

## Original Article

# Moderating effect of selenium intake on the association between obesity and sex hormone levels in children and adolescents: NHANES 2013-2016

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**Background and Objectives:** This study aimed to evaluate the role of selenium intake on the correlation between obesity and sex hormone levels in children and adolescents. **Methods and Study Design:** Children and adolescents (6-19-year-old) with complete body mass index (BMI), selenium intake, and sex hormone level data were included. Applying weighted linear regression model to analyze the relationships of obesity and selenium intake with testosterone, estradiol, and sex hormone-binding globulin (SHBG) levels. Then, interaction terms for different selenium intake levels ( $<Q1$ ,  $\geq Q1$ ) and obesity (no, yes) were constructed, to investigate the moderating effect of selenium intake on the correlation between obesity and sex hormones. **Results:** A total of 3,380 participants were enrolled. Although selenium intake showed no direct relationship with testosterone, estradiol, or SHBG levels in any group ( $p > 0.05$ ), it demonstrated a significant interaction with obesity in terms of sex hormone levels. In females aged less than 12 years, there was an interaction between obesity and selenium intake on testosterone levels ( $p_{\text{interaction}} = 0.007$ ). The interaction of obesity and selenium intake on SHBG levels was observed in both males and females (all  $p_{\text{interaction}} < 0.001$ ). Moreover, a trend was observed for the effects of these interaction terms on testosterone, estradiol and SHBG levels (all  $p_{\text{trend}} < 0.05$ ). **Conclusions:** Selenium intake may play a moderating effect in the relationship between obesity and sex hormones.

**Key Words:** sex hormone, obesity, selenium intake, moderating effect, NHANES

## INTRODUCTION

Sex hormones play a crucial role in the growth and development of children and adolescents, affecting not only the reproductive and non-reproductive systems of the organism, but are also essential in the maintenance of bones, muscles, and the balance of metabolic states.<sup>1, 2</sup> Obesity is rapidly rising among children and adolescents and has become one of the major global public health problems.<sup>3</sup> Oxidative stress and chronic low-grade inflammation are drivers of obesity-related diseases and affect sex hormone levels and development in children and adolescents.<sup>4, 5</sup> Obese children and adolescents had significantly lower sex hormone-binding globulin (SHBG) levels than normal weight individuals, and obese males were linked to lower testosterone levels and higher estrogen levels.<sup>6, 7</sup> In addition, weight loss can cause elevated SHBG and testosterone levels in males, and reduced testosterone levels in females in obese children and adolescents.<sup>8</sup>

Selenium, an indispensable trace element, plays a pivotal role in human health by integrating into selenoproteins, which exhibit potent anti-inflammatory and antioxidant properties.<sup>9</sup> Selenium intake is indispensable for the optimal functioning of the cardiovascular, endocrine, nervous, and immune systems.<sup>10</sup> Selenium can reduce

free radical production and lipoprotein peroxidation and is involved in processes related to the immune and reproductive systems.<sup>11, 12</sup> Previous studies have found serum selenium levels to be positively correlated with testosterone and estradiol levels and negatively linked to SHBG levels in male children and adolescents.<sup>13</sup> Inadequate selenium intake may be correlated with delayed pubertal growth in male children and adolescents.<sup>14</sup> Several studies demonstrated that selenium supplementation was associated with higher testosterone levels and improve fertility in infertile men.<sup>15, 16</sup> In addition, reduced activity of glutathione peroxidases (selenoprotein) has been found in overweight and obese children and adolescents.<sup>17</sup> We suspect that selenium intake may influence the risk of

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obesity-related sex hormone abnormalities in children and adolescents. However, the moderating role of selenium intake in the relationship between obesity and sex hormones has not been reported. This represents a research gap that precludes nutritional interventions for sex hormone disorders in obese children and adolescents. Therefore, this study aimed to clarify selenium's moderating effect on the obesity-sex hormone association, providing empirical evidence for nutritional intervention strategies targeting obesity-related endocrine abnormalities in children and adolescents.

## METHODS

### *Study design and participants*

The National Health and Nutrition Examination Surveys (NHANES) is a nationally representative survey that assesses the health and nutritional status of the U.S. population and is conducted every two years (<https://www.cdc.gov/nchs/nhanes/participant.htm>). This cross-sectional study used 2013-2016 (2013-2014 and 2015-2016 cycles) NHANES data. NHANES uses a complex multistage probability sampling design to obtain samples. The NHANES survey consists of interviews and physical examinations and includes demographic, health-related, socioeconomic, dietary, medical, physiological measurements, and laboratory test data. Eligibility individuals for this study were those aged 6-19 years, with examination of sex hormones, with complete information on selenium intake, and with complete body mass index (BMI) data. The National Center for Health Statistics (NCHS) Research Ethics Review Board approved all NHANES protocols. Written informed consent was obtained from each participant or their family members.

### *Exposure and outcome variables*

The moderating effect of selenium intake on the correlation between obesity and sex hormones was investigated. Obesity was set as the exposure variable, sex hormones levels were set as the outcome variable, and selenium intake was set as the moderator variable. BMI for children and adolescents was converted to a BMI z-score that accounted for age and sex according to the percentile recommended by the Centers for Disease Control and Prevention.<sup>18</sup> Obesity was defined as a BMI z-score  $\geq 95$ th percentile.

Sex hormones levels include testosterone, estradiol, and SHBG. Total testosterone and estradiol were detected by isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) method. Detection of SHBG is according to chemiluminescence of the product generated by the reaction of SHBG with the immune-antibodies. Detailed measurements are available in CDC's Laboratory Methods document.<sup>19</sup> The lower limit of detection for testosterone, estradiol, and SHBG were 0.75 ng/mL, 2.99 pg/mL, and 0.80 nmol/L, respectively. For measurements below the LLOD, it is replaced by LLOD divided by the square root of 2.

Selenium intake was assessed by two 24 hours dietary recall interviews. Participants were interviewed face-to-face for the first dietary recall interview at a mobile examination center (MEC), and a second interview was performed 3-10 days later by telephone. Nutrient content of

all consumed foods/beverages was calculated according to the U.S. Department of Agriculture (USDA) Nutrient Survey database. The principal sources of selenium in the human diet are Grain products, Meat, poultry, fish and mixtures (Supplementary Figure 1).

In this study, dietary selenium intake was the average of selenium intake from the two interviews. Selenium intake included dietary intake and supplemental intake. Selenium intake levels in this study were categorized according to the first quartile of the quartiles ( $<Q1$ ,  $\geq Q1$ ) (Supplementary Table 1) because most of the population had selenium intake greater than the recommended levels ( $<55$  mcg),<sup>20</sup> but did not exceed the tolerable upper intake level of selenium as required by the Institute of Medicine. Selenium intake levels in this study were grouped as follows: males  $<12$  years ( $<69$   $\mu\text{g}$ ,  $\geq 69$   $\mu\text{g}$ ), males  $\geq 12$  years ( $<74$   $\mu\text{g}$ ,  $\geq 74$   $\mu\text{g}$ ), females  $<12$  years ( $<60$   $\mu\text{g}$ ,  $\geq 60$   $\mu\text{g}$ ), and females  $\geq 12$  years ( $<56$   $\mu\text{g}$ ,  $\geq 56$   $\mu\text{g}$ ).

### *Covariates*

Covariates were collected including race, ratio of family income to poverty (PIR), physical activity (not ideal, ideal), sedentary time ( $<3$  hours,  $\geq 3$  hours), sex hormones use (no, yes), cotinine ( $<0.05$  ng/mL,  $\geq 0.05$  ng/mL), time of venipuncture (morning, afternoon, evening), carbohydrate intake, protein intake, total fat intake (%), total energy (kcal), season of sample collection (November 1 through April 30, May 1 through October 31), vitamin D intake, zinc intake, copper intake, and magnesium intake. Physical activity was evaluated by recommended metabolic equivalent (MET)  $\times$  exercise time for the corresponding activity (minutes). Participants exercising at  $\geq 180$  MET-min/day or  $\geq 60$  min/day were considered to be ideal physical activity. Serum cotinine levels were utilized to determine tobacco exposure, with cotinine  $\geq 0.05$  ng/mL indicating the presence of tobacco exposure.<sup>21</sup>

### *Statistical analysis*

Continuous data were described as mean  $\pm$  standard error (SE) and categorical data were reported as frequencies and percentages. Variance analysis, chi-squared test or rank sum test were applied to compare differences between the groups. All participants were divided into four groups based on sex and age to be analyzed separately [males ( $<12$  years), males ( $\geq 12$  years), females ( $<12$  years), and females ( $\geq 12$  years)]. Multivariable weighted linear regression model was applied to evaluate the relationships of obesity and selenium intake with testosterone, estradiol, and SHBG. Multivariable model adjusted for race, PIR, physical activity, sedentary time, sex hormones use, cotinine, carbohydrate intake, protein intake, total fat intake, time of venipuncture, season of sample collection, vitamin D intake, zinc intake, copper intake, and magnesium intake. To investigate the moderating effect of selenium intake on the correlation between obesity and sex hormones (testosterone, estradiol, and SHBG), interaction terms for different selenium intake levels ( $<Q1$ ,  $\geq Q1$ ) and obesity (no, yes) were constructed. In addition, participants were divided into four groups based on selenium intake ( $<Q1$ ,  $\geq Q1$ ) and obesity (yes, no) [the selenium  $\geq Q1$  & non-obesity group (reference group), the selenium  $<Q1$  & non-obesity group, the sele-

nium  $\geq$ Q1 & obesity group, and the selenium <Q1 & obesity group], and trend effects between these groups were analyzed for sex hormone (testosterone, estradiol, and SHBG). Beta values ( $\beta$ ) and 95% confidence intervals (CI) were utilized to characterize correlations. Statistical analyses were completed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).  $p < 0.05$  (two-sided) was considered statistically significant.

## RESULTS

### Characteristics of participants

In the 2013-2016 cycle of NHANES, 5,451 participants aged 6-19 years were recorded. A total of 2,071 participants were excluded, of whom 1,658 had no data on examination of sex hormones, 400 had no information on selenium intake, and 13 had no complete BMI data. Table 1 lists the characteristics of the 3,380 participants who were included. There were 710 males <12 years of age, 1,002 males  $\geq$ 12 years of age, 698 females <12 years of age, and 970 females  $\geq$ 12 years of age. The mean (SE) selenium intake was 106 (1.44)  $\mu$ g and 826 (23.5%) participants were obese. The mean testosterone [368 (7.17) ng/dL vs. 14.7 (1.93) ng/dL] and estradiol [18.6 (0.45) pg/mL vs. 2.43 (0.07) pg/mL] levels were significantly higher in males aged  $\geq$ 12 years than in males aged <12

years. In females, participants in the  $\geq$ 12-year-old group had higher testosterone [26.8 (0.60) ng/dL vs. 7.93 (0.37) ng/dL] and estradiol [81.7 (3.20) pg/mL vs. 13.2 (1.36) pg/mL] levels compared to participants in the <12-year-old-group. In both males and females, participants in the <12-year-old group had higher SHBG levels than those in the  $\geq$ 12-year-old group [males: 101 (3.85) nmol/L vs. 40.8 (1.46) nmol/L; females: 91.3 (2.76) nmol/L vs. 68.3 (2.69) nmol/L].

### Relationships of obesity and selenium intake with sex hormones

The relationships of obesity and selenium intake with testosterone, estradiol, and SHBG are listed in Figure 1. Obesity was negatively linked to testosterone levels ( $\beta = -0.29$ , 95%CI: -0.45, -0.12) in males aged  $\geq$ 12 years, whereas it was positively correlated with testosterone levels ( $\beta = 0.26$ , 95%CI: 0.13, 0.40) in females aged <12 years. Estradiol levels were positively associated with obesity only in males aged <12 years ( $\beta = 0.09$ , 95%CI: 0.03, 0.16) and males aged  $\geq$ 12 years ( $\beta = 0.19$ , 95%CI: 0.07, 0.32). In terms of SHBG levels, SHBG levels were negatively correlated with obesity in males aged <12 years ( $\beta = -0.69$ , 95%CI: -0.82, -0.57), males aged  $\geq$ 12 years ( $\beta = -0.59$ , 95%CI: -0.67, -0.52), females aged <12

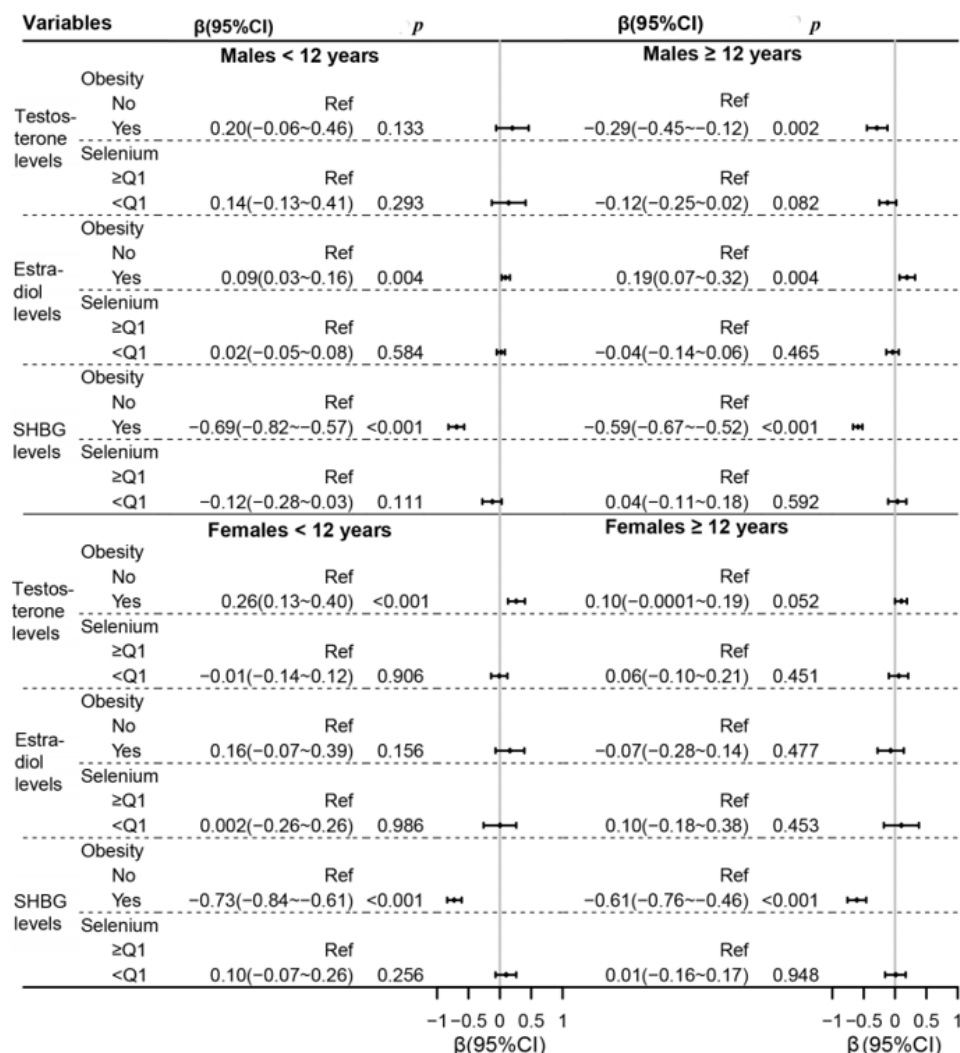


Figure 1. The relationships of obesity and selenium intake with testosterone, estradiol, and SHBG

**Table 1.** Characteristics of children and adolescents (6-19-year-old)

Variables	Total (n=3,380)	Males <12 years (n=710)	Males ≥12 years (n=1,002)	Females <12 years (n=698)	Females ≥12years (n=970)	<i>p</i>
Testosterone, ng/dL, Mean (SE)	127 (4.28)	14.7 (1.93)	368 (7.17)	7.93 (0.37)	26.8 (0.60)	<0.001
Estradiol, pg/mL, Mean (SE)	33.1 (1.41)	2.43 (0.07)	18.6 (0.45)	13.2 (1.36)	81.7 (3.20)	<0.001
SHBG, nmol/L, Mean (SE)	70.8 (1.94)	101 (3.85)	40.8 (1.46)	91.3 (2.76)	68.3 (2.69)	<0.001
Selenium intake, mcg, Mean (SE)	106 (1.44)	101 (2.90)	131 (4.13)	89.7 (1.83)	91.2 (1.88)	<0.001
Race, n (%)						0.203
Non-Hispanic White	906 (51.2)	199 (53.2)	289 (53.4)	179 (46.0)	239 (50.8)	
Non-Hispanic Black	731 (13.4)	165 (13.5)	224 (13.8)	150 (13.1)	192 (12.9)	
Others	1743 (35.4)	346 (33.3)	489 (32.8)	369 (41.0)	539 (36.3)	
PIR, n (%)						0.130
≤1.3	1518 (34.5)	315 (32.2)	436 (31.7)	338 (40.0)	429 (35.7)	
1.3-3.5	1238 (39.8)	256 (38.3)	372 (41.9)	245 (39.6)	365 (38.9)	
>3.5	624 (25.7)	139 (29.6)	194 (26.4)	115 (20.4)	176 (25.4)	
Physical activity, n (%)						<0.001
Not ideal	1158 (33.3)	271 (40.3)	227 (21.2)	302 (44.1)	358 (34.6)	
Ideal	2222 (66.7)	439 (59.7)	775 (78.9)	396 (55.9)	612 (65.4)	
Sedentary time, n (%)						<0.001
<3hours	1362 (41.4)	275 (43.2)	319 (30.8)	358 (53.7)	410 (43.9)	
≥3hours	2018 (58.6)	435 (56.9)	683 (69.2)	340 (46.3)	560 (56.2)	
Sex hormones use, n (%)						
No	3332 (97.7)	710 (100)	1002 (100)	698 (100)	922 (92.2)	
Yes	48 (2.35)	0 (0.00)	0 (0.00)	0 (0.00)	48 (7.84)	
BMI, kg/m <sup>2</sup> , Mean (SE)	22.3 (0.23)	19.0 (0.30)	24.2 (0.33)	18.8 (0.23)	24.8 (0.32)	<0.001
BMI obesity, n (%)						0.137
No	2554 (76.5)	520 (72.3)	767 (76.2)	531 (80.8)	736 (77.2)	
Yes	826 (23.5)	190 (27.7)	235 (23.8)	167 (19.2)	234 (22.8)	
Cotinine, n (%)						0.005
<0.05 ng/mL	2042 (61.1)	440 (66.2)	546 (54.5)	422 (64.0)	634 (62.6)	
≥0.05 ng/mL	1338 (38.9)	270 (33.8)	456 (45.5)	276 (36.0)	336 (37.4)	
Carbohydrate, %, Mean (SE)	52.3 (0.30)	53.1 (0.49)	50.9 (0.53)	53.4 (0.46)	52.4 (0.49)	0.002
Protein, %, Mean (SE)	14.8 (0.14)	14.5 (0.27)	15.7 (0.32)	14.0 (0.26)	14.5 (0.26)	0.006
Total fat, %, Mean (SE)	34.0 (0.23)	33.6 (0.40)	34.2 (0.31)	33.8 (0.35)	34.2 (0.41)	0.295
Total energy, kcal, Mean (SE)	1986 (24.5)	1999 (41.2)	2313 (47.0)	1785 (28.4)	1759 (33.5)	<0.001
Time of venipuncture, n (%)						<0.001
Morning	1451 (36.3)	254 (25.4)	460 (39.2)	273 (35.7)	464 (41.4)	
Afternoon	1232 (34.8)	291 (38.8)	364 (35.6)	267 (32.2)	310 (32.7)	
Evening	697 (28.9)	165 (35.8)	178 (25.3)	158 (32.1)	196 (26.0)	

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

**Table 2.** The relationship of obesity with sex hormone levels at different selenium intakes

Outcomes	Variables	Males <12 years			Males ≥12 years		
		β (95% CI)	<i>p</i>	<i>p</i> <sub>interaction</sub>	β (95% CI)	<i>p</i>	<i>p</i> <sub>interaction</sub>
Testosterone levels	Group: selenium ≥Q1	-	-	-	-0.31 (-0.49, -0.12)	0.002	0.058
	Obesity	-	-				
Estradiol levels	Group: selenium <Q1	-	-	0.074	-0.19 (-0.56, 0.18)	0.308	0.087
	Obesity	0.09 (0.02, 0.15)	0.010		0.18 (0.04, 0.33)	0.015	
SHBG levels	Group: selenium ≥Q1	0.18 (0.03, 0.32)	0.020	<0.001	0.29(0.10, 0.49)	0.005	<0.001
	Obesity	-0.68 (-0.75, -0.60)	<0.001		-0.60 (-0.69, -0.50)	<0.001	
	Group: selenium <Q1	-0.75 (-1.00, -0.50)	<0.001		-0.66 (-0.79, -0.53)	<0.001	
	Obesity						
Outcomes	Variables	Females <12 years			Females ≥12 years		
		β (95% CI)	<i>p</i>	<i>p</i> <sub>interaction</sub>	β (95% CI)	<i>p</i>	<i>p</i> <sub>interaction</sub>
Testosterone levels	Group: selenium ≥Q1	0.19 (0.04, 0.35)	0.017	0.007	-	-	-
	Obesity	0.50 (0.23, 0.76)	<0.001		-	-	
Estradiol levels	Group: selenium <Q1	-	-	-	-	-	-
	Obesity	-	-		-	-	
SHBG levels	Group: selenium ≥Q1	-0.74 (-0.86, -0.61)	<0.001	<0.001	-0.60 (-0.76, -0.45)	<0.001	<0.001
	Obesity	-0.68 (-0.90, -0.45)	<0.001		-0.61 (-0.85, -0.37)	<0.001	
	Group: selenium <Q1						
	Obesity						

SHBG, sex hormone-binding globulin; β, beta values; 95% CI, 95% confidence interval; Ref, reference; Q1, first quartile of the quartiles;

All analyses were multivariable weighted linear regression model adjusted for race, PIR, physical activity, sedentary time, sex hormones use, cotinine, carbohydrate intake, protein intake, total fat intake, time of venipuncture, season of sample collection, vitamin D intake, zinc intake, copper intake, and magnesium intake.

*p*<sub>interaction</sub> is the test value of the multiplicative interaction term between obesity and selenium intake.

years ( $\beta = -0.73$ , 95%CI: -0.84, -0.61), and females aged  $\geq 12$  years ( $\beta = -0.61$ , 95%CI: -0.76, -0.46). However, no relationship of selenium intake with testosterone, estradiol, and SHBG was found in either males or females ( $p > 0.05$ ).

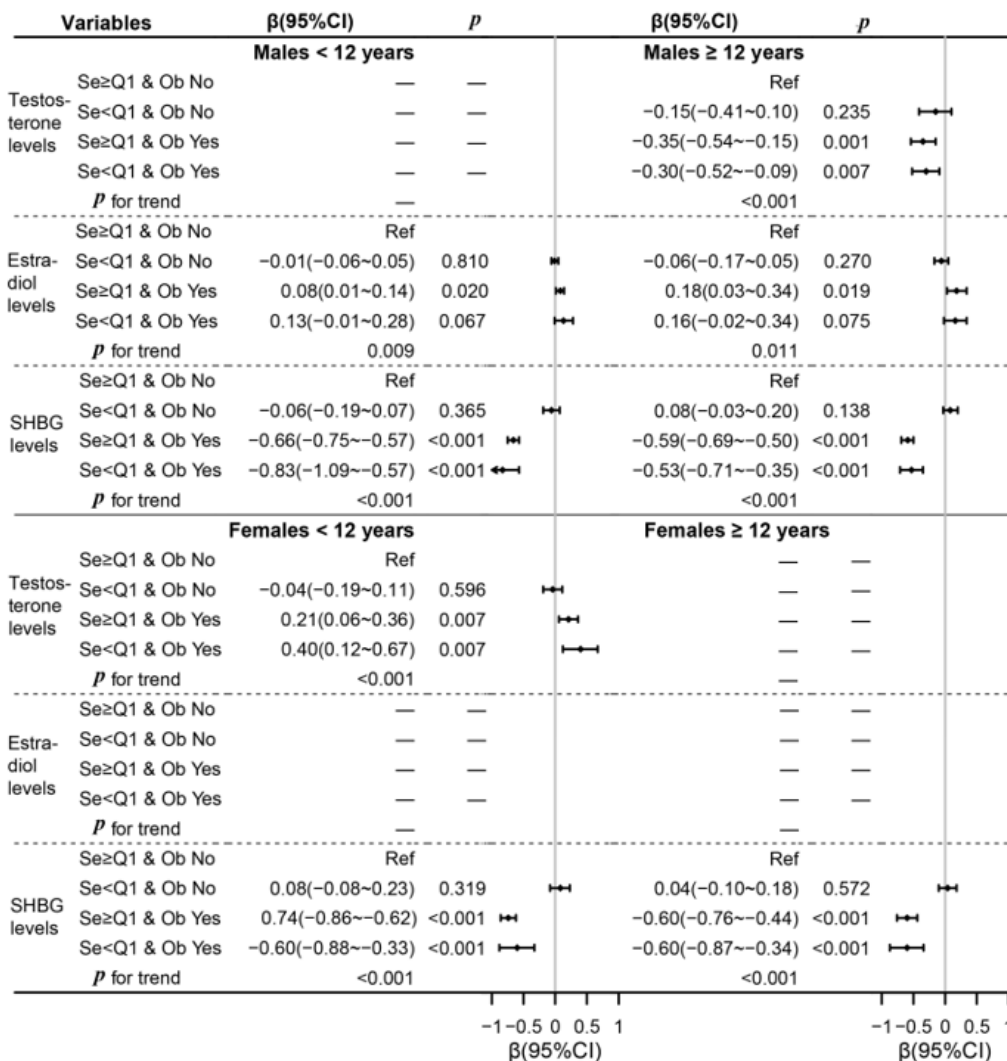
#### **Moderating effect of selenium intake on the association between obesity and sex hormones**

Table 2 demonstrates the relationship of obesity with testosterone, estradiol, and SHBG at different selenium intakes. In participants with selenium intake  $\geq Q1$ , obesity was negatively linked to testosterone levels ( $\beta = -0.31$ , 95%CI: -0.49, -0.12) in males aged  $\geq 12$  years, while it was positively correlated with testosterone levels ( $\beta = 0.19$ , 95%CI: 0.04, 0.35) in females aged  $< 12$  years. Among participants with selenium intake  $< Q1$ , obesity was still positively correlated with testosterone levels ( $\beta = 0.50$ , 95%CI: 0.23, 0.76) in females aged  $< 12$  years. There may be a multiplicative interaction between obesity and selenium intake on testosterone levels ( $p_{\text{interaction}} = 0.007$ ). Obesity was observed to be positively related to estradiol levels in males aged  $< 12$  years [selenium intake  $\geq Q1$ :  $\beta = 0.09$ , 95%CI: 0.02, 0.15; selenium intake  $< Q1$ :  $\beta = 0.18$ , 95%CI: 0.03, 0.32] and males aged  $\geq 12$  years [selenium intake  $\geq Q1$ :  $\beta = 0.18$ , 95%CI: 0.04, 0.33; sele-

nium intake  $< Q1$ :  $\beta = 0.29$ , 95%CI: 0.10, 0.49] at different selenium intakes. No interaction between obesity and selenium intake on estradiol levels was observed ( $p_{\text{interaction}} > 0.05$ ). Furthermore, a negative correlation between obesity and SHBG levels was found in both males and females of all ages at different selenium intakes (all  $p < 0.05$ ). Multiplicative interaction between obesity and selenium intake on SHBG levels were found in all sex and age groups (all  $p_{\text{interaction}} < 0.001$ ).

Figure 2 presents the trend analysis of the effects of obesity and selenium intake on testosterone, estradiol, and SHBG. In males aged  $\geq 12$  years, participant in the selenium  $\geq Q1$  & obesity group ( $\beta = -0.35$ , 95%CI: -0.54, -0.15) and the selenium  $< Q1$  & obesity group ( $\beta = -0.30$ , 95%CI: -0.52, -0.09) were negatively linked to testosterone levels compared to those in the selenium  $\geq Q1$  & non-obesity group (reference group).

For testosterone, highly significant trends ( $p_{\text{trend}} < 0.001$ ) were observed across the risk groups, but in opposite directions depending on sex and age. In males aged  $\geq 12$  years, there was a progressive reduction in testosterone levels, whereas in females aged  $< 12$  years, a progressive elevation was found. Trends in the effect of these groups on estradiol levels were observed in males aged  $< 12$  years ( $p_{\text{trend}} = 0.009$ ) and males aged  $\geq 12$  years ( $p_{\text{trend}}$



**Figure 2.** Trend analysis of the effects of obesity and selenium intake on testosterone, estradiol, and SHBG. Se, Selenium; Ob, Obesity

= 0.011). The positive beta ( $\beta$ ) values for the obesity groups show that obesity is the primary driver for higher estradiol, and this effect follows a gradient. In addition, there were trends in the effects of these groups on SHBG levels across sex and age subgroups [males aged <12 years,  $p_{\text{trend}} < 0.001$ ; males aged  $\geq 12$  years,  $p_{\text{trend}} < 0.001$ ; females aged <12 years,  $p_{\text{trend}} < 0.001$ ; and females aged  $\geq 12$  years,  $p_{\text{trend}} < 0.001$ ]. The negative beta ( $\beta$ ) values become more pronounced in the groups with obesity, with the lowest levels often seen in the Selenium <Q1 & Obesity group. This indicates that the adverse effect of obesity on SHBG levels follows a strong gradient, and low selenium intake may further exacerbate this reduction.

Moreover, to exclude the effect of selenium dietary supplements on the results, we excluded participants using selenium supplements ( $n = 58$ ) and performed sensitivity analyses with the remaining participants without selenium supplements ( $n = 3,322$ ). Sensitivity analyses demonstrated that the moderating effect of selenium intake on the association between obesity and sex hormones remains (Supplementary Tables 2 to 4).

## DISCUSSION

The current study examined the relationships of obesity and selenium intake with sex hormones in children and adolescents (6-19 years old). Our findings showed sex-specific associations between obesity and sex hormones: obesity was negatively associated with testosterone in males but positively associated with testosterone in females, and positively correlated with estradiol only in males; notably, obesity was negatively linked to SHBG across all sex-age subgroups. No direct association was observed between selenium intake and any sex hormone, but further analyses revealed an interaction between obesity and selenium intake, suggesting selenium may moderate the obesity-sex hormone association.

Sex hormones play a crucial role in the development of children and adolescents. Obesity affects the level of sex hormones in the body, and the prevalence of obesity is rising rapidly in children and adolescents.<sup>3</sup> It was reported that there are sex differences in the effect of sex hormones on obesity.<sup>22, 23</sup> Elevated testosterone levels reduce abdominal obesity and metabolic risk in males, whereas elevated testosterone levels and lower SHBG levels are positively associated with abdominal and visceral adipose tissue in females.<sup>22, 23</sup> Our results demonstrated that obesity in males was negatively related to testosterone levels, whereas obesity in females was positively associated with testosterone levels. Several epidemiologic studies have shown that obesity is negatively correlated with testosterone levels.<sup>24, 25</sup> For estradiol levels, our results found that estradiol levels were positively associated with obesity only in males. Previous studies reported that higher estrogen exposure exists in obese males than in lean males during the early stages of puberty.<sup>6</sup> This may be explained by the higher metabolic activity of testosterone in adipose tissue leads to elevated estradiol levels in obese males, and adipose tissue also affects the secretion of gonadotropins, which in turn affects androgen formation in the testes.<sup>26</sup> In addition, our results showed that a negative link between obesity and SHBG levels was found in both males and females. The association of obe-

sity with reduced SHBG levels may involve inhibition of hepatic SHBG synthesis by elevated insulin concentrations.<sup>27, 28</sup>

Selenium assumes a multifaceted role in pediatric obesity, serving concurrently as a vital nutrient and a potential biomarker. Selenium exerts anti-obesity effects through multiple pathways.<sup>13</sup> Its dynamic interactions with metabolic pathways, dietary exposure patterns, and bioavailability dynamics represent critical determinants for unraveling the pathogenesis of obesity in children and adolescents.<sup>29</sup>

Selenium, as a component of iodothyronine deiodinase (DIO), is involved in thyroid hormone metabolism. Since thyroid hormones are associated with the regulation of sex hormone secretion, selenium deficiency may disrupt this regulatory process and affect sex hormone levels.<sup>11</sup> Selenium has been reported to influence pubertal development through several pathways including its involvement in the production of sex hormones. Insulin-like growth factor 1 (IGF-1) has been demonstrated to promote pubertal development by elevating serum testosterone levels. Reduced IGF-1 levels may be associated with heightened inflammatory responses and oxidative stress, potentially induced by low selenium status. These factors may subsequently delay genital development and reduce testicular volume.<sup>14</sup> Selenium, as a core component of glutathione peroxidase, protects gonadal cells through its antioxidant properties, promotes the synthesis of testosterone and estradiol, and simultaneously reduces SHBG levels. The mechanism may involve mitigating oxidative stress-induced damage to endocrine cells.<sup>13</sup>

Previous study indicated that elevated serum selenium levels were related to higher testosterone and estradiol levels and lower SHBG levels.<sup>13</sup> However, our results did not find a relationship of selenium intake with testosterone, estradiol, and SHBG in males or females. This may be due to our exposure being dietary selenium intake.

Further analyses found that selenium intake may play a moderating effect in the link between obesity and sex hormones. There was a statistically significant trend in correlations with testosterone, estradiol, and SHBG levels for children and adolescents in the association of the selenium <Q1 & non-obesity group, the selenium  $\geq$ Q1 & obesity group, and the selenium <Q1 & obesity group compared to those in the selenium  $\geq$ Q1 & non-obesity group. However, no previous studies have reported the effect of selenium intake on the relationship between obesity and sex hormone levels, and the associated mechanisms of action are unclear.

Selenium plays a complex role in regulating insulin signaling as well as lipid metabolism.<sup>30</sup> Selenium may act as an insulin-mimetic, mediating many insulin-like effects such as stimulating glucose uptake and regulating metabolic processes.<sup>31</sup> In addition, selenoproteins may block adipogenesis by regulating preadipocyte proliferation and lipogenic differentiation and by interfering with insulin signaling to regulate lipolysis.<sup>32, 33</sup> However, the effects of selenium intake in conjunction with obesity on sex hormones in children and adolescents may require further study. Our findings may provide dietary recommendations for adolescents that adequate selenium intake

(greater than or equal to the recommended selenium intake, but not exceeding the maximum allowable intake) should be maintained in their daily diet as selenium intake may reduce the adverse effects of obesity on sex hormone levels.

Selenium is essential for human health, but maintaining an appropriate selenium intake is crucial. Insufficient intake can result in selenium deficiency, while excessive consumption, particularly supraphysiological levels, may cause adverse effects like selenium toxicity. The margin between adequate and toxic doses of selenium is relatively small.<sup>34</sup> Hence, a balanced diet and judicious use of supplements are vital to ensure selenium intake remains within a safe and effective range.

Sensitivity analyses excluding participants using selenium supplements showed that the moderating effect of selenium intake on the link between obesity and sex hormones remained statistically significant. Previous research has found that selenium intake from diet but not from supplements was associated with birth weight and SGA. The potential reason may be that dietary selenium intake levels are close to those associated with optimal selenoprotein expression, and additional selenium from supplements does not further enhance selenoprotein expression.<sup>35, 36</sup>

This study grouped populations by sex (males, females) and age (6-12-year-old, 12-19-year-old) when analyzing the effects of selenium intake and obesity on sex hormones due to age and sex differences in sex hormones. Moreover, we adjusted for some potential confounders such as the season and time of blood collection during analysis. The possible moderating role of selenium intake in the relationship between obesity and sex hormones in this study may provide some rationale for dietary interventions in obese children and adolescents. Nevertheless, the limitations of the present study cannot be ignored. First, the cross-sectional study design of the present study could not confirm a causal correlation between obesity and selenium intake and sex hormones. Second, since the NHANES database does not have accurate information on the stage of puberty, this may affect the accurate analysis of puberty status although this study was grouped according to age and gender. Third, selenium intake in this study was measured by recall interviews, which may have affected the accuracy of selenium intake.

### Conclusions

This study provides new evidence on the complex interplay between obesity, nutrition, and endocrine function in a nationally representative cohort of children and adolescents. We confirmed and extended previous findings by demonstrating distinct sex- and age-specific associations between obesity and sex hormones. Although the direct relationship between selenium intake and sex hormones was not statistically significant, selenium intake may play a moderating role in the link between obesity and sex hormones. Our study suggest that maintaining adequate selenium intake may alleviate the adverse effects of obesity on sex hormones, offering a potential low-cost dietary intervention strategy for mitigating obesity-related endocrine complications. The mechanism of role of sele-

nium on the correlation between obesity and sex hormones needs to be further explored.

### DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

In this study, all processes including data collection, data analysis, and creation of images or graphical elements were independently completed by the authors without the assistance of any artificial intelligence or AI-assisted technologies.

The authors reviewed and edited the content and takes full responsibility for the content of the publication.

### CONFLICT OF INTEREST AND FUNDING DISCLOSURES

All authors declare that they have no conflict of interests.

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