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ORIGINAL ARTICLE

Male Health

Associations of sex hormone levels with body mass index (BMI) in men: a cross-sectional study using quantile regression analysis

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Body mass index (BMI) has been increasing globally in recent decades. Previous studies reported that BMI was associated with sex hormone levels, but the results were generated via linear regression or logistic regression, which would lose part of information. Quantile regression analysis can maximize the use of variable information. Our study compared the associations among different regression models. The participants were recruited from the Center of Reproductive Medicine, The First Hospital of Jilin University (Changchun, China) between June 2018 and June 2019. We used linear, logistic, and quantile regression models to calculate the associations between sex hormone levels and BMI. In total, 448 men were included in this study. The average BMI was 25.7 (standard deviation [s.d.]: 3.7) kg m^{-2}; 29.7% (n = 133) of the participants were normal weight, 45.3% (n = 203) of the participants were overweight, and 23.4% (n = 105) of the participants were obese. The levels of testosterone and estradiol significantly differed among BMI groups (all P < 0.05). In linear regression and logistic regression, BMI was associated with testosterone and estradiol levels (both P < 0.05). In quantile regression, BMI was negatively associated with testosterone levels in all quantiles after adjustment for age (all P < 0.05). BMI was positively associated with estradiol levels in most quantiles (≤80th) after adjustment for age (all P < 0.05). Our study suggested that BMI was one of the influencing factors of testosterone and estradiol. Of note, the quantile regression showed that BMI was associated with estradiol only up to the 80th percentile of estradiol.

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INTRODUCTION

With lifestyle changes, the number of overweight and obese individuals according to body mass index (BMI) has increased in recent decades. The mean age-standardized BMI increased from 21.7 kg m^{-2} in 1975 to 24.2 kg m^{-2} in 2014 in men and from 22.1 kg m^{-2} in 1975 to 24.4 kg m^{-2} in 2014 in women.[1] From 1980 to 2015, the prevalence of obesity doubled in more than 70 countries, and continuous increases were recorded in most other countries.[2] The prevalence rates of overweight and obesity were reported as 28.1% and 5.2%, respectively, in China.[3] It was estimated that the numbers of overweight and obese adults in the world will reach 1.35 billion and 573 million, respectively, by 2030.[4]

Increased BMI is associated with increased risks of coronary heart disease, type 2 diabetes, and stroke.[5–7] It is well known that BMI is related to changes in sex hormone levels. Some studies have indicated that follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were not significantly correlated with BMI.[8,9] However, other studies found that FSH levels were higher among slim men, and LH levels significantly differed among the BMI groups.[10,11] BMI was inversely associated with serum testosterone levels and positively associated with estradiol levels.[8,10,12] Calderón *et al.*[13] found that serum total testosterone levels increased after bariatric surgery. In addition, Keskin *et al.*[14] reported that BMI was inversely associated with prolactin levels. Previous studies also observed inverse associations of BMI with sex hormone-binding globulin and inhibin B levels in men.[9,15,16] Although numerous studies examined the association between BMI and sex hormone levels, there were no consistent conclusions.

Previous studies on sex hormones were based on linear regression or logistic regression. However, linear regression has strict requirements regarding variable distribution, and logistic regression may lose some variable information. Quantile regression is a flexible statistical tool with wide applications in many fields of science. Quantile regression analysis was first introduced to the statistical community by Koenker and Bassett,[17] and permitted conditional estimation of the outcome at a specific quantile or multiple quantiles. Quantile regression analysis is based on minimizing the sum of weighted absolute residuals, and it allows one to model any quantile of the outcome distribution.[18] Unlike traditional mean regression methods, quantile regression does not require assumptions about the distribution of the response, which makes it practical, robust, and amenable to various distributions, especially skewed (response) distributions.[19] Quantile regression is vastly more robust to outliers than ordinary least square regression because observations far from the mean may have high leverage and may cause significant bias in estimates of the mean.[20] Quantile regression also enables an assessment of the effects of a covariate on

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all parts of the distribution rather than only the mean, differing from linear regression, and it fully considers heterogeneity.[20] However, to our knowledge, few studies used quantile regression to assess the associations between sex hormone levels and BMI.

Our study explored whether BMI is related to sex hormone levels among men visiting the Center of Reproductive Medicine, The First Hospital of Jilin University (Changchun, China) and examined the associations between BMI and sex hormone levels based on quantile regression.

PARTICIPANTS AND METHODS

Study design

Between June 2018 and June 2019, men (18–55 years of age) were recruited from the Center of Reproductive Medicine in The First Hospital of Jilin University. The participants were outpatients who underwent routine prepregnancy semen analysis or visited the Center of Reproductive Medicine because of potential reproductive problems. After we introduced the content of the investigation and the purpose of the research, participants who voluntarily agreed to participate were included in the study. Participants first completed a questionnaire. The questionnaire assessed basic information about the participants (*e.g.*, age, height, weight, ethnicity, education levels, occupation category, smoking, and alcohol consumption) and their medical histories (*e.g.*, infectious diseases, cardiovascular diseases, urogenital diseases, and history of urogenital surgery). Then, participants underwent a physical examination by an uroandrologist to dismiss the possibilities of cryptorchidism, gynecomastia, thin pubic hair, torsion of the epididymis, hydrocele, and varicocele. Finally, we collected laboratory data on sex hormone levels from the participants. The height and weight were measured with assistance from the nursing team when creating the electronic medical record. All participants were free to withdraw from the study at any point. This study was approved by the ethics committee of The First Hospital of Jilin University (approval No. AF-IRB-032-06).

Study population

In total, 504 men were enrolled, 56 of whom were excluded because of incomplete weight and height data (n = 8), hepatitis B (n = 18), tuberculosis (n = 2), hypertension (n = 1), kidney stones (n = 2), history of surgery (n = 16), or outliers (detected on the interquartile range [IQR] method, n = 9). All participants signed the informed consent form.

Definition of variables

BMI was calculated as weight divided by height squared. Participants were categorized by BMI into four groups based on the Chinese BMI classification criteria[21] as follows: underweight (BMI <18.5 kg m^{-2}), normal (BMI ≥18.5 kg m^{-2} and <24 kg m^{-2}), overweight (BMI ≥24 kg m^{-2} and <28 kg m^{-2}) and obese (BMI ≥28 kg m^{-2}). We used the median values as cutoff points for testosterone (12.7 nmol l^{-1}) and estradiol (29.3 pg ml^{-1}) during logistic regression.

Regarding race, participants were divided into two groups: Han and others (Chaoxian, Hui, Man, or Menggu). Education was classified into three levels: low (junior school, primary school, or never attended school), middle (high school or secondary vocational school), and high (university or above). According to the type and characteristics of the occupation, occupations were divided into six categories: professional workers (*e.g.*, architect, engineer, designer, examiner, accountant, doctor, or teacher), staffs (*e.g.*, civil servant or office clerk), servicers (service attendant or other server/waiter), farmers, equipment operators (*e.g.*, factory workers, electrician, or welder), and others (self-employed or freelancer). Nonsmokers were individuals who self-reported smoking no more than 100 cigarettes, and others were defined as smokers. Participants who consumed any kind of alcoholic beverage during the past year before the investigation were defined as drinkers.

Evaluation of sex hormone levels

Blood samples were collected between 8:00 a.m. and 10:00 a.m after fasting. Five milliliters of peripheral blood were drawn into a procoagulant tube. After the serum was separated, prolactin, FSH, LH, total testosterone, and estradiol levels were detected by commercial kits (Roche Diagnostics GmbH, Mannheim, Germany). Hormone levels were analyzed using a Roche automatic electrochemical luminescence immunoassay analyzer (Roche Diagnostics GmbH).

Statistical analyses

Mean and standard deviation (s.d.) were used to describe age and BMI. The characteristics of men were reported as frequencies and percentages. Sex hormone levels were reported as the median and IQR. The Kruskal–Wallis test was adopted to compare sex hormone levels among the different BMI groups.

Linear, logistic, and quantile regression models were fitted to the data to evaluate the associations between sex hormone levels and BMI. Age was included as a covariate. Linear regression and

Table 1: Demographic characteristics and sex hormone levels of the participants (n=448)

Variable	*Value*
Age (year), mean±s.d.	34.9±5.9
BMI (kg m^{-2}), mean±s.d.	25.7±3.7
BMI groups, *n* (%)	
Underweight	7 (1.6)
Normal	133 (29.7)
Overweight	203 (45.3)
Obese	105 (23.4)
Race, *n* (%)	
Han	395 (88.2)
Others	53 (11.8)
Education level, *n* (%)	
Low	134 (29.9)
Middle	158 (35.3)
High	156 (34.8)
Occupation, *n* (%)	
Professional workers	60 (13.4)
Staffs	145 (32.4)
Servicers	95 (21.2)
Farmers	24 (5.4)
Equipment operators	41 (9.1)
Others	83 (18.5)
Smoke, *n* (%)	
No	260 (58.0)
Yes	188 (42.0)
Alcohol consumption, *n* (%)	
No	436 (97.3)
Yes	12 (2.7)
PRL (μIU ml^{-1}), median (IQR)	226.8 (175.7–308.7)
FSH (mIU ml^{-1}), median (IQR)	3.7 (2.8–5.2)
LH (mIU ml^{-1}), median (IQR)	3.9 (2.9–5.3)
T (nmol l^{-1}), median (IQR)	12.7 (9.7–16.6)
E_2 (pg ml^{-1}), median (IQR)	29.3 (23.9–36.9)

IQR: interquartile range; s.d.: standard deviation; BMI: body mass index; PRL: prolactin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T: testosterone; E_2: estradiol

logistic regression were performed using SPSS version 23.0. (IBM Corp., Armonk, NY, USA). R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) was used for quantile regression. The package "quantreg" was used for quantile regression. $P < 0.05$ was interpreted as statistically significant.

RESULTS

In total, 448 men were included in this study. The age (mean ± s.d.) of the participants was 34.9 ± 5.9 (range: 22–53) years. The BMI (mean ± s.d.) was 25.7 ± 3.7 kg m^{-2}. Of the 448 men recruited into the study, 7 (1.6%) were underweight, 133 (29.7%) had a normal BMI, 203 (45.3%) were overweight, and 105 (23.4%) were obese. The most common occupation groups were staffs (32.4%, $n = 145$) and servicers (21.2%, $n = 95$). The study included more nonsmokers (58.0%, $n = 260$) than smokers (42.0%, $n = 188$), and most participants did not drink alcohol (97.3%, $n = 436$). The demographic characteristics of the participants are presented in **Table 1**.

The sex hormone levels of the participants were inconsistent with a normal distribution, and thus, these variables were presented as the median and IQR. The median testosterone and estradiol levels were 12.7 nmol l^{-1} and 29.3 pg ml^{-1}, respectively. The median sex hormones levels were all within the normal reference ranges (**Table 1**).

Prolactin, FSH, and LH levels did not differ among the different BMI groups (all $P > 0.05$). Overweight or obese men had lower testosterone levels than those with a normal BMI ($P < 0.001$; **Table 2**). However, overweight or obese men had higher estradiol levels than men with a normal BMI ($P = 0.002$; **Table 2**).

Linear regression and logistic regression were performed to evaluate the associations of testosterone and estradiol levels with BMI (**Table 3**). The results of univariate linear regression analysis and age-adjusted multiple linear regression indicated that BMI was negatively associated with testosterone levels, and positively associated with estradiol levels (both $P < 0.05$). In the logistic regression analyses, before and after adjusted for age, BMI was significantly associated with increased odds of testosterone levels below 12.7 nmol l^{-1} ($P < 0.001$) and estradiol levels above 29.3 pg ml^{-1} ($P < 0.001$).

The quantile regression model was fitted to the data to evaluate the associations of testosterone and estradiol levels with BMI in different quantiles. **Table 4** presents the quantiles of testosterone and estradiol at different quantiles. **Table 5** presents the quantile regression coefficients and 95% confidence intervals (CIs) of BMI for different quantiles of testosterone and estradiol. BMI was negatively associated with testosterone levels in each quantile ($P < 0.05$). After adjustment for age, the quantile regression coefficient of BMI for the median quantile of testosterone was −0.58 (95% CI: −0.70 – −0.49). Quantile regression between BMI and estradiol indicated that BMI was positively associated with estradiol levels in most quantiles (excluding the 80th and 90th quantiles). After adjustment for age, BMI was positively associated with estradiol levels in all quantiles except the 90th quantile.

DISCUSSION

Although a number of researchers have investigated the associations between BMI and sex hormone levels, our study revealed new findings using a quantile regression approach. We found that BMI had a negative association with testosterone levels, and the association increased with increasing of testosterone levels. We also found that BMI had a positive association with estradiol in most quantiles (≤80th), and the association decreased with increasing estradiol levels.

The association between BMI and testosterone levels was similar to the results of a retrospective study in Turkey[22] and a multi-institutional cohort study in America.[8] Baydilli *et al*.[23] observed a significant negative correlation between increasing BMI and total testosterone levels

Table 2: Description of sex hormones between different body mass index groups

Variable	*Normal and underweight (n=140)*	*Overweight (n=203)*	*Obese (n=105)*	*H*[a]	*P*
PRL (μIU ml^{-1})	221.8 (161.7–310.2)	234.7 (175.8–313.4)	227.1 (188.6–305.6)	0.894	0.639
FSH (mIU ml^{-1})	3.6 (2.9–5.1)	3.8 (2.8–5.1)	3.7 (2.8–5.5)	0.659	0.719
LH (mIU ml^{-1})	3.9 (2.8–5.3)	3.9 (2.9–5.4)	3.7 (2.8–5.1)	0.867	0.648
T (nmol l^{-1})	16.7 (12.8–20.5)	12.1 (9.6–15.9)	10.9 (8.7–13.0)	77.6	<0.001
E_2 (pg ml^{-1})	27.0 (22.4–36.2)	29.2 (23.5–36.9)	31.8 (26.9–38.0)	12.7	0.002

[a]Statistics of Kruskal–Wallis test. Data are presented as median (IQR). IQR: interquartile range; PRL: prolactin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T: testosterone; E_2: estradiol

Table 3: Association of body mass index with testosterone and estradiol using linear and logistic regressions

Variable	*Linear regression*		*Logistic regression*	
	β (95% CI)	*P*	*OR (95% CI)*	*P*
T				
Model 1	−0.667 (−0.806 – −0.527)	<0.001	1.267 (1.189–1.350)	<0.001
Model 2	−0.667 (−0.806 – −0.527)	<0.001	1.264 (1.186–1.347)	<0.001
E_2				
Model 1	0.348 (0.030–0.666)	0.032	1.118 (1.060–1.180)	<0.001
Model 2	0.358 (0.039–0.677)	0.028	1.122 (1.064–1.185)	<0.001

Model 1 includes BMI only; Model 2 includes BMI and age. T: testosterone; E_2: estradiol; β: regression coefficients; CI: confidence interval; OR: odds ratio; BMI: body mass index

Table 4: Quantiles of testosterone and estradiol at different quantiles

Variable	*10th*	*20th*	*30th*	*40th*	*50th*	*60th*	*70th*	*80th*	*90th*
T (nmol l^{-1})	7.53	8.90	10.58	11.58	12.68	14.68	16.06	17.54	20.64
E_2 (pg ml^{-1})	18.89	22.80	24.80	27.40	29.30	32.04	34.63	38.50	43.16

T: testosterone; E_2: estradiol

Table 5: Association of body mass index with testosterone and estradiol using quantile regression

Variable	*Quantiles*								
	10th	*20th*	*30th*	*40th*	*50th*	*60th*	*70th*	*80th*	*90th*
T									
Model 1	−0.27* (−0.52 – −0.21)	−0.44* (−0.64 – −0.32)	−0.64* (−0.77 – −0.41)	−0.64* (−0.80 – −0.50)	−0.64* (−0.70 – −0.50)	−0.58* (−0.73 – −0.51)	−0.65* (−0.75 – −0.48)	−0.69* (−0.88 – −0.57)	−0.89* (−0.93 – −0.76)
Model 2	−0.26* (−0.46 – −0.22)	−0.45* (−0.61 – −0.31)	−0.64* (−0.73 – −0.43)	−0.60* (−0.72 – −0.51)	−0.58* (−0.70 – −0.49)	−0.57* (−0.71 – −0.49)	−0.65* (−0.75 – −0.47)	−0.66* (−0.91 – −0.59)	−0.88* (−0.94 – −0.76)
E_2									
Model 1	0.60* (0.16–1.18)	0.53* (0.29–0.70)	0.53* (0.16–0.68)	0.50* (0.25–0.70)	0.50* (0.35–0.68)	0.49* (0.17–0.67)	0.34* (0.16–0.68)	0.20 (−0.09–0.64)	0.26 (−0.28–0.63)
Model 2	0.55* (0.39–1.05)	0.60* (0.28–0.77)	0.52* (0.22–0.71)	0.52* (0.25–0.67)	0.47* (0.36–0.64)	0.42* (0.14–0.69)	0.36* (0.06–0.78)	0.20* (0.04–0.54)	0.25 (−0.27–0.61)

*P<0.05. Data are presented as β (95% CI). Model 1 includes BMI only; Model 2 includes BMI and age. T: testosterone; E_2: estradiol; β: regression coefficients; CI: confidence interval; BMI: body mass index

after adjusting for age. Our results revealed a negative association between testosterone levels and BMI after adjusting for age. However, a longitudinal prospective study reported no correlation between BMI and testosterone levels after adjusting for age.[24] In addition, a bidirectional Mendelian randomization study suggested that BMI had a causal effect on serum testosterone levels in men.[25] Wood *et al*.[26] found that total testosterone levels were more than two-fold higher after bariatric surgery in men. On the basis of quantile regression, we found that the association between BMI and testosterone levels was weaker when testosterone levels were lower than 10.58 nmol l^{-1}.

We found that BMI was positively associated with estradiol levels up to 80th quantile. This meant that estradiol levels and BMI were not correlated at particularly high estradiol levels. Most previous studies indicated that estradiol levels were positively associated with BMI.[8,10,27] Chavarro *et al*.[15] found that estradiol levels were only slightly elevated in obese men. By contrast, Stárka *et al*.[28] reported no significant differences in estradiol levels among men with varying BMIs. Studies indicated that the male hypothalamus-pituitary-gonadal axis is extremely sensitive to circulating estradiol levels and that estradiol has an inhibitory effect on the release of male gonadotropins.[29,30] Men have higher estradiol levels, and increased estradiol levels provide feedback to the hypothalamic-pituitary-testicular axis, thereby decreasing the secretion of gonadotropins and overall testosterone levels.[31] Higher estradiol levels result in lower testosterone levels in obese men, thereby reducing the levels of the precursor for estradiol synthesis.[29] One-half to three quarters of circulating estradiol levels are generated via the peripheral aromatization of testosterone, particularly in adipose tissue.[32] Therefore, when estradiol levels are particularly high, this hormone may be not associated with BMI. Additionally, although immunoassays technologies have a number of theoretical advantages, they may also display considerable variability. The sensitivity and specificity of direct immunoassays were poor, especially when estradiol levels were low. The serum estradiol level is extremely low in men, and inadequate sensitivity may limit the interpretation of epidemiological studies of estradiol and anthropometric values.[33–35]

Although we observed associations of testosterone and estradiol levels with BMI, our study had some limitations. First, the participants of our study were recruited from reproductive clinics, potentially resulting in recruitment bias, and they may not be fully representative of all men. Second, the sample size was relatively small. Third, although immunoassays have several advantages, such as the limited amount of training required for technicians, high-throughput nature, and wide availability globally, mass spectrometric methods are considered more specific than direct immunoassays, and are often used for such analyses. Finally, our study was a cross-sectional study, which cannot identify the identification of causal relationships between factors; therefore, our findings require further verification.

CONCLUSIONS

Both testosterone and estradiol levels differed according to BMI in men. BMI was negatively associated with testosterone levels, and the coefficient of BMI increased with increasing testosterone levels. BMI was positively associated with estradiol levels only in the low and middle quantiles (≤80th). BMI was one of the influencing factors of testosterone and estradiol.

AUTHOR CONTRIBUTIONS

XL conceived of the study, performed the data collection, and drafted the original manuscript. YTJ reviewed and edited the manuscript.

XYZ performed the statistical analysis. LLL contributed to the project administration. HGZ conceived of the study. RZL contributed to data management and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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