Original Article: Clinical Investigation

Association between body mass index and varicocele among 211 989 Chinese reproductive-age males

Xuhuai Hu,^{1,†} Xueying Yang,^{2,3,†} Jun Zhao,^{2,3} Ding Guan,¹ Qiaoyun Dai,^{2,3} Juan Yang,¹ Hongguang Zhang,^{2,3} Dongmei Zhang,¹ Yue Zhang,^{2,3} Li Shang¹ and Xu Ma^{2,3}

¹Shenzhen Health Development Research and Data Management Center, Shenzhen, Guangdong, ²National Research Institute for Family Planning, and ³National Human Genetic Resources Center, Beijing, China

Abbreviations & Acronyms BMI = body mass index CI = confidence interval NFPCP = National Free Preconception Check-up Project OR = odds ratio SD = standard deviation

Correspondence: Jun Zhao Ph.D., National Research Institute for Family Planning, National Human Genetic Resources Center, No. 12 Dahuisi Road, Haidian District, Beijing 100081, China. Email: zj@e-health.org.cn

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Received 17 November 2021; accepted 12 April 2022. Online publication 28 April 2022

[†]These authors contributed equally to this work.

Objectives: To explore the relationship between body mass index and varicocele, the range of body mass index that leads to increased odds of varicocele, and the association between body mass index with the position and grade of varicocele.

Methods: We conducted a cross-sectional study of 211 989 Chinese males aged 18–65 years participated in the National Free Pre-conception Check-up Projects from January 2013 to December 2018. Univariate and multivariate logistic regression models were constructed to assess the association between body mass index and varicocele.

Results: Overweight and obese males had 13.1% (odds ratio 0.869, 95% confidence interval 0.838–0.902) and 32.3% (odds ratio 0.677, 95% confidence interval 0.632–0.725) lower odds of varicocele than those with normal body mass index, respectively. The association between them was non-linear, and males with body mass index of 17.74 to 23.09 kg/m² had an increased odds of varicocele. The overweight and obese males had lower odds of left and bilateral varicocele, but the right varicocele odds was increased by 63.3% in obese males.

Conclusion: Body mass index was associated with the odds of varicocele among reproductive-age males, but the odds varied by position. The effects of weight management and varicocele on fertility should be taken into account in fertility guidance.

Key words: body mass index, China, cross-sectional study, fertility, varicocele.

Introduction

Varicocele is a vascular disease characterized by abnormal expansion, elongation, and tortuosity of the spermatic vein plexus,¹ which is a common cause of male infertility and can lead to pain, discomfort, and the progressive decline of testicular function.^{2,3} The prevalence of varicocele in men seeking treatment for primary and secondary infertility is 45% and 80%, respectively.² Varicocele is more common in young and middle-aged men, with a morbidity of 4.1– 22.6%,^{1,2,4–6} Among patients with varicocele, left varicocele is the most common, followed by bilateral varicocele, and right varicocele is the rarest.^{4,5} This may be attributed to the connection of the left testicular vein to the renal vein, while the right testicular vein drains directly into the larger inferior vena cava at an acute angle.⁷

Most previous studies have found a negative correlation between BMI and varicocele risk,^{3–5,8–14} but few studies have further explored the BMI range of increased varicocele risk. In addition, some studies with small sample sizes did not find an association between them,^{6,15,16} making the relationship still controversial. Similarly, due to the limitation of sample size, few studies further explored the association between BMI with the position and grade of varicocele.^{3,5,6,9–14,17} Currently, there are few studies on the relationship between BMI and varicocele in a large sample of Chinese males preparing to have children who have not previously been diagnosed with infertility.⁵

We carried out a cross-sectional study to investigate the relationship between BMI and varicocele among reproductive-age males who participated in the NFPCP, which is a national health service supported by the Chinese government. The objective of this study was to examine the hypothesis that BMI was negatively associated with the odds of varicocele, and further explore the range of BMI that led to increased odds of varicocele, as well as the

associations between BMI and the position and grade of varicocele, so as to provide scientific basis for intervention of varicocele and weight management in reproductive-age males.

Methods

Design and study population

The NFPCP is a nationwide, population-based study project aimed at providing free pre-pregnancy medical examinations for general reproductive-age couples (not just those with fertility problems) who have made their conception plan in 6 months to improve their reproductive health.¹⁸ This study was an original research based on the NFPCP, and the data were obtained from the NFPCP system. From January 1, 2013 to December 31, 2018, comprising 268 627 males aged 18-65 years participated in the NFPCP and completed prepregnancy eugenic health examinations in Shenzhen, China. According to the exclusion criteria reported in the literature,^{1,3,5} we excluded males who had a history of certain diseases (e.g., tumor, chronic nephritis, orchitis, epididymitis), or whose liver and spleen were palpable on physical examination, or who missed some key information (e.g., height, weight, and varicocele). Since hematuria is one of the most common symptoms for reproductive system diseases, which could be caused by a variety of etiologies, including urolithiasis, urinary tract infection, iatrogenic causes, as well as left renal vein compression,^{19,20} we excluded those with hematuria on urine routine examination (Fig. 1). Finally, a total of 211 989 reproductiveage males were included in the analysis. This study protocol was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology crosssectional guidelines and was approved by the Ethics Committee of the Shenzhen Health Development Research Center, Guangdong Province, People's Republic of China.

Data collection

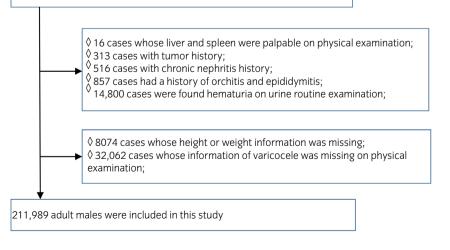
After signing written informed consent forms in local maternal/child health care institutions, all participants were given questionnaires, physical examinations, and clinical examinations by experienced physicians and urologists. Demographic characteristics (including age, ethnicity, occupation, and educational level), history of disease, and lifestyle information (including smoking and alcohol intake) were collected through face-to-face interviews. According to the standard operating procedures, participants' weight (nearest 0.1 kg) and height (nearest 0.1 cm) were measured without shoes and other accessories by calibrated beam balance and tacheometer. In this large-scale population health examination, due to the limited conditions, we did not conduct ultrasound examination, but obtained varicocele information through reproductive health examination.

Variables definition

Varicocele

In this study, varicocele was diagnosed through reproductive health examinations, which was observed in a separate, warm room by experienced urologists above attending physician level with the participants standing. We referred to and used the Dubin/Amelar system to classify the grading of varicocele into four groups:²¹ non/subclinical varicocele, in the absence of ultrasonographic assistance, not be palpable or seen at rest or with Valsalva maneuver; Grade I, can be palpable only with the Valsalva maneuver but cannot be seen; Grade II, can be palpable at rest without the Valsalva maneuver but not easily visible; Grade III, can be palpable at rest without the Valsalva maneuver and visible from a distance. In case of bilateral varicocele with inconsistent grade, the one with higher grade should be included in the statistics. If bilateral

268,627 males aged 18-65 years old who were planning to have children, participated in the NFPCP and completed pre-pregnancy eugenic health examinations from January 1^{st} , 2013 to December 31^{st} , 2018



varicocele was with the same grade, the original grade should be added one grade and the highest grade was Grade III.

Classification of BMI

BMI was calculated based on weight and height as follows: BMI = weight/height² (kg/m²). The participants were categorized as underweight (<18.5 kg/m²), normal (18.5–23.9 kg/ m²), overweight (24.0–27.9 kg/m²), and obese (\geq 28.0 kg/m²) based on the Guidelines for Prevention and Control of Overweight and Obesity of Chinese Adults.²²

Assessment of covariates

With reference to previous relevant literature⁶ and combined with the variables collected in this study, the covariates referred to demographic characteristics and lifestyle information. Age was calculated by the date of examination and birth, measured by continuous variables and further converted to discrete variables (18–29, 30–39, \geq 40 years).⁶ According to the options set in the questionnaire, occupation was categorized as teacher/civil servant/staff, worker, service staff, business, and others. Ethnicity was categorized as Han and others, and educational level was categorized as high school or below and bachelor's degree or above. Self-reported lifestyle information included smoking and alcohol intake. Smoking was defined as ≥ 1 cigarette smoking per day for at least 1 year. Alcohol intake was divided into two levels: never (No) and occasional/frequent drinking (Yes). Height was divided into four groups according to the quartile: ≤ 167 , 168-170, 171-174, and ≥ 175 cm.

Statistical analysis

R 3.5.1 statistical software was used for data cleaning and analysis. Mean (SD) and counts (percentages) were used to describe participants' baseline characteristics. Chi-squared test and Wilcoxon-Mann-Whitney test were used to examine the differences of each variable between groups. We used logistic regression to estimate the ORs and their corresponding 95% CIs for the association between BMI and varicocele. The multivariable-adjusted logistic regression was employed to adjust for age, occupation, educational level, smoking, alcohol intake, and height. Restricted cubic splines were used to explore the relationship between BMI and varicocele. Subgroup analyses were conducted according to demographic characteristics, lifestyle information, and height. Finally, we further explored the association of BMI with the position and grade of varicocele by logistic regression models. Two-sided P values of less than 0.05 were deemed to be statistically significant

Results

The average age of 211 989 reproductive-age males included in this study was 31.20 (SD 4.90) years, among which 16 233 cases were varicocele, with a prevalence of 7.66%. Except for ethnicity, most baseline characteristics between the varicocele and non-varicocele groups were statistically different (P < 0.001). Compared with non-varicocele males, those with varicocele were more likely to be higher educational level, have more alcohol intake, with higher height, and less likely to be smokers, and overweight/obese (Table S1).

In our study population, the prevalence of underweight, overweight, and obesity was 4.65%, 31.97% and 8.15%, respectively. In the multivariable-adjusted model, overweight and obese males had 13.1% (OR 0.869, 95% CI 0.838–0.902) and 32.3% (OR 0.677, 95% CI 0.632–0.725) lower odds of varicocele than those with normal BMI (Table 1). However, there was no significant correlation between BMI and varicocele in the underweight group.

We selected P2.5 (17.93 kg/m²), P35 (22.04 kg/m²), P65 (24.44 kg/m²), and P97.5 (30.44 kg/m²) (BMI = 23.18 kg/m² as reference) to draw a restricted cubic spline curve to further explore the relationship between BMI and varicoccele. The results showed that after adjusting for confounding factors, the association between BMI and varicoccele was non-linear (P < 0.0001). Reproductive-age males with a BMI between 17.74 and 23.09 kg/m² had an increased odds of varicoccele (Fig. 2).

Results of subgroup analyses were shown in Figure S1. We performed logistic regression analysis on age (categorical), occupation, educational level, smoking, alcohol intake, and height separately. The results showed that the association between BMI and varicocele did not appear to be modified by the above baseline characteristics. The obesity group generally had lower ORs than the overweight group in all subgroups. Notably, the positive effect of elevated BMI (either overweight or obesity) on varicocele was more pronounced in younger males than in middle-aged males.

Among 211 989 reproductive-age males, those with left, right, and bilateral varicocele accounted for 5.08%, 0.18%, and 2.38%, respectively. Table 2 showed the results of logistic regression models for the association between different BMIs and varicocele positions. Compared with the normal BMI group, the odds of left varicocele was reduced by 9.9% and 27.4% among overweight and obese males, and the odds of bilateral varicocele was reduced by 20.4% and 47.1%, respectively. Notably, the odds of right varicocele was increased by 63.3% (95% CI 1.157–2.254) in the obesity group, but not statistically significant in the overweight group. However, there was no statistically significant difference in the odds of left, right, or bilateral varicocele in underweight males.

Among 211 989 reproductive-age males, those with Grade I, II, and III varicocele accounted for 3.04%, 4.12%, and

Table 1 Association between BMI and varicocele						
BMI groups	N (%)†	Crude OR (95% CI)	Adjusted OR (95% CI)‡			
Normal	9596 (8.20)	Ref	Ref			
Underweight	755 (7.66)	0.930 (0.860–1.004)	1.001 (0.924–1.082)			
Overweight	4902 (7.23)	0.873 (0.843–0.905)	0.869 (0.838–0.902)			
Obesity	980 (5.67)	0.674 (0.629–0.721)	0.677 (0.632–0.725)			

[†]N referred to the number of males with varicocele in each BMI group, and % referred to the proportion of males with varicocele in each BMI group. [‡]Adjusted ORs were adjusted for age (categorical), occupation, educational level, smoking, alcohol intake, and height.

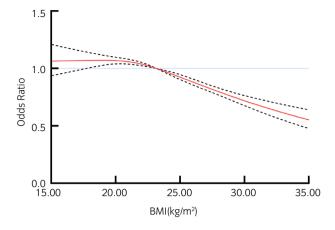


Fig. 2 Restricted cubic spline plot of OR by different BMI levels. The ORs were estimated by restricted cubic spline model adjusting for age (categorical), occupation, educational level, smoking, alcohol intake, and height. The dotted lines represented the 95% CIs.

0.48%, respectively. The average BMIs of the non-varicocele, Grade I, II, and III varicocele males were 23.45 \pm 3.26 kg/ m^2 , $23.41 \pm 3.12 \text{ kg/m}^2$, $22.99 \pm 2.99 \text{ kg/m}^2$, and 22.65 ± 2.97 kg/m², respectively (P < 0.001). We further explored the association between different BMIs and varicocele grades, and found that compared with the normal BMI group, the odds of Grade II and Grade III varicocele decreased in the overweight group, and the odds of all three grades' varicocele decreased in the obese group, but were not significant in the underweight group. Clinical physicians generally consider that Grade II-III varicocele is clinically meaningful among males with varicocele. Therefore, we also analyzed the relationship between BMI and Grade II-III varicocele, and the results were consistent (Table 3).

Discussion

In this study, we found that overweight and obese males had a lower odds of varicocele than those with normal BMI, which was consistent with some previous studies.^{3,4,7,10,17} A meta-analysis of 1 376 658 participants from 11 studies showed that the risk of varicocele was 54% and 30% lower in obese and overweight men than those with normal BMI.⁸ Based on physical examinations of 1.3 million Israeli males, Rais *et al.*¹⁴ found that overweight and obese males had 49% and 65% lower risk of varicocele than the normal BMI males. Liu *et al.*⁵ conducted a cross-sectional study screening 39 559 Chinese rural men and found that overweight and obese men were 12% and 25% less likely to have varicocele, respectively. However, some small sample studies have yielded inconsistent results. Kilic *et al.*¹⁵ found no statistically significant difference in BMI between 52 men with varicocele and 100 men without varicocele. Delaney *et al.*¹⁶ retrospectively studied 50 males with varicocele and found no difference in BMI between young males with varicocele and age-matched controls. The inconsistent results might be caused by differences in basic characteristics of the study population, study design and sample size.

Significantly, we found no increased odds of varicocele in underweight males, which was inconsistent with previous findings. A study from six counties in eastern China showed that BMI was negatively correlated with varicocele (judged by physical examination), and underweight males were more likely to develop varicocele.⁵ A study on 1.3 million Israeli males (average age: 17.5 years) found that underweight (percentile classification) males had a higher risk of varicocele.¹⁴ The main reasons for the different results might be different age structure of the study population, BMI classification criteria, and diagnostic criteria for varicocele. However, another study in an Asian population obtained similar results to ours, showing that BMI was significantly lower in the varicocele group among adolescents, but the difference was not significant among adults.⁷

The association between different BMIs and varicocele positions showed that compared with the normal BMI group, the odds of left and bilateral varicocele was reduced to different degrees in overweight and obese males, but the odds of right varicocele was increased in the obese males. Through literature search, we found it is the first study to explore the relationship between BMI and varicocele position (especially right varicocele). As mentioned earlier, most varicocele occurred on the left side, followed by bilateral varicocele, and isolated right varicocele was fairly rare.4,5 We unexpectedly found an increased odds of right varicocele in obese males, which has not been previously reported and needs to be confirmed by further studies. In addition, the proportion of bilateral varicocele in total varicocele was slightly higher than in some previous studies, which might be due to the difference in baseline characteristics of our subjects from previous studies (such as older age structure and higher proportion of office workers).4,5,23

The association between different BMIs and varicocele grades showed that the odds of Grade II and III varicocele

Table 2 Association between different BMI groups and varicocele positions								
	Left		Right		Bilateral			
BMI groups	N (%)†	Adjusted OR (95% CI)‡	N (%)†	Adjusted OR (95% CI)‡	N (%)†	Adjusted OR (95% CI)‡		
Normal	6208 (5.46)	Ref	183 (0.17)	Ref	3169 (2.86)	Ref		
Underweight	522 (5.43)	1.025 (0.932-1.125)	23 (0.25)	1.523 (0.949–2.323)	207 (2.23)	0.930 (0.803-1.072)		
Overweight	3330 (5.03)	0.901 (0.862-0.942)	122 (0.19)	1.068 (0.841-1.350)	1434 (2.23)	0.796 (0.746-0.849)		
Obesity	698 (4.11)	0.726 (0.668–0.787)	44 (0.27)	1.633 (1.157–2.254)	238 (1.44)	0.529 (0.462–0.605)		

+N referred to the number of males with varicocele in different positions in each BMI group, and % referred to the proportion of males with varicocele in different positions in each BMI group. ‡Adjusted ORs were adjusted for age (categorical), occupation, educational level, smoking, alcohol intake, and height.

Grade I		Grade II		Grade III		Grade II–III		
BMI groups	N (%)†	Adjusted OR (95% CI)‡	N (%)†	Adjusted OR (95% CI)‡	N (%)†	Adjusted OR (95% CI)‡	N (%)†	Adjusted OR (95% CI)‡
Normal	3599 (3.24)	Ref	5336 (4.73)	Ref	629 (0.58)	Ref	5965 (5.26)	Ref
Underweight	275 (2.93)	0.981 (0.863-1.112)	413 (4.34)	0.981 (0.882-1.088)	64 (0.70)	1.271 (0.969–1.637)	477 (4.98)	1.012 (0.916–1.114
Overweight	2090 (3.22)	0.964 (0.912-1.019)	2523 (3.86)	0.821 (0.781-0.862)	279 (0.44)	0.749 (0.648–0.864)	2802 (4.27)	0.813 (0.776–0.852
Obesity	478 (2.85)	0.847 (0.766–0.934)	456 (2.72)	0.587 (0.531-0.647)	44 (0.27)	0.444 (0.321-0.598)	500 (2.98)	0.571 (0.519-0.627

+N referred to the number of males with varicocele of different grades in each BMI group, and % referred to the proportion of males with varicocele of different grades in each BMI group. ‡Adjusted ORs were adjusted for age (categorical), occupation, educational level, smoking, alcohol intake, and height.

decreased in the overweight group, and the odds of all three grades' varicocele decreased in the obese group, but no statistical significance was found in the underweight group, similar to previous studies.^{5,9} Liu *et al.*⁵ found the prevalence of varicocele decreased with the increase of BMI among all three varicocele grades, and varicocele grades were significantly inversely associated with BMI, which was closer to our results. Moreover, a case–control study on 400 males showed that BMI was less in grade III varicocele than other grades.⁹

The etiology and pathogenesis of varicocele cannot be explained by a single theory. The anatomic differences between left and right internal spermatic vein drainage may be related to the different association between BMI and left and right varicocele.²⁴ 'Nutcracker phenomenon'^{5,10,12,25} is now widely accepted as one of the main theories to explain the possible association between BMI and left varicocele. 'Nutcracker phenomenon' suggests that varicocele is caused by increased pressure in the left renal vein as it is compressed between the aorta and the superior mesenteric artery,⁵ while adipose tissue may reduce the compression. 10,12,25 Although the mechanism by which BMI is associated with isolated right varicoceles has not been reported, Linicus et al.²⁶ found that high BMI was associated with a highpressure gradient in the inferior vena cava. The right spermatic vein usually drains directly into the inferior vena cava at an acute angle.²⁷ In addition, some studies^{28,29} supported that obesity could lead to increased intraperitoneal pressure, which over time cause increased inferior vena cava pressure and ultimately to progressive failure of the spermatic vein check valve and venous valve insufficiency. Therefore, we hypothesized that right varicocele in obese males might be more related to venous valve insufficiency and abnormal drainage caused by inferior vena cava hypertension.

It is well known that varicocele is a common reason of male infertility,¹ and abnormal BMI can also adversely affect male fertility.² Some previous studies have looked at males with fertility problems.^{2,3} We investigated the association between BMI and varicocele (including position and grade) in general reproductive-age males (not just those with fertility problems), and explored the range of BMI that led to increased odds of varicocele, which had important public health implications for improving reproductive health of this population. The results also found that the positive effect of elevated BMI on varicocele was more pronounced in younger

males than in middle-aged males. Therefore, the relationship between BMI and the odds of varicocele (including position and grade), and both on male fertility should be taken into account when evaluating fertility in young males. The advantages of this study were as follows. First, this was by far the largest sample size study on the association between BMI and varicocele in Chinese reproductive-age males, and the standardized data collection methods and strict laboratory quality control of the NFPCP ensured data reliability. Second, due to the large sample size, we further explored the association between BMI and varicocele position and grade, and found for the first time that BMI had different effects on left and right varicocele. Finally, this study firstly proposed the BMI range for increased odds of varicocele in reproductiveage males, which was helpful to evaluate the combined effect of varicocele and abnormal BMI on fertility.

This study also had certain limitations. First, some information (e.g., smoking, alcohol intake) was self-reported and inevitably had report bias. Second, varicocele was diagnosed by experienced urologists through physical examination according to standardized guidelines, but no ultrasound was performed on every male. Studies had found that the specificity and positive predictive values of varicocele detected by experienced urologists through physical examination were 82.0% and 81.1%,³⁰ respectively. However, both the American Society for Reproductive Medicine and the American Society for Reproduction Medicine Practice Committees recommended that varicocele can be diagnosed by physical examination. Additionally, Walters et al.¹¹ found that the prevalence of varicocele on both scrotal ultrasound and physical examination were lower in obese males than in normal weight males, suggesting that the lower prevalence of varicocele in obese males was independent of physical examination. Third, due to the large enrollment size of NFPCP, a free primary health care program, and the conservative attitudes of the Chinese people, it was unacceptable and uneconomical to require semen examination for every general male who had not been diagnosed as infertility before. Semen analysis data were not available in our study, which limited further meaningful analytical studies. Fourth, as this was a cross-sectional study, we were unable to confirm whether the association was causal. Finally, the findings should be cautiously extrapolated to general population's fertility guidance, since most of our study subjects were young reproductive-age males preparing to have children.

In summary, the association between BMI and the odds of varicocele was non-linear among reproductive-age males, with an increased odds of varicocele when BMI ranged between 17.74 and 23.09 kg/m². The positive effect of elevated BMI on varicocele was more pronounced in younger males than in middle-aged males. However, obese males had increased odds of right varicocele. These findings suggested that the relationship between BMI and the odds of varicocele, as well as their impact on male fertility, should be considered in fertility guidance among reproductive-age males.

Acknowledgments

This study was supported by the National Key Research and Development Program of China (Grant No. 2016YFC1000307), the Project of National Research Institute for Family Planning (Grant No. 2018NRIFPJ03), the CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant No. 2018-I2M-1-004), and the National Population and Reproductive Health Science Data Center (Grant No. 2005DKA32408), People's Republic of China.

We express our sincere gratitude to the health workers and participants throughout Shenzhen in the NFPCP for their great efforts and collaboration.

Author contributions

Xuhuai Hu: Conceptualization; data curation; writing - original draft; writing - review and editing. Xueying Yang: Conceptualization; formal analysis; visualization; writing original draft; writing - review and editing. Jun Zhao: Conceptualization; formal analysis; project administration; supervision; validation; writing - original draft; writing - review and editing. Ting Guan: Funding acquisition; project administration; supervision; writing - original draft. Qiaoyun Dai: Formal analysis; visualization; writing - original draft. Juan Yang: Data curation; investigation; writing - review and editing. Hongguang Zhang: Data curation; validation; writing review and editing. Dongmei Zhang: Investigation; writing review and editing. Yue Zhang: Formal analysis; visualization; writing - review and editing. Li Shang: Validation; writing - review and editing. Xu Ma: Project administration; supervision; writing - review and editing.

Conflict of interest

None declared.

Disclaimer

The views expressed in the report are authors and do not necessarily reflect the official policy or position of the National Health Commission of the People's Republic of China.

Approval of the research protocol by an Institutional Reviewer Board

This research protocol conforms to the provisions of the Declaration of Helsinki and has been approved by the Ethics Committee of the Shenzhen Health Development Research Center, Guangdong Province, People's Republic of China (Approval No. 2020–002).

Informed consent

All informed consent was obtained from the subjects.

Registry and the Registration No. of the study/trial

N/A.

Animal studies

N/A.

Data availability statement

Data were obtained from the NFPCP and are available from corresponding author.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Subgroup analysis of the association between BMI and varicocele. The normal BMI group served as the reference in all analyses. Models were adjusted for age (categorical), occupation, educational level, smoking, alcohol intake, and height.

Table S1. Baseline characteristics of the study population.