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Body mass index in relation to semen quality, sperm DNA integrity and serum reproductive hormone levels among men attending an infertility clinic

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Abstract

Objective—To examine the association between body weight and measures of male reproductive potential.

Design—Cross-sectional study

Setting—Fertility clinic in an academic medical center.

Patients—483 male partners of subfertile couples.

Interventions—None

Main outcome measures—Standard semen analysis, sperm DNA fragmentation and serum levels of reproductive hormones.

Results—As expected, BMI was positively related to estradiol levels and inversely related to total testosterone and SHBG levels. There was also a strong inverse relation between BMI and inhibin B levels and a lower testosterone:LH ratio among men with a BMI $\geq 35\text{kg/m}^2$. BMI was unrelated to sperm concentration, motility or morphology. Ejaculate volume decreased steadily with increasing BMI levels. Further, men with BMI $\geq 35\text{kg/m}^2$ had a lower total sperm count (concentration $\times$ volume) than normal weight men (Adjusted difference in the median [95% CI] = -86×10^6 sperm [$-134, -37$]). Sperm with high DNA damage were significantly more numerous in obese men than in normal weight men.

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Capsule

Body mass index was related to reproductive hormone levels and total sperm count but unrelated to sperm concentration, motility or morphology in a group of men attending a fertility clinic.

Conclusions—These data suggest that despite major differences in reproductive hormone levels with increasing body weight, only extreme levels of obesity may negatively influence male reproductive potential.

Keywords

BMI; obesity; semen analysis; sperm DNA; hormones; infertility

INTRODUCTION

Overweight and obesity have become a major public health concern worldwide. In the United States alone, 62% of adult women and 71% of adult men are either overweight or obese (Body Mass Index [BMI] ≥ 25 kg/m²) (1) and it has been estimated that by mid-century all American adults could be overweight or obese if the current trends continue (2). Similarly high frequencies have been reported in other developed nations (3,4). In the developing world the prevalence of overweight and obesity is increasing at alarming rates (5–9) and in some countries has reached levels observed in the developed world (9–11). There are major health implications of this epidemic. Increased body weight has been associated with a higher frequency of an ever increasing number of adverse health consequences including hypertension, cardiovascular disease, type 2 diabetes and other metabolic disorders (11); osteoarthritis (12); gallbladder stone disease (13); asthma and other chronic respiratory conditions (14–16); as well as multiple malignancies (17).

Reproductive consequences of overweight and obesity in women have received substantial attention. Excess body weight has been associated with an increased rate of polycystic ovary syndrome, menstrual cycle disturbances, infertility, miscarriage, infertility treatment failure and multiple complications of pregnancy including gestational diabetes, pre-eclampsia, macrosomic fetus and cesarean delivery (18–21). The reproductive consequences of excess body weight in men, however, have been studied to a lesser extent. Obese men are at increased risk of erectile dysfunction (22,23). In addition, it is known that overweight and obesity in men lead to an altered reproductive hormonal profile characterized by decreased testosterone and SHBG levels, increased estradiol levels and, in morbidly obese men, alterations in gonadotropin secretion (24,25). More recently it has also been described that overweight and obesity are related to lower inhibin B levels (26–28), a marker of Sertoli cell function and spermatogenesis. Yet, it is not entirely clear to what extent these hormonal changes affect a man's reproductive potential. The association of body weight with standard semen analysis parameters or male fertility has been recently examined in multiple studies with inconsistent results (26–29). In addition, few studies have examined whether excess body weight affects the integrity of sperm DNA (30), an independent measure of sperm quality (31) that predicts fertility (32). To further examine these issues we analyzed the relations of body weight with standard semen analysis parameters, sperm DNA integrity and serum levels of reproductive hormones in a group of men presenting with their partners for evaluation of infertility to the Massachusetts General Hospital (MGH) Fertility Center.

MATERIALS AND METHODS

Male partners in subfertile couples who presented for evaluation at the MGH Fertility Center between 2000 and 2006 were invited to participate in an ongoing study of environmental factors and fertility (33). Approximately 60 percent of eligible men agreed to participate. Men presenting for post-vasectomy semen analysis were not invited to participate. The study was approved by the Human Subject Committees of the Harvard School of Public Health and the MGH, and informed consent was obtained from all participants.

A semen sample was produced on-site by masturbation into a sterile plastic specimen cup. After collection, the sample was liquefied at 37°C for 20 minutes before analysis. Men were instructed to abstain from ejaculation for 48 hours before producing the semen sample. All semen samples were analyzed for sperm concentration and motion parameters by CASA (Hamilton-Thorn Version 10HTM-IVOS) as previously described (34,35). Sperm morphology was determined using the strict criteria described by Kruger and colleagues (36). Results were expressed as percent normal spermatozoa. Total sperm count was calculated as the product between sperm concentration and ejaculate volume. Total progressive sperm count was calculated as the product between total sperm count and progressive motility.

The neutral comet assay was used to assess sperm DNA integrity using a previously described protocol (37,38). Briefly, 50µL of a semen/agarose mixture was embedded between two additional layers of agarose on microgel electrophoresis glass slides. Slides were then immersed in a cold lysing solution to dissolve the sperm cell membranes and make sperm chromatin available. After 1h of cold lyses slides were transferred to a solution for enzyme treatment with RNase (Amresco, Solon, OH) and incubated at 37°C for 4h. Slides were then transferred to a second enzyme treatment with proteinase K (Amresco) and incubated at 37°C for 18h. Slides were placed on a horizontal slab in an electrophoretic unit and underwent electrophoresis for 1h. DNA in the gel was subsequently precipitated, fixed in ethanol and dried. Slides were stained and observed with a fluorescence microscope. Comet extent (CE), the percentage of DNA located in the tail (%tail) and tail distributed moment (TDM) were measured in 100 sperm cells in each semen sample using the VisComet software (Impulus Computergestützte Bildanalyse GmbH, Gilching, Germany). CE is a measure of the average total comet length from the beginning of the head to the last visible pixel in the tail. %Tail is a measure of the average proportion of DNA that is present in the tail of the comet. TDM is an integrated value that takes into account the distance and intensity of comet fragments. $TDM = \sum(I \times X) / \sum I$, where $\sum I$ is the sum of all intensity values that belong to the head, the body or the tail, and X is the x-position of the intensity value. The number of cells >300µm, which are too long to measure with VisComet, were counted for each subject and used as an additional measure of sperm DNA damage.

A non-fasting blood sample was drawn the same day that the semen sample was produced. Blood was centrifuged and serum was stored at -80°C until analysis. Sera were then thawed and analyzed for luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, estradiol, total testosterone, sex hormone-binding globulin (SHBG) and inhibin B levels. LH, FSH, estradiol and prolactin levels were determined by microparticle enzyme immunoassay using an automated Abbot AxSYM system (Abbott Laboratories, Chicago, IL). The Second International Reference Preparation (WHO 71/223) was used as the reference standard. The assay sensitivities were 1.2 IU/L for LH and 1.1 IU/L for FSH. The intra-assay coefficient of variation (CV) for LH and FSH was less than 3% and less than 5%, respectively. The assay sensitivity for estradiol and prolactin was 20 pg/mL with a within-run CV between 3% and 11%, and the total CV was between 5% and 15%. For prolactin, the assay sensitivity was 0.6ng/mL, the within-run CV was ≤3% and total CV ≤6%. Total testosterone was measured directly using the Coat-A-Count RIA kit (Diagnostic Products, Los Angeles, CA), which has a sensitivity of 4ng/dL, and inter-assay CV of 12% and an intra-assay CV of 10%. SHBG was measured using an automated system (Immulite; DPC Inc, Los Angeles, CA), which uses a solid-phase two-site chemiluminescent enzyme immunometric assay and has an inter-assay CV of less than 8%. Inhibin B was measured using a double-antibody, enzyme-linked immunosorbent assay (Oxford Bioinnovation, Oxford, United Kingdom) with inter-assay CV of 20% and intra-assay CV of 8%. The testosterone:LH ratio, a measure of Leydig cell function, was calculated by dividing total testosterone (nmol/L) by LH (IU/L).

Height and weight were measured on site by trained personnel. In addition, men were asked to complete a questionnaire to report the length of sexual abstinence prior to providing the semen sample and to provide information on medical and reproductive history and lifestyle factors including intakes of caffeine and alcohol and smoking history.

Statistical analysis

Of the 522 men recruited into the study, 504 had complete anthropometric and semen analysis data. Among these 504 men, only 4 were underweight (BMI <18.5 kg/m²). Because this small number precluded any meaningful statistical evaluation of the role of underweight on male reproductive function, these men were excluded from analyses. Further, 17 azoospermic men were also excluded to prevent undue influence from extreme sperm counts and because the mechanism responsible for azoospermia may be related to obstructive or genetic causes rather than environmental influences. This left 483 men (93% of all recruited men) comprising the study population. Additional analyses were performed among all men in the study population with available hormone levels (n=430) or comet assay results (N=413).

Men were divided into 4 groups according to their BMI following reference values proposed by the World Health Organization (39). The reference group comprised all men with a normal body weight (BMI: 18.5–24.99 kg/m²). To examine the associations of BMI with semen quality, sperm DNA integrity and reproductive hormone levels we first calculated the median, 25th and 75th percentile of the parameters of interest in each BMI category. We then used quantile regression (40) to evaluate the association between BMI and the reproductive parameters of interest. Quantile regression is analogous to ordinary least-squares linear regression but rather than fitting conditional models for the mean, it fits conditional models for a specified percentile, in this case the median (50th percentile), without making distributional assumptions of the error term. Because the distribution of several of our outcome measures is highly skewed, the use of this technique allows the estimation of regression parameters for a measure of central tendency that is not sensitive to outliers (the median); permits the analysis of outcome variables in their measured scale without the need for normalizing transformations and back-transformation of the results because this technique does not make distributional assumptions of the residuals; and allows the use of a single analysis strategy across different reproductive parameters. Using quantile regression, we estimated the difference in the median and its 95% confidence interval for each reproductive parameter between men with normal body weight and men at increasing categories of BMI, while accounting for differences in personal characteristics.

We also fitted logistic regression models to estimate the relative odds of abnormal or extreme semen quality, sperm DNA damage and reproductive hormone levels associated with overweight or obesity (BMI ≥25 kg/m²). For outcomes where reference values were available, these were used to dichotomize the reproductive parameters. Sperm concentration (<20 × 10⁶/mL) and sperm motility (<50% motile sperm) were dichotomized according to the WHO reference values (41). Sperm morphology (<4% normal morphology) was dichotomized according to the Tygerberg strict criteria (36). Serum levels of FSH (<1.6 IU/L), LH (<1.6 IU/L), prolactin (>18.5 ng/mL) estradiol (>50 pg/mL), total testosterone (<280 ng/dL) SHBG (<13 nmol/L) were dichotomized according to the laboratory reference values. Because there are no established reference values for neutral comet assay results, serum inhibin B levels or testosterone:LH ratio, men in the highest 10th of the distribution of each of the comet assay results was considered indicative of high DNA damage and men in the lowest 10th of the inhibin B and the testosterone:LH ratio distribution were considered to have low levels.

All multivariate models included terms for age, race, smoking status, caffeine and alcohol intakes, and history of relevant reproductive history (undescended testes and groin injury). Multivariate models for semen analysis and comet assay results included additional terms for

sexual abstinence time. Tests for trend were conducted using a variable with the median BMI in each category as a continuous variable in the regression models. All analyses were conducted using Statistical Analysis Software (SAS) version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Men were primarily Caucasian (85%) with a mean (SD) age of 36.3 (5.4) years. Most men were either overweight or obese ($\text{BMI} \geq 25$) (75%) and had never smoked (71%). About a third of the men (37%) had previously been evaluated for infertility and 41% of them had previously impregnated their partner. Overall, 47% of men had a normal semen analysis while 14% had a sperm concentration below 20 million/mL, 46% of men had less than 50% motile sperm and 21% of men had less than 4% normal morphology sperm. There were no significant differences in lifestyle, reproductive history or semen analysis characteristics across BMI categories, although there was a suggestion of a greater frequency of below reference sperm morphology and history of undescended testes and groin injury with increasing BMI (Table 1).

Total sperm count was inversely related to BMI in crude analyses (Table 2). BMI was also related to lower serum levels of total testosterone, SHBG and inhibin B and to higher serum levels of estradiol. A 1 unit increase in BMI was associated with a difference of -7.4 (-9.8 , -5.1) ng/dL of total testosterone, -1.0 (-1.2 , -0.8) nmol/L of SHBG, -2.9 (-3.6 , -2.3) pg/mL of inhibin B and 0.36 (0.12 , 0.60) pg/mL of estradiol. There was also a suggestion of decreased ejaculate volume, increased number of sperm with high DNA damage and decreased serum levels of LH and testosterone:LH ratio with increasing BMI but these results did not reach statistical significance. BMI was unrelated to the remaining reproductive hormone levels, semen analysis or comet assay parameters.

Adjusting for lifestyle characteristics, reproductive history and abstinence time did not appreciably change most results (Table 3). Yet, after adjustment, higher BMI was significantly associated with a lower ejaculate volume and a greater number of sperm with high DNA damage. In addition, overweight men had a significantly higher total progressive sperm count compared to normal weight men. Furthermore, FSH levels and the testosterone:LH ratio were significantly lower among extremely obese men ($\text{BMI} \geq 35 \text{ kg/m}^2$) and there was a suggestion of an inverse relation between BMI and serum levels of FSH and LH across the observed range of body weight. When the associations between BMI and hormone levels were examined separately among men with a normal semen analysis and among men with at least 1 abnormal semen analysis parameter, higher BMI was related to lower LH and FSH levels only among men with an abnormal semen analysis (Table 4). There were no apparent differences in hormone levels in subgroups defined by history of previous pregnancy or history of previous infertility examination (data not shown).

Dichotomized analyses for semen analysis parameters further suggested that overweight and obesity was associated with a small, non-significant higher frequency of below reference sperm concentration and a higher frequency of below reference sperm morphology (Table 5). The association with sperm morphology persisted despite adjustment for multiple potential confounders and was similar when the comparison group comprised all men with above reference sperm morphology and when the comparison group was restricted to men with above reference values in all semen analysis parameters, although the later analysis failed to reach statistical significance. Dichotomized analyses for comet assay parameters and serum hormone levels closely mirrored the results of the analyses using continuous variables and did not provide any additional insights (data not shown).

DISCUSSION

We evaluated the association of BMI and multiple markers of male reproductive potential in a large group of men attending a fertility clinic and found that overweight and obesity were associated with abnormalities in serum levels of reproductive hormones and to a lesser extent with abnormalities in standard semen analysis and measures of sperm DNA integrity. However, overweight men had a slightly higher total progressive sperm count compared to normal weight men. Overall, these data suggest that despite marked changes in reproductive hormone levels with relatively small changes in body weight, only extreme levels of obesity may negatively influence male reproductive potential as assessed by semen quality and sperm DNA integrity.

We found strong inverse associations of BMI with serum levels of total testosterone, SHBG and inhibin B and a positive association with serum estradiol levels. These associations are well documented effects of excess body weight on these hormones. Excess adiposity leads to increased aromatization of androgens in the adipose tissue leading to higher circulating estradiol levels (42,43). Hyperinsulinemia, secondary to obesity-related insulin resistance, decreases SHBG production in the liver (44,45). Low testosterone levels are thought to be the result of decreased SHBG binding capacity (46), direct action of leptin and other adipocyte-derived hormones on Leydig cells (47–49) and, in morbidly obese men, impaired functioning of the hypothalamic-pituitary-testicular (HPT) axis (50–52) possibly as a result of enhanced negative feedback on gonadotropin secretion by estradiol (52,53). Overweight and obesity have been related to lower testosterone and SHBG levels and higher estradiol levels in multiple studies (26–28,46,50,51,53,54) and body weight has been found to explain a greater proportion of the variability in testosterone levels than age and lifestyle practices (54). Further, testosterone increases after weight loss in massively obese men (50,55,56). Our findings regarding inhibin B levels are in agreement with four previous reports of the relationship between body weight and inhibin B in adult men (26–28,57). Moreover, in a study among severely obese men who underwent gastrectomy, inhibin B levels increased after surgery among the men with the greatest amount of weight loss (on average 50 kg or 16.9 kg/m²) (55). The observed lower testosterone:LH ratio among the most obese men also suggests decreased Leydig cell function among these men and is consistent with a report of impaired LH-stimulated testosterone production among morbidly obese men (47). The consistency of these findings across studies and the reversibility of this pattern following weight loss suggest a causal role of increased body weight on the hormonal pattern described above.

We also found inverse associations between BMI and gonadotropin levels which were more marked among men with abnormal semen analysis results. In men with an intact HPT axis lower levels of testosterone and inhibin B, as those observed with increasing levels of body weight, would be expected to result in higher levels of LH and FSH, respectively. Our findings suggest that excess body weight can lead to an impairment of the feedback regulation of the HPT axis, particularly among men who eventually develop semen quality abnormalities. Several studies have reported no relation between excess body weight and gonadotropin levels (26–28,53,54,58). Yet, our interpretation is in agreement with reports of decreased LH pulse amplitude (46,51), decreased total LH secretion over a 12 hour period (51) and increased LH levels following weight loss among massively obese men (50). Similarly, total FSH secretion over a 24 hour period decreases with increasing body weight in men (52,59) and plasma FSH levels increase after massive weight loss (56). Previous investigations have not examined whether the effect of body weight on gonadotropin secretion may differ according to other personal characteristics, as suggested by our results. This possibility should be further evaluated in other studies.

We did not observe statistically significant differences in sperm concentration, sperm morphology or sperm motility across levels of BMI. Only ejaculate volume was significantly

lower in overweight and obese men relative to normal weight men. In addition, total sperm count (ejaculate volume $\times$ sperm concentration) was significantly lower in the group of most obese men ($\text{BMI} \geq 35 \text{ kg/m}^2$); a difference that could be explained to some extent by our results for ejaculate volume. Furthermore, we found that overweight men had a slightly higher total progressive sperm count than normal weight men. This could represent a chance finding given that the past two studies reporting on the relation between body weight or abdominal adiposity and progressive motility have found that this parameter decreases with increasing adiposity (60,61). Others have reported that increased adiposity is related to decreased fertility (29,62–64) and negatively affects nearly every semen analysis parameter including concentration (26,60,65–67), ejaculate volume (61), total sperm count (26,61,66), motile count (61) and progressive motility (60). The most consistent positive finding across studies has been lower sperm concentration among overweight and obese men compared to normal weight men. This has been reported by five previous studies (26,60,65–67) while another three (27,28,58) did not find this association. When our results are included with these past studies, almost just as many studies have reported a null association between overweight and obesity and sperm concentration as have been studies reporting lower sperm concentration with increased body weight. Null findings on other parameters have been more consistent. Our null findings regarding the potential role of BMI on motility and morphology are in agreement with six of the seven past studies that have reported on motility (26–28,58,66,67) and all the previous studies that have reported on morphology (26,28,58,66). Similarly consistent, but in contrast with our results, have been reports of no association between adiposity and ejaculate volume (26,28,58,61,66). Unfortunately, there does not appear to be any pattern in terms of study setting and size, participant personal characteristics or type of statistical analysis used that seem to differentiate between studies reporting deleterious effects of overweight and obesity on semen characteristics from those that do not. An additional complication is that some studies have reported their results in a way that is not easy to interpret and does not necessarily imply compromised spermatogenesis. For example, Kort and colleagues reported an inverse association between BMI and total normal-motile spermatozoa count (volume $\times$ concentration $\times$ %motility $\times$ %normal morphology) (30). Because results for the individual parameters were not reported it is not possible to know which were affected and complicates interpretation as a significant difference in any one parameter could explain the association with this composite outcome. Clearly more studies are needed in this area to clarify the role of body weight on semen quality.

We found that obese men, but not overweight men, had a greater number of sperm cells with high DNA damage as assessed with the comet assay. However, there was no relation between BMI and the other three standard measures of sperm DNA integrity in this assay. Only one study has previously reported on the relationship between BMI and sperm DNA integrity. Using the SCSA assay to assess chromatin integrity, Kort and collaborators found that overweight and obese men had a significantly higher percentage of sperm with DNA damage when compared to normal weight men (30). It is important to note, however, that SCSA and the comet assay measure different aspects of sperm DNA integrity (SCSA measures susceptibility of sperm chromatin to DNA denaturation while the comet assay measures the extent of sperm DNA fragmentation in individual sperm). Because of this, and since BMI was unrelated to the other three measures of sperm DNA integrity in our study, the apparent consistency between these two studies should be viewed with caution.

Strengths of our study include the direct assessment of anthropometric measures and our ability to account for multiple potential confounders neither of which has been the case in some previous studies. A salient limitation is the fact that only a single measure of hormone levels and semen analysis are available. Nevertheless, despite the circadian, pulsatile and circannual variation in the levels of specific reproductive hormones, a single blood sample can provide an adequate measure of testosterone over a year in adult men (68) and the between-person

variation in testosterone, inhibin B, LH, FSH and SHBG serum levels is greater than their within-person variation over a 17-month period (69) indicating that a single measure of these hormones may also adequately represent long-term levels. Further, obtaining multiple semen samples per subject in a population based study is not superior to obtaining a single semen sample (70,71) and standard semen analysis parameters are stable over a 4 year period (72).

In summary, we observed the well known relationships between body weight and reproductive hormone levels in a group of men attending an infertility clinic. Despite the significant differences in hormone levels, only obesity was associated with increased sperm DNA damage and only the most obese men ($\text{BMI} \geq 35 \text{ kg/m}^2$) had a lower total sperm count when compared to normal weight men. These data suggest that differences in reproductive hormone levels due to increased body weight do not necessarily lead to impaired reproductive potential in men.

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Table 1

Characteristics of the study population by body mass index (N=483)

	Body Mass Index (kg/m ²)				P
	18.5 – 24.9	25 – 29.9	30 – 34.9	≥ 35	
N	123	233	87	40	
<i>Personal Characteristics</i>					
Age, years	35.7 (5.2)	36.3 (5.2)	37.2 (5.9)	35.7 (5.6)	0.33
Body mass index, kg/m ²	23.0 (1.5)	27.2 (1.4)	31.8 (1.3)	39.4 (5.2)	<0.001
Height, cm	179.7 (7.4)	179.0 (7.3)	179.4 (6.2)	180.6 (7.0)	0.64
Caffeine intake, mg/day	98 (111)	109 (131)	130 (153)	110 (161)	0.22
Alcohol intake, drinks/day	0.4 (0.6)	0.6 (0.8)	0.5 (0.8)	0.3 (0.5)	0.39
Smoking status, %					0.17
Never smoker	79.7	70.4	68.9	62.5	
Past smoker	13.0	21.9	18.4	20.0	
Current smoker	6.5	7.7	11.5	15.0	
Unknown status	0.8	0	1.2	2.5	
Race/ethnicity					0.50
White/Caucasian	83.7	84.1	87.3	90.0	
Black/African American	4.9	3.9	2.3	5.0	
Asian	6.5	3.0	5.7	2.5	
Other	4.9	9.0	4.6	2.5	
<i>Reproductive history</i>					
Ever made partner pregnant, %	39.0	40.8	48.2	37.5	0.51
Previous infertility examination, %	34.9	36.1	47.1	30.0	0.18
Testes always in scrotum, %	98.4	94.9	92.0	90.0	0.09
Groin injury, %	26.8	35.2	42.5	37.5	0.12
Reproductive surgery *, %	5.7	6.9	6.9	0	0.39
<i>Semen Analysis</i>					
Abstinence time, days	3.9 (2.3)	4.1 (3.0)	3.9 (2.7)	4.9 (5.3)	0.19
Concentration <20 million/mL, %	10.6	15.0	12.6	20.0	0.43

	Body Mass Index (kg/m ²)				P
	18.5 – 24.9	25 – 29.9	30 – 34.9	≥ 35	
N	123	233	87	40	
Motility <50% motile, %	52.0	45.1	43.7	42.5	0.52
Morphology <4% normal, %	13.8	24.4	20.7	27.5	0.09

* Varicocelectomy, orchidopexy or hydrocelectomy.

Table 2 Semen quality parameters (Median [25th – 75th percentile]) by BMI levels.

	Body Mass Index (kg/m ²)				<i>p, trend</i>
	18.5 – 24.9	25 – 29.9	30 – 34.9	≥ 35	
<i>Semen Analysis (N)</i>	123	233	87	40	
Total sperm count (millions)	257 [102 – 477]	229 [87 – 414]	204 [92 – 390]	167 [78 – 293]	0.04
Total progressive sperm count (millions)	63 [22 – 164]	71 [19 – 173]	71 [24 – 130]	55 [9 – 132]	0.90
Ejaculate volume (mL)	3.2 [2.2 – 4.2]	2.9 [1.9 – 4.1]	3.0 [1.8 – 3.5]	2.6 [1.9 – 4.0]	0.09
Sperm concentration (millions/mL)	76 [35 – 155]	81 [32 – 172]	87 [41 – 154]	77 [23 – 148]	0.72
Sperm motility (% motile)	49 [30 – 70]	55 [35 – 69]	54 [30 – 71]	55 [25 – 68]	0.30
Sperm morphology (% normal)	7 [5 – 10]	7 [4 – 10]	7 [5 – 10]	6 [3 – 9]	0.99
<i>Sperm DNA fragmentation (N)</i>	108	200	71	34	
Comet extent (μm)	132 [107 – 158]	131 [109 – 151]	127 [98 – 155]	130 [102 – 162]	0.66
Percent DNA in tail (%)	31 [21 – 48]	27 [19 – 43]	24 [20 – 39]	26 [21 – 42]	0.23
Tail distributed moment (μm)	56 [49 – 67]	57 [48 – 67]	57 [45 – 69]	60 [48 – 67]	0.42
Cells with high DNA damage, (n)	4 [0 – 12]	4 [1 – 10]	5 [1 – 11]	7 [2 – 21]	0.09
<i>Reproductive hormone levels (N)</i>	112	208	76	34	
FSH, IU/L	7.1 [5.6 – 9.9]	7.8 [5.9 – 10.3]	7.9 [5.1 – 10.6]	6.0 [4.8 – 7.4]	0.38
LH, IU/L	10.4 [7.9 – 13.8]	9.7 [7.1 – 13.3]	9.3 [6.8 – 11.4]	9.4 [6.2 – 12.3]	0.10
Prolactin, ng/mL	10.9 [8.2 – 15.0]	12.1 [8.6 – 16.5]	11.0 [7.8 – 13.9]	12.9 [10.0 – 16.0]	0.19
Estradiol, pg/mL	29.5 [22.5 – 38.0]	29.0 [21.5 – 35.0]	33.5 [23.0 – 38.0]	34.5 [29.0 – 45.0]	0.01
Total testosterone, ng/dL	461 [381 – 560]	401 [321 – 492]	369 [298 – 443]	343 [263 – 442]	<0.001
SHBG, nmol/mL	32.7 [25.6 – 41.4]	25.8 [20.7 – 32.3]	21.1 [15.5 – 26.3]	19.7 [11.4 – 27.0]	<0.001
T:LH ratio	1.5 [1.2 – 1.9]	1.4 [1.1 – 1.9]	1.5 [1.1 – 1.9]	1.3 [1.0 – 1.5]	0.08
Inhibin B, pg/mL	177 [141 – 227]	161 [118 – 195]	147 [112 – 187]	120 [87 – 171]	<0.001

Table 3

Adjusted * median difference (95% confidence interval) in semen quality parameters by BMI levels.

	Body Mass Index (kg/m ²)				
	18.5 – 24.9	25 – 29.9	30 – 34.9	≥35	p, trend
Semen Analysis					
Total sperm count (millions)	ref.	23 (–22, 68)	–29 (–93, 35)	–86 (–134, –37)	0.04
Total progressive sperm count (millions)	ref.	19 (5, 34)	4 (–14, 21)	–8 (–38, 21)	0.84
Ejaculate volume (mL)	ref.	–0.5 (–0.8, –0.1)	–0.5 (–0.8, –0.2)	–0.6 (–0.9, –0.2)	0.01
Sperm concentration (millions/mL)	ref.	12 (–6, 30)	5 (–15, 26)	0.9 (–26, 28)	0.96
Sperm motility (% motile)	ref.	7 (2, 14)	8 (–0.2, 16)	6 (–3, 16)	0.15
Sperm morphology (% normal)	ref.	–0.6 (–1.8, 0.7)	0.3 (–0.9, 1.6)	–1.6 (–3.6, 0.5)	0.92
Sperm DNA fragmentation					
Comet extent (μm)	ref.	–2 (–13, 9)	–9 (–20, 3)	1 (–15, 17)	0.59
Percent DNA in tail (%)	ref.	–3.1 (–8.7, 2.6)	–4.9 (–11, 1.2)	–1.6 (–9.9, 6.7)	0.21
Tail distributed moment (μm)	ref.	–1 (–5, 3)	0 (–5, 5)	3 (–4, 10)	0.72
Cells with high DNA damage, (n)	ref.	1 (–1, 3)	2 (0.1, 3)	5 (0.3, 9)	0.03
Reproductive hormone levels					
FSH, IU/L	ref.	0.7 (–0.2, 1.5)	–0.1 (–1.2, 1.0)	–1.6 (–2.6, –0.5)	0.09
LH, IU/L	ref.	–0.6 (–2.0, 0.8)	–1.1 (–2.7, 0.4)	–1.1 (–3.4, 1.1)	0.08
Prolactin, ng/mL	ref.	1.2 (–0.1, 2.6)	–0.2 (–1.6, 1.3)	2.0 (–0.2, 4.1)	0.13
Estradiol, pg/mL	ref.	–0.8 (–3.9, 2.2)	3.6 (–0.8, 7.9)	4.1 (–0.2, 8.6)	0.003
Total testosterone, ng/dL	ref.	–56 (–90, –22)	–97 (–133, –61)	–121 (–164, –79)	<0.001
SHBG, nmol/L	ref.	–7.8 (–10.8, –4.8)	–12.5 (–15.7, –9.2)	–15.0 (–20.3, –9.8)	<0.001
T:LH ratio	ref.	–0.1 (–0.2, 0.04)	–0.1 (–0.3, 0.2)	–0.4 (–0.6, –0.2)	0.01
Inhibin B, pg/mL	ref.	–13 (–26, –1)	–29 (–42, –16)	–59 (–85, –32)	<0.001

* Adjusted for age, race/ethnicity, abstinence time, smoking history, intakes of alcohol and caffeine, history of undescended testes and history of groin injury. Models for reproductive hormones are not adjusted for abstinence time.

Table 4

Adjusted * median difference (95% confidence interval) in reproductive hormone levels according to BMI stratified by semen analysis results

	Body Mass Index (kg/m ²)				
	18.5 – 24.9	25 – 29.9	30 – 34.9	≥ 35	p, trend
Normal Semen Analysis (N =207)					
FSH, IU/L	ref.	0.8 (–0.2, 1.7)	0.5 (–0.7, 1.8)	–0.8 (–2.3, 0.6)	0.85
LH, IU/L	ref.	–0.4 (–2.5, 1.7)	–1.0 (–3.5, 1.4)	0.6 (–1.9, 3.0)	0.77
Prolactin, ng/mL	ref.	0.2 (–2.2, 2.6)	–0.3 (–2.6, 2.0)	2.4 (1.5, 6.3)	0.30
Estradiol, pg/mL	ref.	1.3 (–3.9, 6.5)	4.9 (–1.7, 11.7)	5.7 (0.2, 11.3)	<0.001
Total testosterone, ng/dL	ref.	–46 (–92, 1)	–128 (–180, –76)	–112 (–190, –35)	<0.001
SHBG, nmol/L	ref.	–7.8 (–12.4, –3.3)	–12.8 (–17.8, –7.8)	–16.3 (–21.5, –11.1)	<0.001
T:LH ratio	ref.	0.0 (–0.2, 0.2)	0.0 (–0.4, 0.4)	–0.4 (–0.7, –0.01)	0.17
Inhibin B, pg/mL	ref.	–13.4 (–38.2, 11.9)	–33.3 (–66.9, 0.3)	–59.0 (–98.2, –19.8)	<0.001
Abnormal Semen Analysis (N =223)					
FSH, IU/L	ref.	0.8 (–0.6, 2.1)	–1.4 (–3.6, 0.8)	–2.2 (–5.9, 1.6)	0.02
LH, IU/L	ref.	–0.4 (–1.9, 1.1)	–1.4 (–3.1, 0.4)	–1.7 (–4.6, 1.2)	0.02
Prolactin, ng/mL	ref.	2.4 (1.1, 3.8)	0.7 (–0.7, 2.1)	2.3 (–1.1, 5.8)	0.49
Estradiol, pg/mL	ref.	–2.5 (–6.3, 1.2)	4.8 (–1.6, 11.3)	5.4 (–0.4, 11.1)	0.01
Total testosterone, ng/dL	ref.	–80 (–124, –35)	–78 (–132, –23)	–103 (–181, –24)	<0.001
SHBG, nmol/mL	ref.	–8.4 (–13.4, –3.5)	–12.7 (–19.6, –5.8)	–12.5 (–18.1, –6.9)	<0.001
T:LH ratio	ref.	–0.2 (–0.4, 0.0)	–0.1 (–0.4, 0.2)	–0.5 (–1.1, –0.2)	0.04
Inhibin B, pg/mL	ref.	–12.9 (–32.6, 6.9)	–31.4 (–51.1, –10.7)	–68.8 (–136, –1.9)	0.01

* Adjusted for age, race/ethnicity, smoking history, intakes of alcohol and caffeine, history of undescended testes and history of groin injury.

Table 5

Odds Ratios for below reference semen parameters

	Body Mass Index (kg/m ²)			<i>Compared to above reference for all semen parameters</i>
	18.5 – 24.9	≥ 25	18.5 – 24.9	≥ 25
	<i>Compared to above reference for same semen parameter</i>			
Sperm concentration <20×10 ⁶ /mL				
Below reference / Above reference	13 / 110	54 / 306	13 / 57	54 / 169
Age-adjusted	ref.	1.48 (0.78, 2.83)	ref.	1.39 (0.70, 2.73)
Multivariate-adjusted *	ref.	1.45 (0.74, 2.84)	ref.	1.51 (0.73, 3.11)
Motile sperm <50%				
Below reference / Above reference	64 / 59	160 / 200	64 / 57	160 / 169
Age-adjusted	ref.	0.72 (0.47, 1.08)	ref.	0.81 (0.53, 1.24)
Multivariate-adjusted *	ref.	0.70 (0.46, 1.08)	ref.	0.80 (0.52, 1.24)
Normal morphology sperm <4%				
Below reference / Above reference	17 / 106	86 / 274	17 / 57	86 / 169
Age-adjusted	ref.	1.95 (1.11, 3.44)	ref.	1.68 (0.92, 3.06)
Multivariate-adjusted *	ref.	1.80 (1.00, 3.23)	ref.	1.56 (0.83, 2.94)

* Adjusted for age, race/ethnicity, abstinence time, smoking history, intakes of alcohol and caffeine, history of undescended testes and history of groin injury.