


# Body Mass Index Changes in Relation to Male Reproductive Hormones: Longitudinal Results From a Community-Based Cohort Study

American Journal of Men's Health  
September-October 1–10  
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DOI: 10.1177/15579883211049044  
journals.sagepub.com/home/jmh  


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## Abstract

The objective of the current study was to explore the relationship between longitudinal change in body mass index (BMI) and reproductive hormones in middle-aged and elderly Chinese men. A cohort study was conducted in a rural area of China. Local male residents aged 40–80 years were recruited at baseline in 2012 and were followed up in 2016. Information about weight, height, waist circumference, sex hormones, smoking status, and medical history were obtained. The change in BMI reported no significant relationship with the change in total testosterone (TT), calculated free testosterone (cFT), and bioavailable testosterone (BioT) in Pearson correlation analyses. When the change in BMI was divided into three groups—“great loss,” “normal fluctuation,” and “great gain”—TT, cFT and BioT had the highest increase (or the lowest decrease) in men with “normal fluctuation” in BMI compared with the other two groups. The advantage of maintaining a stable BMI was more evident for those who were overweight, non-smoking, and disease-free. There was a tendency of a continuous increase in cFT and BioT with BMI increase in smoking and diseased populations. Maintaining a stable BMI is associated with maintaining normal levels of reproductive hormones, especially in overweight, non-smoking, and healthy men aged over 40 years.

## Keywords

body mass index (BMI), reproductive hormones, testosterone

Received May 24, 2021; revised July 11, 2021; accepted September 8, 2021

Obesity is well-established and has substantial negative outcomes in most areas of health. In reproductive system, body mass index (BMI) has been identified as an independent risk factor for subfertility (Ramlau-Hansen et al., 2007). For females, the probability of a spontaneous pregnancy declined linearly with a BMI > 29 kg/m<sup>2</sup> (Van der Steeg et al., 2008). For males, overweight and obesity are associated with an increased prevalence of azoospermia or oligozoospermia (Sermondade et al., 2013). Obesity is an independent contributor to erectile dysfunction (Bacon et al., 2003; Derby et al., 2000). An inverse correlation between BMI and total testosterone (TT) has been reported in our population in previous publications using cross-sectional data materials (Zhao et al., 2017). This result is consistent with a systemic review of 31 studies with strong evidence of a negative relationship between TT, free

testosterone (FT), and increased BMI (Macdonald et al., 2010). However, few studies have tested whether weight loss can result in a rise in testosterone levels. Several randomized, controlled clinical trials and cohort studies with interventions on obese subjects have attempted to address this question, which obtained positive conclusions (Corona et al., 2013). However, participants in these studies were extremely obese: for those who received low-calorie diet the average BMI was mostly >35 Kg/m<sup>2</sup>; for those who underwent bariatric surgery, the mean BMI was morbidly higher than 44 Kg/m<sup>2</sup>. The weight loss was extraordinarily sharp over a short period in their studies. Conclusions obtained based on these studies are not applicable to the general population.

In large population-based studies, American (the Massachusetts Male Aging Study, MMAS) and European



(the European Male Ageing Study, EMAS) males are studied on the relationship between weight and testosterone changes. However, these results were inconsistent. The EMAS reported that weight loss was associated with a rise in TT and FT, and as well as with weight gain (Camacho et al., 2013). However, the MMAS only observed a greater decline in TT in normal people who became overweight at follow-up (Mohr et al., 2006). In addition, only about 10% of participants in these studies were defined as having significant weight changes, and the remaining 90% were not studied further. As is well known, the Asian population is different from Americans and Europeans, in terms of BMI distributions and degrees of weight change. Studies conducted in China were indispensable in elucidating the relationship between BMI and reproductive hormone levels.

Testosterone is a marker of general health. A lower level was always related to symptoms of hypogonadism, such as decreased physical endurance and erectile dysfunction, in later life. Whether noninvasive self-management methods, such as weight control, can benefit people suffering from these symptoms is significant.

We conducted this study in middle-aged and elderly men. Observational methods were adopted without any intentional intervention to reveal the association between changes in BMI and testosterone levels.

## Materials and Methods

### Study Population

A cohort study was performed in a rural area of Jiashan County, Zhejiang Province, which is a representative area of East China. Local male residents aged 40–80 years living in the three villages that were selected using a two-stage cluster sampling method were recruited and participated voluntarily. The inclusion and exclusion criteria are detailed in previous publications (Zheng et al., 2019). This study was initiated in 2012 and was followed up in 2016. We will use the baseline data in 2012 for all

subjects and the overlapped ones who had been followed up in 2016 to perform our analysis, which refers to 956 and 493 subjects, respectively.

### Clinical Assessments

At baseline and follow-up, all participants were asked to complete a uniform questionnaire and attend physical and laboratory examinations. Sociodemographic information was obtained from the questionnaire; smoking habits and medical history were added in 2016. Anthropometric indicators were measured by professional physicians; weight, height, and waist circumference were recorded. BMI was calculated as weight in kilograms divided by height in square meters ( $\text{kg}/\text{m}^2$ ). All blood samples were drawn in the morning after an overnight fast. Measurements of sex hormones, including TT, sex hormone-binding globulin (SHBG), and luteinizing hormone (LH), were performed by the same laboratory. Serum levels of calculated free testosterone (cFT) and bioavailable testosterone (Bio-T) were evaluated according to the equation (Vermeulen et al., 1999).

### Statistical Analysis

Baseline data from 2012 ( $N = 956$ ) were used to conduct a partial correlation analysis between BMI and reproductive hormones under the control of age. Overlapping subjects at the two time points ( $N = 493$ ) were applied for longitudinal analysis, in which the change in BMI was explored in relation to the change in hormones.

Respondents were classified into four age groups by decade. The change of BMI was the difference of BMI between the two time points. It was classified into three groups according to quartiles: the lower quartile with BMI change  $< -1.5$  was defined as “great loss” group; the upper quartile with BMI change  $> 1.5$  was “great gain” group; and the middle two quartiles with BMI change between  $-1.5$  and  $1.5$  were “normal fluctuation”

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group. The “great loss,” “great gain,” and “normal fluctuation” groups represented 24%, 24%, and 52% of the followed subjects, respectively.

Baseline body type was categorized into three groups based on BMI in 2012: underweight and normal ( $< 24$ ), overweight (24–28), and obese ( $> 28$ ), according to the recommendations for Chinese adults. Current status of smoking in 2016 were “Yes” and “No.” To control the influence of disease, medical history was carefully screened and classified into two groups of “healthy” and “disease.” Diseases included hypertension, diabetes, fracture, cardiovascular disease and cirrhosis, malignant tumor, thyroid disease, immune disease, taking proton pump inhibitors, and lying-in bed for more than 3 months.

The chi-square test was used to compare the categorical variables. Student’s t-test and analysis of variance (ANOVA) were applied to compare the means of continuous variables in different groups. To evaluate the effects of BMI changes, a general linear model (GLM) was applied using hormone changes as dependent variables and respective baseline hormone levels and BMI change groups as independent variables. Confounders of smoking status and medical history were controlled using a stratified method.

All statistical analyses were performed using the SAS9.1.3 package (SAS Institute, Cary, NC). A two-tailed  $p$  value of  $< .05$ , was considered significant.

## Results

Details of this cohort study have been reported in our previous publications (Zheng et al., 2019). A total of 969 subjects were recruited in 2012. Among them, 13 were excluded because of missing values or extreme values of BMI and hormone levels. Additionally, 493 participants were followed up in 2016, with a retention rate of 51.6%. The retention rates among age groups were different, with higher proportions of men dropping out in younger (40–49 years) and older (70–80 years) age groups. Means of BMI changes, waist circumference changes, and hormone levels at baseline were not significantly different between the follow-up and the lost to follow-up groups within the same age period, except for BioT and LH in the 70s age group (Table 1).

For the followed subjects, baseline age, BMI, and waist circumference was  $57 \pm 8$  years,  $23.8 \pm 2.7$  Kg/m<sup>2</sup>, and  $82.4 \pm 6.7$  cm, respectively. BMI, TT, and cFT did not change significantly 4 years later in 2016. In contrast, BioT reported a significant decrease; SHBG and LH reported a significant increase (Table 2).

BMI was negatively associated with TT and SHBG in cross-sectional correlation analysis controlling for age ( $r = -0.19$  and  $-0.20$ , respectively,  $p < .001$ ). The reverse relationship between BMI and SHBG remained ( $r = -0.16$ ,

$p < .001$ ) while using the longitudinal change data for analysis; however, the relationship with TT disappeared ( $r = -0.07$ ,  $p = .146$ ). Since the differences in changes in BMI and hormones between the four age groups did not reach statistical significance (Table 2), the following analysis did not consider the effects of age.

Further exploration of BMI change grouped into “great loss,” “normal fluctuation,” and “great gain” reported that TT, cFT, and BioT had the highest increase (or the lowest decrease) in men with “normal fluctuation” in BMI, as compared with the other two groups (Figure 1). These differences were statistically significant in the GLM analysis, adjusting for respective baseline hormone levels. Since BioT changes were highly correlated with changes in TT and cFT, and their correlations with BMI were similar, we only reported the effects of BioT in the figures.

Baseline body type was associated with changes in both BMI and hormone levels. To assess the effects, we stratified the subjects into three subgroups. For those with normal weight or obesity at baseline, changes in cFT and BioT were not significantly different among the BMI change groups. However, for those who were overweight at baseline, the “great loss” group had a significant greater decrease of testosterone; on the contrary, the “normal fluctuation” group had the highest increase in hormones (Figure 2).

Smoking status and medical history were not associated with changes in hormone levels in the univariate analyses (Table 2). However, after using a stratified method to further explore the effect of smoking and medical history, the lowest decrease of testosterone rise in the “normal fluctuation” group appeared in people who were either currently smoking or diseased (statistically nonsignificant) or neither (statistically significant in overweight group) (Figures 3A–C). In smokers who were also affected, a continuous increasing trend of cFT (data not shown) and BioT changes was observed with an increase in BMI; the trend was significant among overweight groups (Figure 3D).

## Discussion

In this study, we revealed the relationship between BMI and reproductive hormones in both cross-sectional and longitudinal data. In the longitudinal analyses, a consistent reduction of TT with increasing BMI growth, as expected from the inverse correlation between BMI and TT in cross-sectional data, was not observed. In contrast, the highest increase (or the lowest decrease) of TT, cFT, and BioT was observed in those who maintained a stable BMI. This effect is more evident for those who were overweight, non-smokers, and disease-free. There is a tendency for a continuous increase in cFT and BioT with BMI increase in smoking and diseased populations.

**Table 1.** Comparison of Means of BMI and Hormones at Baseline in Different Follow-Up Groups Within the Same Age Period.

Age Group	40–49			50–59			60–69			70–80			Total	
	Follow-up	Lost to follow-up	t test p value	Follow-up	Lost to follow-up	t test p value	Follow-up	Lost to follow-up	t test p value	Follow-up	Lost to follow-up	t test p value	Follow-up	Lost to follow-up
N	120	148		185	169		162	114		26	32		493	463
Retention rate (%)	44.78			52.26			44.83						51.6	
$\chi^2$ p value	<b>.0085</b>													
BMI <sub>2012</sub> (kg/m <sup>2</sup> )	24.13	24.05	.822	23.90	23.41	.078	23.60	23.68	.837	23.35	22.53	.314	23.83	23.62
WC <sub>2012</sub> (cm)	83.24	82.86	.651	82.16	81.47	.297	82.01	82.32	.709	82.65	78.84	.078	82.40	81.95
TT <sub>2012</sub> (ng/mL)	3.90	3.91	.954	4.00	4.02	.875	4.14	4.33	.154	4.44	4.19	.367	4.05	4.07
cFT <sub>2012</sub> (ng/L)	74.66	75.76	.590	68.62	68.79	.919	62.56	63.21	.685	59.86	54.85	.145	67.63	68.68
BioT <sub>2012</sub> (ng/mL)	1.97	2.01	.501	1.79	1.79	.943	1.60	1.63	.547	1.55	1.37	.041	1.76	1.79
SHBG <sub>2012</sub> (nmol/L)	33.37	32.43	.635	40.53	41.40	.613	50.12	53.65	.127	59.32	64.09	.372	42.93	43.12
LH <sub>2012</sub> (mIU/ml)	4.45	4.73	.429	5.46	5.72	.356	6.53	7.39	.078	7.85	11.69	.024	5.69	6.23

Note. The data in the table were collected in 2012.

BMI = body mass index; WC = waist circumference; cFT = calculated free testosterone; BioT = bioavailable testosterone; SHBG = sex hormone-binding globulin; LH = luteinizing hormone. Significant results are presented in bold.

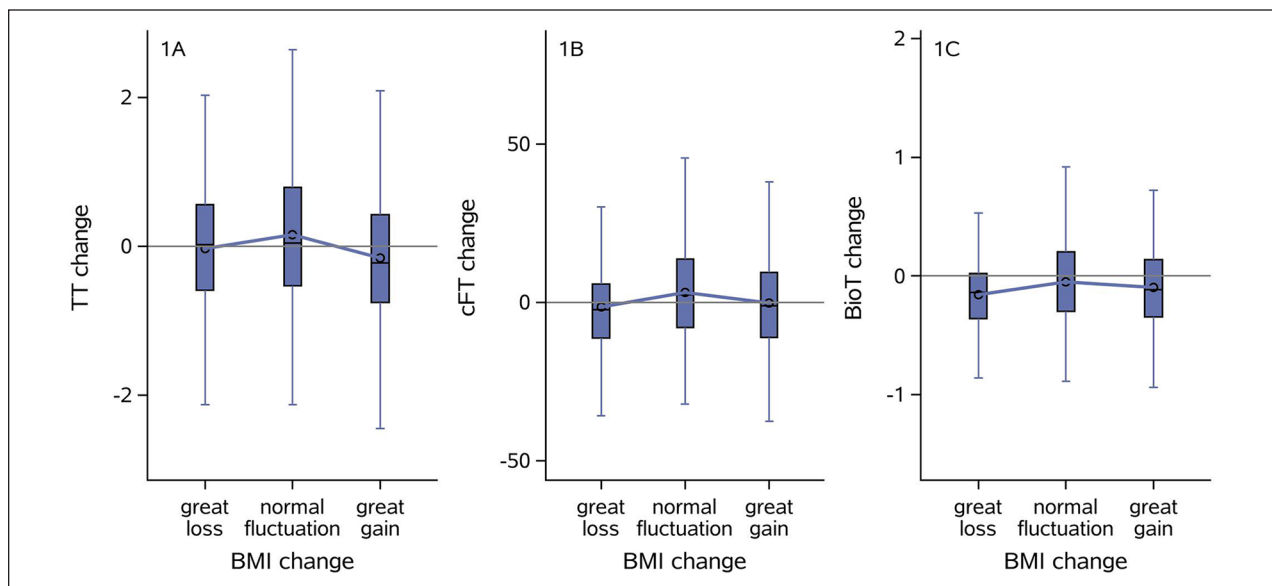
**Table 2.** Comparison of Means of BMI and Hormone Changes in Subgroups of Factors.

	N	BMI Change	TT Change	cFT Change	BioT Change	SHBG Change	LH Change
<b>Mean</b>	493	-0.04	0.032	1.22	-0.09	2.33	0.54
t test, p value (H0=0)		.760	.449	.110	<b>&lt;.001</b>	<b>&lt;.001</b>	<b>&lt;.001</b>
<b>Age group</b>							
40~	120	-0.01	0.080	2.09	-0.08	2.42	0.87
50~	185	-0.02	0.003	1.50	-0.08	1.55	0.45
60~	162	-0.12	0.024	0.17	-0.10	3.15	0.37
70~	26	0.17	0.075	1.78	-0.06	2.40	0.68
ANOVA, p value		.959	.909	.797	.970	.642	.429
<b>Baseline BMI group</b>							
Normal/Underweight	266	0.95	-0.059	-0.73	-0.13	2.51	0.73
Overweight	188	-0.98	0.119	3.10	-0.05	2.22	0.33
Obese	39	-2.28	0.233	5.43	0.00	1.68	0.25
ANOVA, p value		<b>&lt;.001</b>	.054	<b>.016</b>	<b>.043</b>	.902	.235
<b>BMI change group</b>							
Great loss	119	/	-0.032	-1.49	-0.16	4.48	0.51
Normal fluctuation	254	/	0.152	3.12	-0.05	2.56	0.51
Great gain	120	/	-0.158	-0.11	-0.10	-0.28	0.64
ANOVA, p value		/	<b>.009</b>	<b>.03</b>	.065	<b>.005</b>	.886
<b>Smoking status</b>							
No	215	0.17	-0.022	0.53	-0.10	1.97	0.64
Yes	260	-0.30	0.097	1.93	-0.07	2.91	0.50
t test, p value		.073	.178	.374	.439	.386	.601
<b>Medical history</b>							
Healthy	227	-0.40	0.045	1.25	-0.09	2.67	0.54
Disease	266	0.27	0.021	1.20	-0.08	2.04	0.54
t test, p value		<b>.009</b>	.778	.974	.772	.546	.997

Note. t-test or analysis of variance (ANOVA) was used.

BMI = body mass index; TT = total testosterone; cFT = calculated free testosterone; BioT = bioavailable testosterone; SHBG = sex hormone-binding globulin; LH = luteinizing hormone.

Significant results are presented in bold.



**Figure 1.** The change of TT (1A), cFT (1B), and BioT (1C) with BMI change groups.

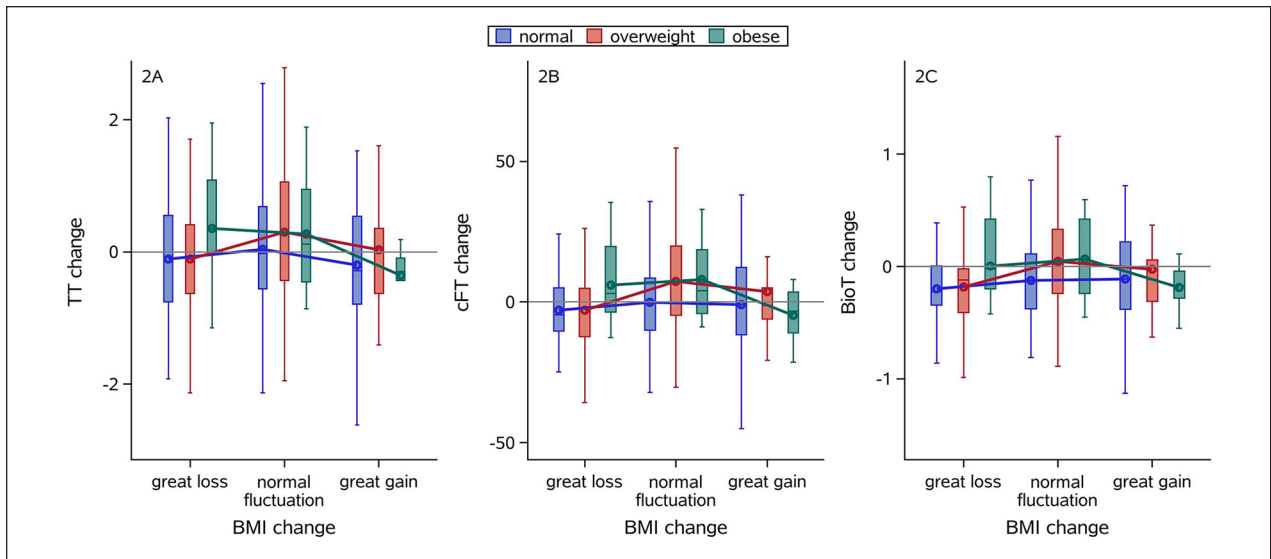


Figure 2. The change of TT (2A), cFT (2B), and BioT (2C) with BMI change groups according to baseline body types.

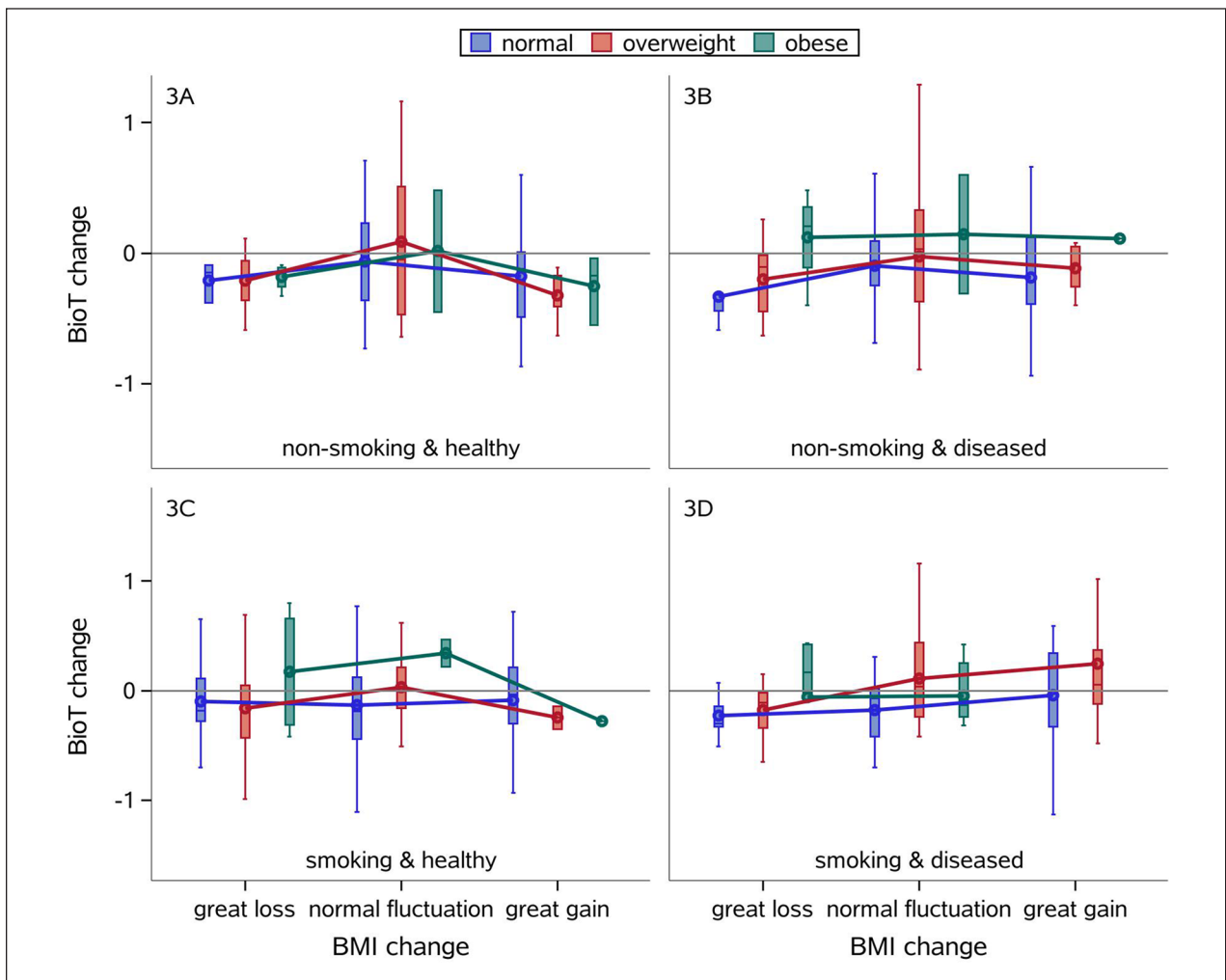


Figure 3. Effect of smoking status and medical history on the change of BioT with BMI change groups.

As expected from the inverse correlation between BMI and TT in the cross-sectional data, we observed a higher decrease of testosterone levels in people with a higher BMI increase. This result agrees with the Massachusetts Male Aging Study (MMAS), which reported a greater rate of decline in TT in men who became obese at follow-up, as compared with those who were non-obese at both waves (Mohr et al., 2006). The mechanism of obesity on lower levels of testosterone is believed to be via the inhibition of the central hypothalamic-pituitary axis, mediated by the role of insulin resistance, inflammatory mediators, and leptin in addition to the negative feedback regulation by increased estrogen (Singh and Dobs et al., 2019).

In previous studies, for extremely obese men, significant weight loss, either through diet modification or bariatric surgery, was associated with an increase in testosterone (Corona et al., 2013). However, we did not observe a similar result in our study. In contrast, a greater decrease in testosterone was observed in participants with weight loss compared to those who maintained a stable BMI.

The EMAS study identified an overall dose–response relationship between weight and testosterone changes: men who lost the most weight reported the greatest increase (Camacho et al., 2013). We consider this discrepancy to be attributable to the differences in BMI distributions and degrees of weight loss. The EMAS had a much higher baseline BMI (27.6 vs. 23.8) and proportion of obese subjects (23.9% with BMI  $\geq 30$  vs. 7.9% with BMI  $\geq 28$ ) than our study. Their definition of weight loss was much greater than ours (10% vs. a comparable 6.3%). Thus, their conclusions were drawn from a more obese population with greater potential to develop greater weight loss. As reported in their findings, weight loss had a greater influence on testosterone in obese than in non-obese men. Thus, it seems reasonable that obese participants who lost weight had lower testosterone levels in our study. More subjects in the obese category are needed to further clarify this relationship. The potential impact of weight loss strategy on the non-obese population may be a factor in clinical intervention.

Interestingly, we observed a negative effect of great weight loss in maintaining hormone levels in the general male population. Previous studies did not show similar results, but clues could be found in studies on exercise and testosterone levels. A progressive increase in testosterone occurs during moderate exercise (Hackney, 2001). However, acute heavy resistance exercise results in lowered testosterone levels (Hooper et al., 2019; Nindl et al., 2001). In male athletes who were chronically endurance-trained, lower levels of testosterone were reported, as compared with matched untrained controls (Hackney, 2001; Hackney et al., 2003). This has been interpreted by

some researchers as a central dysfunction of the hypothalamic-pituitary-testicular regulatory axis; injections of GnRH have been detected in endurance-trained males with low testosterone, thereby causing an attenuated release of lutropin (Hackney, 2008; Macconnie et al., 1986). This suggests that extreme exercise, reduced weight, and low-fat mass caused hypogonadism. However, because our study did not collect detailed information of physical activity or exercise, further studies are needed to test this hypothesis. Although we did not collect the data on exercise, we interviewed some of the participants during the investigation. We found that the villagers had seldom exercise consciousness; if any, they complained that they did not know how to exercise. In our study, weight loss may have been due to physical, psychological, and social conditions, or age-related changes, which are common in elderly people. Studies have reported that unintentional weight loss or involuntary decline in total body weight over time is associated with adverse health outcomes (Alibhai et al., 2005). This may explain why subjects with weight loss had decreased hormone levels in our study.

The relationship between BMI and mortality is U-shaped, with the minimum hazard appearing in the range of BMI 27–30 (overweight) for American men aged over 70 (Allison et al., 1997). Studies on health-related quality of life also suggested that overweight middle-aged and elderly men seem to show a better quality of life than these “normal” ones (Zhu et al., 2009). This evidence implies the benefits of “overweight” in the overall health of elderly people. A high rate of weight fluctuation is an independent predictor of all-cause mortality in middle-aged and elderly men and is a risk factor for coronary heart disease (Bangalore et al., 2017; Nguyen et al., 2007). A significant change in weight may reflect difficulties in maintaining homeostasis in older age groups. In combination with this evidence, maintaining a stable state of overweight seems to be the optimal choice for elderly people who are to be healthy. In our study, a lower decrease in testosterone level was observed in men with stable BMI especially in those who were overweight. This result is in agreement with previous studies at the reproductive level.

Smoking has been reported to be related to higher testosterone concentrations in some large studies (Svartberg and Jorde, 2007; Shiels et al., 2009). However, other studies with a similar design have not reported differences between smokers and non-smokers regarding this finding (Haik et al., 2019; Halmenschlager et al., 2009). Smoking subjects were observed to have a higher level of testosterone in our study (data not shown), but they did not show a greater potency of longitudinal increase. Together with chronic diseases, smoking seems to be a modifier between changes in BMI and testosterone

levels. Similar results have not been reported by other authors. However, some researchers observed higher LH levels in smokers than in non-smokers (Blanco-Munoz et al., 2012), which suggests a possible incentive effect of tobacco on the hypothalamus, increasing GNRH release. This function may resist the blunt effect of obesity on the hypothalamic-pituitary axis, resulting in a consistent increase in testosterone with BMI gains. However, we did not observe a parallel increase in LH levels in weight gain subjects in our study. This hypothesis needs to be further verified.

We only reported the association between BMI changes and hormone changes in our study. The association between waist circumference and TT or SHBG in our study is consistent with the correlations reported between BMI and TT or SHBG in either cross-sectional or longitudinal analyses. Since waist circumference changes were highly correlated with changes in BMI, and they showed a similar relationship with reproductive hormone changes after analysis, the results of waist circumference were not shown.

The major strength of this study is that this is the first cohort study on general aging Chinese males focusing on BMI and reproductive hormone changes, providing representative data to the normal Asian population. This is an observational study without any intentional interventions, especially on weight control. Observations about the weight change was totally spontaneous, which was closer to the true situation of the elderly population. One limitation is that information about physical activity and exercise frequency was not included in this study and was not controlled during the analysis. However, some studies revealed no significant association between physical activity or exercise and hormone changes (Camacho et al., 2013). A meta-analysis reported that moderate and high-intensity exercises increased levels of testosterone, but mild physical activity did not (D'andrea, S et al., 2020). Given that the health literacy of men in rural areas is insufficient, lifestyle improvements were proven difficult. Therefore, we speculated that they may not have regularly exercise at a moderate or high intensity, which may indicate that the absence of physical information has limited influence on our results. In view of the lack of good health literacy, participants may follow local dietary habits and structures without changes.

Body weight can also be passively influenced by mental factors, such as depression, psychological pressure, and negative family events, with reported links to hormone level alterations (Berglund et al., 2011; Chichinadze and Chichinadze, 2008). However, materials for this were not collected. Another limitation is that we did not include more alternative measures, such as waist-to-hip ratio, to further validate the results. The drawback that the smoking habits and medical history were only recorded once at

the last wave cannot be neglected; there must be some ex-smokers in our "non-smoking" group, as well as new diseased ones in the "disease" group. Shifts in smoking or disease status may have completely different functions on health, but we cannot evaluate it now. Finally, although our cohort study indicated, to a certain extent, the natural process and potential association of BMI and reproductive hormone changes without intentional interventions on participants, the small sample size within the category of obesity limited the power to detect associations in this range. It may be helpful to recruit a larger population with more obese individuals or to extend the observation time. Although our study cannot provide strong evidence for causal inference, the interesting associations observed in our study can still provide useful clues for future studies.

## Conclusions

Maintaining a stable BMI is associated with maintaining normal levels of reproductive hormones, especially in overweight, non-smoking, and healthy men aged over 40 years. Considering the multiple negative health outcomes that obesity could lead to, future studies should focus on the possible causal relationship between BMI change and reproductive hormones, to offer more evidence-based recommendations about weight change.

## Acknowledgments

The authors thank Natural Science Foundation of Shanghai and National Science and Technology Basic Work Program of China.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding


The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Natural Science Foundation of Shanghai [grant number 19ZR1444600] and National Science and Technology Basic Work Program of China [grant number 2013FY110500].

## Ethical approval

This study was approved by the Ethics Committee of the Shanghai Institute for Biomedical and Pharmaceutical Technologies (2013-07, PJ2015-18). Written informed consent was obtained from all subjects.

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