 (16.8, 35.1)	0.076
Estradiol (nmol/L), Median (IQR)	67.3 (32.9, 132.5)	66.1 (31.7, 130.0)	75.2 (44.5, 149.5)	0.003

PIR - poverty income ratio, BMI - body mass index, SHBG - sex hormone-binding globulin.

Table 2. Odds ratios (95% confidence intervals) of infertility across quartiles of serum SHBG.

Serum SHBG (nmol/L)	Event (%)	Model 1		Model 2		Model 3	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Serum SHBG	214 (12)	1 (0.99 - 1)	0.019	1 (0.99 - 1)	0.022	0.99 (0.99 - 1)	0.002
Quartiles							
Q1 (< 39.26)	72 (16.1)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (39.26 - 58.84)	57 (12.8)	0.76 (0.52 - 1.11)	0.158	0.69 (0.47 - 1.01)	0.056	0.59 (0.39 - 0.88)	0.01
Q3 (58.85 - 92.02)	49 (11)	0.64 (0.44 - 0.95)	0.026	0.58 (0.39 - 0.87)	0.008	0.48 (0.31 - 0.73)	0.001
Q4 (> 92.02)	36 (8)	0.46 (0.3 - 0.7)	< 0.001	0.42 (0.27 - 0.65)	< 0.001	0.33 (0.21 - 0.53)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001

Model 1 adjusted for none.
Model 2 adjusted for age and race.
Model 3 adjusted for all covariates including age, race, PIR, education levels, BMI, serum testosterone, serum estradiol, menstrual regular period, smoking status, work activity, dietary factors like magnesium intake, folate, fiber, vitamin D, calcium and alcohol consumption.

Table 3. Odds ratios (95% confidence intervals) of infertility across quartiles of serum SHGB stratified by age, NHANES 2013 - 2018.

Serum SHBG (nmol /L)	N Event %	Model 1		Model 2		Model 3	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age 20 - 34							
Serum SHGB	84 (8.5)	0.99 (0.99 - 1)	0.002	0.99 (0.98 - 1)	0.002	0.99 (0.98 - 1)	0.001
Q1 (< 39.26)	37 (13.8)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (39.26 - 58.84)	23 (10)	0.7 (0.4 - 1.22)	0.207	0.61 (0.34 - 1.09)	0.097	0.59 (0.32 - 1.07)	0.084
Q3 (58.85 - 92.02)	15 (6.6)	0.44 (0.24 - 0.83)	0.011	0.43 (0.22 - 0.82)	0.01	0.45 (0.23 - 0.89)	0.022
Q4 (> 92.02)	9 (3.5)	0.23 (0.11 - 0.48)	< 0.001	0.19 (0.09 - 0.43)	< 0.001	0.18 (0.08 - 0.43)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
Age 35 - 45							
Serum SHGB	130 (16.2)	1 (1 - 1)	0.936	1 (1 - 1)	0.681	1 (0.99 - 1)	0.149
Q1 (< 39.26)		1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (39.26 - 58.84)	34 (15.7)	0.76 (0.45 - 1.28)	0.299	0.71 (0.41 - 1.22)	0.213	0.64 (0.37 - 1.12)	0.118
Q3 (58.85-92.02)	34 (15.5)	0.75 (0.45 - 1.26)	0.28	0.64 (0.37 - 1.1)	0.108	0.56 (0.32 - 1)	0.049
Q4 (> 92.02)	27 (14.3)	0.68 (0.39 - 1.18)	0.171	0.55 (0.31 - 0.97)	0.04	0.44 (0.23 - 0.81)	0.009
P for trend			0.188	0.82 (0.68 - 0.99)	0.039		0.009

Model 1 adjusted for none.
Model 2 adjusted for race, PIR and education level.
Model 3 adjusted for all covariates including race, PIR, education levels, BMI, serum testosterone, serum estradiol, menstrual regular period, smoking status, work activity, dietary factors like magnesium intake, folate, fiber, vitamin D, calcium and alcohol consumption.

correlation between serum SHBG alteration and female infertility has not been addressed. Sex hormone-binding globulin (SHBG) mainly synthesized in the liver [19] has been viewed as the main protein that binds circulating sex hormones with high affinity [20-22]. The SHBG gene was regulated by the transcription of hepatic nuclear factor 4 A (HNF4A) [23,24] and the constitutive androstane receptor [25], as well as peroxisome proliferator activating receptor gamma and chicken ovalbumin upstream promoter transcription factors [26-27]. On the other hand, when the production or function of HNF4A is genetically abnormal, it may also lead to reduced SHBG expression in the liver, which is associated with the risk of abnormal glucose metabolism in young people [28]. Polymorphism of human SHBG gene is also related to differences in serum SHBG levels

Table 4. Threshold effect analysis of serum SHGB on infertility based on segmented linear regression model.

Outcome	OR (95% CI)	p for value
Infertility		
Inflection point	58.84 nmol/L	
< 58.84	0.98 (0.98, 0.99)	< 0.001
> 58.84	1.0 (1.0 - 1.0)	0.85
Log likelihood ratio test	0.005	

Log likelihood ratio test results comparing linear regression model with two-piecewise linear regression model adjusted for age and race, PIR - education level, BMI - serum testosterone, serum estradiol, magnesium, float, fiber, calcium, vitamin D, alcohol consumption, regular period, work activity and smoking status.

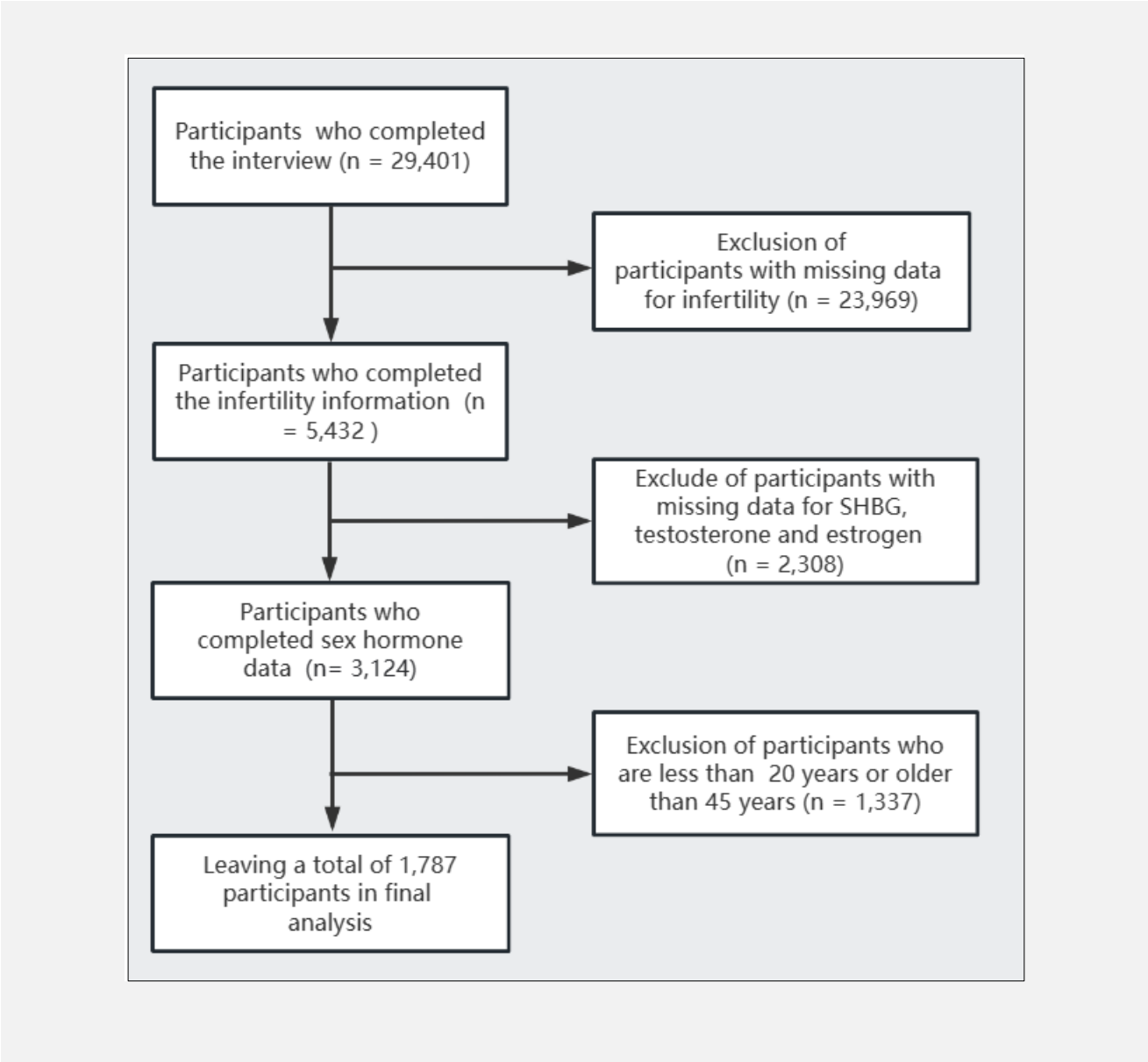

Figure 1. The flow chart for subject selection.

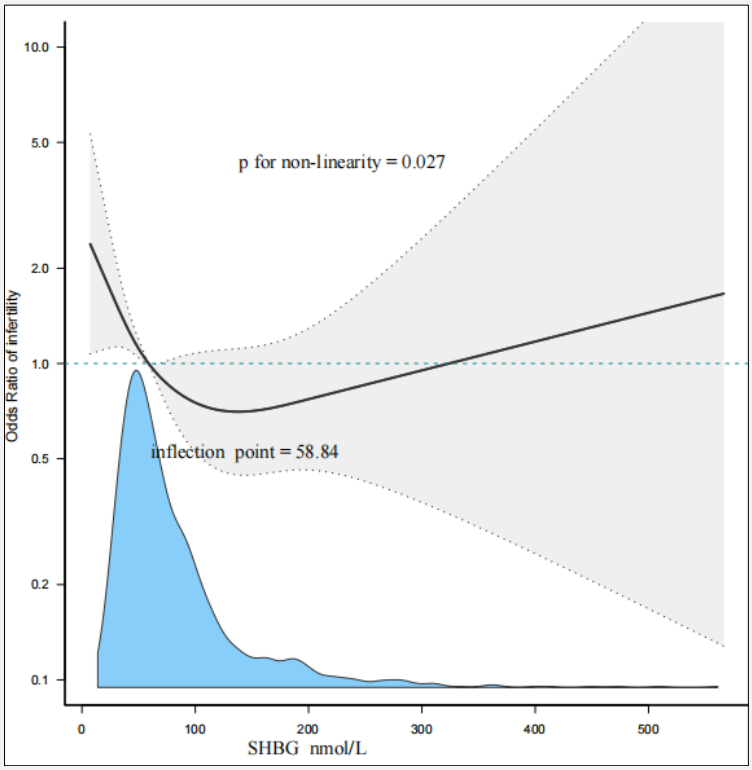

Figure 2. The relationship between serum SHBG and infertility based on generalized additive model (GAM).

The GAM - model adjusted for age and race, PIR - education level, BMI - testosterone, estradiol, regular periods, work activity, smoking status, and dietary factors (including magnesium, fiber, float, calcium, vitamin D, alcohol consumption).

[29,30]. Among them, polymorphic TAAAA(n) pentanucleotide repeat of the SHBG transcription site [31], has been associated with abnormal plasma SHBG level in PCOS patients, age of menarche, and semen quality in men [32]. Therefore, it is conceivable that low serum SHBG may affect the pathogenesis of female infertility through metabolic disorders. This explanation needs further proving in future investigation.

Only a few epidemiological studies have assessed the relationship between serum SHBG and infertility. Liao et al. showed that SHBG expression levels are associated with male infertility, mainly by affecting sperm count and semen quality [33]. Another research suggested that infertile males have lower serum SHBG compared with healthy males [34]. A similar experiment also indicated that SHBG levels are significantly associated with sperm motility which may affect the function of sperm that is related to male fertility [35]. A systematic review and meta-analysis showed that serum SHBG levels are negatively associated with the risk of PCOS [36]. In agreement with our results, our research provided a novel insight that raising serum SHBG to a safe range can reduce the risk of female infertility. To sum up, changing lifestyle habits are particularly important for obese patients. Weight loss through dietary control and physical exercise can significantly alleviate hyperandrogenemia, appropriately increase serum SHBG concentration, improve menstruation, restore ovulation and improve the chance of conception.

Our study has certain advantages. To our knowledge, this is the first study that reports a non-linear association with serum SHBG and female infertility, using a large sample size to elevate statistical efficiency. The GAM model and smooth curve fitting model (penalty curve method) were used to explore the nonlinear relationships. Therefore, our analysis provided new insight into clinical intervention, which has not been reported in previous studies. Several sensitivity analyses were performed including stratification by age to establish the stability of our study results. However, our research still has several limitations. First, serum SHBG levels from single detection may not be ideal biomarkers and several repeated measurements may better explain long-term levels. Second, due to the limit characteristic of the

cross-sectional investigation, our study has an inadequate ability to manifest the causal inference. Third, we cannot define whether they undergoing primary or secondary infertility, and the time when infertility occurs is unidentified. Finally, our findings were susceptible to unaccounted confounding variables, such as male semen quality. Therefore, large-scale prospective studies in future are still needed to further explore the mechanism of the relationship between SHBG and female infertility.

CONCLUSION

The present analysis provides evidence of a non-linear association between serum SHBG and the prevalence of female infertility. Serum selenium levels below 58.84 nmol/L showed a significant inverse correlation, whereas no significant statistical difference was found above 58.84 nmol/L. We hope that our study can provide a safer range of serum SHBG levels for females trying to become pregnant. This finding needs to be further confirmed in future large-scale prospective cohort studies.

Declaration of Interest:
The authors declare that there was no conflict of interest.

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