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ORIGINAL ARTICLE *Andrology*

The relationship between male BMI and waist circumference on semen quality: data from the LIFE study

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STUDY QUESTION: What is the relationship between body size, physical activity and semen parameters among male partners of couples attempting to become pregnant?

SUMMARY ANSWER: Overweight and obesity are associated with a higher prevalence of low ejaculate volume, sperm concentration and total sperm count.

WHAT IS KNOWN ALREADY: Higher BMI is associated with impaired semen parameters, while increasing waist circumference (WC) is also associated with impaired semen parameters in infertile men.

STUDY DESIGN, SIZE, DURATION: Data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study were utilized. The LIFE study is a population-based prospective cohort of 501 couples attempting to conceive in two geographic areas (Texas and Michigan, USA) recruited in 2005–2009. Couples were recruited from four counties in Michigan and 12 counties in Texas to ensure a range of environmental exposures and lifestyle characteristics. In person interviews were conducted to ascertain demographic, health and reproductive histories followed by anthropometric assessment.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We categorized BMI (kg/m^2) as <25.0 (underweight and normal), 25.0–29.9 (overweight) 30.0–34.9 (obese, class I) and ≥35 (obese, class II) for analysis. Data were available for analysis in 468 men (93% participation), with a mean ± SD age of 31.8 ± 4.8 years, BMI of 29.8 ± 5.6 kg/m^2 and WC of 100.8 ± 14.2 cm. The majority of the cohort (82%) was overweight or obese with 58% reporting physical activity <1 time/week. The median sperm concentration for the men in the cohort was 60.2 M/ml with 8.6% having oligospermia (<15 M/ml).

MAIN RESULTS AND THE ROLE OF CHANCE: When examining semen parameters, ejaculate volume showed a linear decline with increasing BMI and WC ($P < 0.01$). Similarly, the total sperm count showed a negative linear association with WC ($P < 0.01$). No significant relationship was seen between body size (i.e. BMI or WC) and semen concentration, motility, vitality, morphology or DNA fragmentation index. The percentage of men with abnormal volume, concentration and total sperm increased with increasing body size ($P < 0.05$). No relationship between physical activity and semen parameters was identified.

LIMITATIONS, REASONS FOR CAUTION: Our cohort was largely overweight and sedentary, which may result in limited external validity, i.e. generalizability. The lack of physical activity did preclude examination of exercise more frequently than once per week, thus our ability to examine more active individuals is limited.

WIDER IMPLICATIONS OF THE FINDINGS: Body size (as measured by BMI or WC) is negatively associated with semen parameters with little influence of physical activity. Our findings are the first showing a relationship between WC and semen parameters in a sample of men without known infertility. Given the worldwide obesity epidemic, further study of the role of weight loss to improve semen parameters is warranted.

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Key words: male infertility / oligospermia / fertility / obesity / overweight

Introduction

The obesity epidemic is a growing public health concern. Indeed, the American Medical Association recently classified obesity as a disease (A.M. A. 2013). While much of the focus on the impairments caused by obesity is on somatic health, recent data suggest that reproductive health may also be impacted. While it is generally accepted that female BMI impacts fecundity, the relationship with male measures of body adiposity is less certain. Some studies have suggested that an elevated male BMI can lead to impaired sperm production (Jensen *et al.*, 2004; Sermondade *et al.*, 2013). In contrast, other studies have found no relationship between male BMI and semen parameters (Aggerholm *et al.*, 2008; MacDonald *et al.*, 2010). Further complicating our understanding of the relationship between body size and semen production is the important role of weight loss. While case series of bariatric surgery demonstrate impairment of sperm production with dramatic weight loss, lifestyle-based programs demonstrate an improvement in semen parameters (Hakonsen *et al.*, 2011; Lazaros *et al.*, 2012; Sermondade *et al.*, 2012).

Most previous analyses of adiposity and male fertility have explored BMI as an indication of overall adiposity without considering body fat distribution (MacDonald *et al.*, 2010; Sermondade *et al.*, 2013). However, other studies of anthropometric measures have shown that abdominal fat may be a risk factor for several diseases independent of BMI (Janssen *et al.*, 2004). To date, only limited studies have explored waist circumference (WC) in infertile men in relation to semen parameters (Fejes *et al.*, 2005; Hammiche *et al.*, 2012). In addition, physical activity is known to strongly impact body size. However, the impact of exercise on a man's fertility is uncertain (Vaamonde *et al.*, 2006, 2012).

As infertility affects up to 15% of all couples with significant impacts on quality of life, the identification of potentially modifiable risk factors may allow some patients to more easily achieve reproductive goals. Moreover, as obesity rates are increasing, the necessity for exploring reproductive impacts becomes more urgent. Given the interplay between BMI, WC and physical activity, we sought to determine their separate and combined effects on male fertility.

Materials and Methods

Study population

The design of and methods used in the Longitudinal Investigation of Fertility and the Environment (LIFE) study have been described previously (Buck Louis *et al.*, 2011). Briefly, the LIFE study is a prospective cohort of 501 couples attempting to conceive in two geographic areas (Texas and Michigan, USA) in 2005–2009. Couples were recruited from four counties in Michigan and 12 counties in Texas to ensure a range of environmental exposures and lifestyle characteristics. Personalized letters were sent to the target study population ($n = 424\,423$) with the *a priori* expectation that 1% of couples would be planning a pregnancy in the next few months (Buck *et al.*, 2004; Slama *et al.*, 2006). The challenge in identifying and recruiting couples from targeted populations upon discontinuation of contraception in order to become pregnant, given the absence of such sampling frameworks, is evident in that only 1188 (2%) of the 51 715 individuals screened met the minimal eligibility criteria: female age 18–44 years and male age 18+ years; in a committed relationship; ability to communicate in English or Spanish; menstrual cycles between 21 and 42 days; no hormonal contraception injections during past year; and no sterilization procedures or physician diagnosed infertility. The study cohort comprised 501 (42%) of screened eligible couples; a complete description is presented elsewhere (Buck Louis *et al.*, 2011). The most frequent reasons for ineligibility included: age (27%), not interested in pregnancy at this time (19%), not in a committed relationship (19%) and moving outside study area (16%). Full human subjects' approval was granted prior to obtaining informed consent from all couples.

Data collection and operational definitions

All participants completed baseline interviews that queried men about their medical and reproductive history, lifestyle including physical activity. For study purposes, physical activity was defined by men's responses to the following question:

> During the past 12 months, have you followed a regular vigorous exercise program? By vigorous exercise, I mean a leisure time physical activity that made you sweat and your heart beat faster, such as tennis, running, bicycling, aerobics, basketball, swimming, or brisk walking.
>
> No
>
> Yes, specify average number of days per week: __

Research nurses performed the standardized anthropometric assessment using the methodology adapted from the NHANES III survey. Specifically, all men were weighed using the digital self-calibrating Health-O-Meter scale after removing shoes and excessive clothing (e.g. shoes, coats, jackets and sweaters). The nurse was instructed to take two measurements and record weight to the nearest pound. If the measurements differed by more than one pound, a third measurement was taken. The scale is reported to be accurate up to 330 pounds and for men with weights in excess of this value, we relied upon self-reported weight.

Height was measured using a standardized cloth tape measure. The male was asked to remove shoes, stand erect with his back to the wall and shoulders relaxed at the sides and looking straight ahead. The nurse took two measurements rounded to the nearest 0.5 inch and a third if the difference was more than 0.5 inch.

WC also was measured with the standardized cloth tape measure, which was placed over the skin or light clothing while the participant was standing. The placement of the tape measure was made with the nurse standing to the right of the participant and after locating the lowest rib on the right side of the iliac crest. The tape measure was placed in the center of the distance between these two points with a horizontal plane around the abdomen starting at the midpoint. The participant held the tape measure in place while the nurse ensured the tape measure was in a plane parallel to the floor and was snug without compressing the skin. Two measurements were taken with a third if the difference was 0.25 inch or more.

We categorized BMI (kg/m^2) as <25.0 (underweight and normal), 25.0–29.9 (overweight), 30.0–34.9 (obese, class I) and ≥35 (obese, class II) for analysis.

Biospecimen collection and analysis

Semen samples (one or two per participant) were collected via masturbation without the use of any lubricant following 2 days of abstinence using home collection kits that comprised an insulated shipping container (Hamilton Research, Beverly, MA, USA) for maintaining sperm integrity. All semen samples were received at the National Institute for Occupational Safety and Health's andrology laboratory. An aliquot of semen was placed in a 20 μm deep chamber slide (Leja, Luzemestraat, Netherlands), and sperm motility was assessed using the HTM-IVOS (Hamilton Thorne, Beverly, MA, USA) computer assisted semen analysis system (CASA). Sperm concentration was also measured using the IVOS system and the IDENT™ stain. Microscope slides were prepared for sperm morphometry and morphology assessment. An aliquot of the whole semen was diluted in Tris NaCl EDTA buffer [50 mm Tris–HCl (pH 7.4), 100 mm NaCl, 0.1 mm EDTA] with glycerol and frozen for the sperm chromatin stability assay (SCSA®) analysis (Evenson *et al.*, 2002). Sperm viability was determined by hypo-osmotic swelling (HOS assay; Schrader *et al.*, 1990).

To ensure the integrity of the 24-h analysis, several steps were taken to ensure the quality of the semen samples. First, a thermometer was attached to all collection jars to ensure that samples were maintained within acceptable temperature limits. Secondly, the andrology laboratory assessed the integrity of the sample upon receipt. All were found to be acceptable. Motility end-points are most sensitive and were excluded from our analysis. Other investigators have successfully utilized such approaches in large population studies (Luben *et al.*, 2007; Olshan *et al.*, 2007).

Statistical analysis

Descriptive analyses were conducted to assess distributions of semen outcomes, body adiposity measures and physical activity. For semen measures that were available for two semen samples from one participant, we accounted for the correlation by using random intercept models, in the context of either linear regressions (when the outcome is continuous) or logistic regression (when the outcome is dichotomous). All regression models were adjusted for a set of *a priori* selected covariates: age (≤24, 25–29, 30–34, ≥35 years), college education (yes/no) and serum cotinine (≤9.99 for non-smoker and >10.0 for active smoker). In particular, we used the established literature to identify biologically meaningful covariates that meet contemporary definitions for confounding, i.e. associated with BMI/physical activity and semen quality, not on the causal pathway (or a descendent of a variable on the causal pathway) and arising from the same source. For categorized adiposity (BMI or WC) and physical activity, we assessed their relationship with semen outcomes by first conducting a linear trend test and then estimated the odds ratios (ORs) and their 95% confidence intervals (CIs) of each level of the covariate compared with a reference level. Abnormal semen parameters were defined based on the World Health Organization 5th edition of the manual on semen analyses (Cooper *et al.*, 2010). Azoospermic men ($n = 5$) were excluded from all analyses. We assumed that data were missing at random that enables us to conduct likelihood-based estimation and inference without resorting to multiple imputations. To evaluate the effects of misspecification of the model, a sensitivity analysis was performed, where we transformed semen parameters so that they were normally distributed. Specific transformation on each semen parameter was obtained by considering the Box and Cox (1964) transformation class. CIs that excluded 1.0 or *P*-values of <0.05 were interpreted as statistically significant. All analyses were implemented using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

A description of the study cohort is provided in Table I, and reflects that the cohort comprised men who mostly reported being white (81%), college educated (93%) and who had never fathered a child (53%). The mean ± SD age was 31.8 ± 4.8 years with a mean BMI of 29.8 ± 5.6 kg/m^2 and WC of 100.8 ± 14.2 cm. Overall, 41% of men were found to be obese (26% Obese I and 15% Obese II; BMI > 30 kg/m^2), 58% were reported to engage in physical activity <1 time/week and 78% had serum cotinine concentrations consistent with non-smoking status. Semen samples were obtained from 468 (93% participation) men, of whom 378 (80%) provided two samples. The median sperm concentration for the men in the cohort was 60.8 M/ml with 8.6% having oligospermia (<15 M/ml, Table I).

When examining semen parameters, only semen volume was associated with both BMI and WC ($P < 0.01$) in adjusted analyses (Table II). Moreover, there was a linear association between WC and total sperm count with men in the highest category of WC having a 22% lower total sperm count compared with men in the lowest category. No other semen parameters were associated with adiposity. In addition, no parameters were associated with physical activity. We obtained the same findings after Box–Cox transforming some of the semen outcomes (data not shown), suggesting robustness of the results to misspecification of the normality assumptions.

There was a linear association between higher BMI and increased incidence of low semen volume (<1.5 ml), low sperm concentration (<15 M/ml) and low total sperm count (<39 M, Table III). For example, while 6% of men with normal BMI were oligospermic, 17% of obese men were oligospermic (<15 M/ml). A higher BMI was associated with a lower incidence of abnormal sperm DNA Fragmentation Index (>30%). WC was correlated with both low sperm concentration ($P = 0.025$) and low total sperm count ($P = 0.008$). Again, no impairments in semen parameters were associated with physical activity.

In our cohort, obese men had a 19 times higher odds of a low total sperm count (95% CI 2.2–177.3) compared with men with a normal BMI. WC was associated with sperm concentration and total sperm count. A man with a waist >101.6 cm had a 7-fold higher odds of oligospermia (95% CI 1.2–36.4). No level of physical activity achieved statistical significance. In addition, we ran a sensitivity analysis using data stratified by physical activity levels and no significant interactions between activity level and adiposity were identified.

Discussion

To our knowledge, the LIFE study is the first prospective cohort study with preconception enrollment of couples that utilized standardized protocols for the measurement of body size and shape and collection of up to two semen samples per male for the assessment of anthropometric characteristics and semen quality. Our findings are the first show a relationship between WC and semen parameters in a sample of men without known infertility (Tables II–IV).

We observed that adiposity is related to sperm production when assessed by BMI as well as WC. Overweight and obese men had a higher incidence of low ejaculate volume, semen concentration and total sperm count. Moreover, physical activity in this relatively sedentary population did not significantly impact semen parameters.

Table I Baseline characteristics of men, from the LIFE study (n = 468).

Characteristics	BMI			≥35 (n = 72)	Total
	<25 (n = 83)	25 to <30 (n = 191)	30 to <35 (n = 122)		
Age (years) n (%)					
≤24	0 (0.0)	6 (3.14)	8 (6.56)	1 (1.4)	15 (3.2)
25–29	29 (34.9)	55 (28.8)	41 (33.6)	26 (36.1)	151 (32.3)
30–34	31 (37.4)	70 (36.7)	41 (33.6)	31 (43.1)	173 (37.0)
≥35	23 (27.7)	60 (31.4)	32 (26.2)	14 (19.4)	129 (27.6)
Mean (±SD)	32 (4.8)	32 (4.8)	31.4 (4.9)	31.6 (4.8)	31.8 (4.8)
Self-reported race, n (%)					
White	67 (80.7)	157 (82.2)	97 (79.5)	56 (77.8)	377 (80.6)
Others	16 (19.3)	34 (17.8)	25 (20.5)	16 (22.2)	91 (19.4)
College education, n (%)					
Yes	77 (92.8)	180 (94.2)	109 (89.3)	62 (86.1)	428 (91.5)
No	6 (7.2)	11 (5.8)	13 (10.7)	10 (13.9)	40 (8.6)
Prior paternity, n (%)					
Yes	39 (47.0)	85 (44.5)	68 (55.7)	32 (44.4)	224 (47.9)
No	44 (53.0)	104 (54.5)	54 (44.3)	40 (55.6)	242 (51.7)
WC (cm), n (%)					
<93.9	76 (91.6)	72 (37.7)	4 (3.3)	2 (2.8)	154 (32.9)
94.0–101.5	5 (6.0)	94 (49.2)	28 (23.0)	0 (0.0)	127 (27.1)
≥101.6	0 (0.0)	25 (13.1)	89 (73.0)	69 (95.8)	183 (39.1)
Mean (±SD)	86.1 (5.1)	95.9 (8.3)	105.4 (6.9)	122.6 (14.5)	100.8 (14.2)
Vigorous physical activity (weekly), n (%)					
<1	52 (62.7)	102 (53.4)	72 (59.0)	44 (61.1)	270 (57.7)
≥1	31 (37.4)	89 (46.6)	50 (41.0)	28 (38.9)	198 (42.3)
Mean (±SD)	1.1 (1.6)	1.5 (1.8)	1.4 (1.8)	1.5 (2.1)	1.4 (1.8)
Serum cotinine (ng/ml), n (%)					
≤9.99 (non-smoker)	66 (79.5)	158 (82.7)	89 (73.0)	53 (73.6)	366 (78.2)
>10.0 (active smoker)	17 (20.5)	31 (16.2)	29 (23.8)	19 (26.4)	96 (20.5)
Semen volume (ml), n (%)					
<1.5	4 (4.8)	22 (11.5)	11 (9.0)	11 (15.3)	48 (10.3)
≥1.5	79 (95.2)	169 (88.5)	111 (91.0)	61 (84.7)	420 (89.7)
Median (IQR)	3.5 (2.4–4.8)	3.4 (2.1–4.7)	3.2 (2.3–4.1)	2.8 (1.8–3.9)	3.2 (2.2–4.4)
Sperm concentration (M/ml), n (%)					
<15	3 (3.6)	16 (8.4)	10 (8.2)	11 (15.3)	40 (8.6)
≥15	80 (96.4)	175 (91.6)	112 (91.8)	61 (84.7)	428 (91.4)
Median (IQR)	55.3 (34.4–94.1)	63.2 (38.0–92.5)	62.4 (31.9–100.4)	60.0 (25.5–100.4)	60.8 (34.7–94.7)
Total sperm count (M), n (%)					
<39	3 (3.6)	17 (8.9)	9 (7.4)	13 (18.1)	42 (9.0)
≥39	80 (96.4)	174 (91.1)	113 (92.6)	59 (81.9)	426 (91.0)
Median (IQR)	198.5 (112.8–336.9)	190.6 (100.3–338.1)	186.5 (99.1–305.1)	141.7 (58.4–286.5)	186.0 (97.8–319.3)
Sperm vitality, n (%)					
<58	10 (12.1)	37 (19.4)	17 (13.9)	7 (9.7)	71 (15.2)
≥58	73 (87.9)	154 (80.6)	105 (86.1)	63 (87.5)	395 (84.4)
Median (IQR)	70.7 (64.8–75.5)	67.6 (60.1–73.4)	66.6 (60.3–73.2)	70.2 (61.7–75.9)	68.5 (61.7–73.9)
Morphology (% WHO normal), n (%)					
<30%	36 (43.4)	88 (46.1)	51 (41.8)	33 (45.8)	208 (44.4)
≥30%	44 (53.0)	90 (47.1)	66 (54.1)	28 (38.9)	228 (48.7)

Continued

Table I *Continued*

Characteristics	BMI			≥35 (*n* = 72)	Total
	<25 (*n* = 83)	25 to <30 (*n* = 191)	30 to <35 (*n* = 122)		
Median (IQR)	31.8 (21.0–39.3)	30.0 (22.0–39.0)	32.5 (23.5–40.0)	29.5 (21.0–37.0)	30.5 (21.8–39.0)
Morphology (% strict criteria), *n* (%)					
<4%	2 (2.4)	8 (4.2)	4 (3.3)	4 (5.6)	18 (3.9)
≥4%	78 (94.0)	170 (89.0)	113 (92.6)	57 (79.2)	418 (89.3)
Median (IQR)	21.3 (12.5–27.5)	19.3 (12.5–25.5)	20.5 (14.5–29.0)	17.0 (12.5–24.0)	20.0 (13.0–27.0)
DNA (% fragmentation index), *n* (%)					
<30%	6 (7.2)	20 (10.5)	7 (5.7)	1 (1.4)	34 (7.3)
≥30%	76 (91.6)	171 (89.5)	112 (91.8)	66 (91.7)	425 (90.8)
Median (IQR)	11.9 (9.1–18.3)	13.1 (8.6–20.2)	12.8 (8.2–18.5)	11.5 (8.1–19.3)	12.4 (8.5–19.3)

IQR, interquartile range; WHO, World Health Organization.
We categorized BMI (kg/m^2) as <25.0 (underweight and normal), 25.0–29.9 (overweight), 30.0–34.9 (obese, class I) and ≥35 (obese, class II).

Two recent meta-analyses have explored the relationship between BMI and semen production and arrived at disparate conclusions, possibly a reflection of the selective samples comprising men seeking clinical care and reliance on self-reported BMI. MacDonald *et al.* (2010) reviewed 31 studies with 5 included in the pooled meta-analysis (MacDonald *et al.*, 2010). Among the studies analyzed, no significant relationship was found between BMI and semen parameters. Importantly, one of the included studies represented self-reported BMI and two of the five studies represented men seeking infertility evaluation, which may affect results. In addition, the strict inclusion criteria and lack of primary data limited the number of included studies. Nevertheless, data from nearly 7000 men were analyzed. Two years later, Sermondade *et al.* (2013) performed a similar analysis but were able to access more primary data thus expanding inclusion to 21 studies and over 13 000 men. Again, no linear relationship was identified between BMI and sperm concentration. However, given the skewed distribution of many semen parameters, the authors also looked at men with abnormal sperm counts (i.e. oligospermia or azoospermia) and found that overweight and obese men had significantly higher levels of abnormal semen parameters compared with men with normal parameters. Importantly, over half the studies included self-reported measures of BMI and included infertile men where the relationship with sperm production may be altered. Moreover, both meta-analyses were limited to assessing adiposity only with BMI.

Reports have suggested that the distribution of body fat, as assessed by WC, may provide a more robust measure of the adverse metabolic implications of excess body size rather than BMI (Janssen *et al.*, 2004). Other investigators have examined the relationship between WC and semen parameters, but only in infertile men. Groups in Hungary and the Netherlands identified a negative correlation between sperm counts and WC (Fejes *et al.*, 2005; Hammiche *et al.*, 2012). However, it is unclear if a similar relationship exists in men who are not infertile.

The etiology that explains the relationship between adiposity and sperm production is uncertain and likely complex. Alterations in the hypothalamic–pituitary–gonadal axis can lead to relative declines in gonadotrophin levels (Michalakis *et al.*, 2013). Moreover, aromatization of testosterone to estradiol can lead to abnormal testosterone:estradiol ratios which are thought to impair the normal intratesticular hormonal milieu required for optimal spermatogenesis (Bray, 1997; Pavlovich *et al.*, 2001; Raman and Schlegel, 2002). Excess abdominal adipose tissue has also been hypothesized to insulate the scrotum and thereby elevate scrotal temperatures (Shafik and Olfat, 1981).

It is important to note that the lack of physical activity did preclude examination of exercise more frequently than once per week, thus an inability to more fully examine the role of physical activity relative to semen quality and BMI. Given the sedentary habits of our participants, it is conceivable that more rigorous activity may impact semen parameters. Indeed, the literature does suggest that exercise may improve semen parameters and hypothalamic–pituitary–gonadal hormone levels such as serum testosterone levels (Safarinejad *et al.*, 2009; Hakonsen *et al.*, 2011; Bobbert *et al.*, 2012).

Several limitations of the study warrant mention. Our cohort was largely overweight and sedentary, which may result in limited external validity, i.e. generalizability. Moreover, the assessment of physical activity based upon the number of self-report days may inadequately capture subjects' exertion. While this cohort may reflect the distribution of patients in the recruitment areas, the percentage of overweight or obese (82%) is slightly higher than that reported in the contemporary NHANES study (74%; Flegal *et al.*, 2012). Semen parameters are relatively gross measures of fertility despite our attempt to examine functional parameters, such as DNA fragmentation index (Bonde *et al.*, 1998; Bungum *et al.*, 2007; Practice Committee of the American Society for Reproductive Medicine 2013). As such, the relationship to true sperm function and fertility cannot be known with certainty. While statistically significant associations were identified, some CIs were wide, reflecting small sample sizes for select variables. Therefore, our findings in relation to physical activity require cautious interpretation. While our target population was large, the number of eligible patients who participated was relatively small thus there may be some selection bias. However, we are unaware of data that suggest BMI or semen quality impact participation in the study. Nevertheless, as with any observational study, we cannot entirely eliminate possible selection bias or residual confounding.

The current report suggests an inverse relationship between adiposity and sperm production. Body size was assessed with two parameters, namely BMI and WC, which gave similar findings. Physical activity did

Table II Anthropometric measurements and physical activity by semen quality parameters—continuous outcomes, LIFE study.

Characteristic	Category	Volume (ml) median (IQR) (n = 468)	Concentration (M/ml) median (IQR) (n = 468)	Sperm count (M) median (IQR) (n = 468)	% Vitality median (IQR) (n = 466)	% WHO normal morphology median (IQR) (n = 436)	% Strict morphology median (IQR) (n = 436)	% DFI median (IQR) (n = 459)
BMI (kg/m^2)	<25.00	3.3 (2.5, 4.6)	55.6 (33.5, 94.4)	9.0 (3.0, 20.0)	197.6 (107.1, 301.9)	69.0 (61.2, 74.7)	31.8 (21.0, 39.3)	21.3 (12.5, 27.5)
	25.00–29.99	3.4 (2.2, 4.6)	64.5 (36.1, 97.5)	9.0 (3.0, 17.0)	196.8 (101.6, 342.1)	67.3 (59.8, 73.4)	30.0 (22.0, 39.0)	19.3 (12.5, 25.5)
	30.00–34.99	3.1 (2.2, 4.1)	60.9 (32.0, 100.5)	9.0 (3.0, 18.0)	168.5 (100.7, 294.0)	66.7 (59.8, 72.8)	32.5 (23.5, 40.0)	20.5 (14.5, 29.0)
	≥35.00	2.8 (1.8, 3.8)	60.6 (29.4, 103.7)	7.0 (2.0, 21.0)	153.0 (56.6, 308.8)	70.0 (62.1, 75.3)	29.5 (21.0, 37.0)	17.0 (12.5, 24.0)
	P-trend*	0.005	0.564	0.344	0.986	0.607	0.534	0.116
Waist circumference (cm)	<93.99	3.4 (2.4, 4.6)	62.3 (35.7, 104.3)	10.0 (12.0, 20.0)	209.0 (110.9, 356.0)	67.6 (60.4, 74.6)	31.8 (22.0, 39.0)	20.5 (12.0, 27.0)
	94.00–101.59	3.4 (2.2, 4.5)	64.8 (36.0, 96.1)	8.0 (3.0, 17.0)	196.0 (104.0, 312.0)	67.3 (60.1, 72.7)	29.5 (21.0, 40.5)	19.5 (12.5, 28.5)
	≥101.60	2.9 (2.1, 3.9)	56.2 (30.4, 97.0)	8.0 (2.0, 19.0)	156.0 (85.4, 281.1)	68.1 (61.0, 73.8)	30.5 (22.0, 38.5)	19.5 (13.5, 25.0)
	P-trend*	0.003	0.228	0.004	0.834	0.524	0.635	0.692
Vigorous weekly activity	<1	3.2 (2.2, 4.2)	63.0 (32.7, 104.6)	9.0 (2.0, 19.0)	182.4 (97.8, 305.1)	67.6 (60.2, 73.8)	30.5 (22.5, 39.3)	20.0 (13.8, 27.0)
	≥1	3.3 (2.4, 4.3)	58.7 (34.7, 92.4)	9.0 (3.0, 17.0)	189.2 (98.1, 324.9)	67.7 (60.4, 73.7)	30.0 (20.5, 38.8)	19.8 (12.0, 27.0)
	P-trend*	0.235	0.213	0.978	0.481	0.141	0.207	0.188

DFI, DNA fragmentation index.
Q1 and Q3 denote the first and third quartiles, respectively.
**P*-values of trend test based on linear models. In particular, linear mixed effects models were used for end-points measured in two semen samples, including volume, concentration, motility, total sperm count and vitality, while linear regression models were used for % WHO normal and the DFI. All models adjusted for age (≤24, 25–29, 30–34, ≥35 years), college education (yes/no) and serum cotinine (non-smoker/active smoker).

Table III Association of abnormal semen quality end-points with anthropometric measurements and physical activity.

Characteristic	Category	Volume <1.5 ml, n (%)	Concentration <15 M/ml, n (%)	Sperm count <39 M, n (%)	Vitality <58% n (%)	WHO normal morphology <30%, n (%)	Strict morphology < 4%, n (%)	DFI > 30%, n (%)
BMI (kg/m^2)	<25.0	8 (5.03)	9 (5.66)	9 (5.66)	25 (15.72)	36 (45.00)	2 (2.50)	6 (7.32)
	25.0–29.99	33 (9.59)	27 (7.85)	24 (6.98)	67 (19.48)	88 (49.44)	8 (4.49)	20 (10.47)
	30.0–34.99	19 (8.92)	17 (7.98)	17 (7.98)	40 (18.78)	51 (43.59)	4 (3.42)	7 (5.88)
	≥35.0	19 (15.20)	21 (16.80)	24 (19.20)	16 (13.11)	33 (54.10)	4 (6.56)	1 (1.49)
	P-trend*	0.033	0.028	0.005	0.791	0.549	0.252	0.035
Waist circumference (cm)	<93.99	19 (6.62)	17 (5.92)	16 (5.57)	53 (18.47)	65 (44.52)	5 (3.42)	9 (5.88)
	94.0–101.59	26 (11.35)	17 (7.42)	15 (6.55)	42 (18.34)	62 (50.82)	5 (4.10)	16 (12.70)
	≥101.6	34 (10.73)	38 (11.99)	41 (12.93)	48 (15.29)	79 (47.88)	8 (4.85)	9 (5.08)
	P-trend*	0.099	0.025	0.008	0.459	0.479	0.377	0.882
Vigorous weekly activity	<1	56 (11.64)	44 (9.15)	51 (10.60)	87 (18.16)	116 (46.03)	10 (3.97)	19 (7.17)
	≥1	23 (6.39)	30 (8.33)	23 (6.39)	61 (16.99)	92 (50.00)	8 (4.35)	15 (7.73)
	P-trend*	0.053	0.64	0.422	0.8	0.287	0.972	0.532

Each semen end-point was dichotomized as normal/abnormal according to WHO standard.
Semen parameters dichotomized per WHO 5th edition.
**P*-values of trend test based on linear models. In particular, linear mixed effects models were used for end-points measured in two semen samples, including volume, concentration, motility, total sperm count and vitality, while linear regression models were used for % WHO normal and the DFI. All models adjusted for age (≤24, 25–29, 30–34, ≥35 years), college education (yes/no) and serum cotinine (non-smoker/active smoker).

Table IV Anthropometric measures and physical activity and odds of abnormal semen parameters, LIFE study

Characteristic	Category	Volume <1.5 ml OR (95% CI)	Concentration <15 M/ml OR (95% CI)	Total sperm count <39 M OR (95% CI)	Vitality <58% OR (95% CI)	WHO normal morphology <30% OR (95% CI)	Strict morphology <4% OR (95% CI)	DFI > 30% OR (95% CI)
BMI (kg/m^2)	<25.0	Referent	Referent	Referent	Referent	Referent	Referent	Referent
	25.0–29.99	3.94 (0.54, 28.88)	1.23 (0.13, 11.48)	1.68 (0.26, 11.01)	1.38 (0.65, 2.95)	1.22 (0.71, 2.08)	1.88 (0.39, 9.12)	1.41 (0.53, 3.74)
	30.0–34.99	4.35 (0.50, 37.56)	1.33 (0.12, 15.01)	2.37 (0.33, 17.32)	1.32 (0.58, 3.02)	0.98 (0.55, 1.75)	1.60 (0.28, 9.00)	0.82 (0.26, 2.60)
	≥35.0	**15.15 (1.43, 160.19)**	3.97 (0.35, 44.59)	**19.55 (2.16, 177.25)**	0.86 (0.33, 2.30)	1.46 (0.74, 2.87)	3.29 (0.57, 19.01)	0.19 (0.02, 1.65)
WC (cm)	<93.99	Referent	Referent	Referent	Referent	Referent	Referent	Referent
	94.0–101.59	5.32 (0.88, 32.06)	2.08 (0.35, 12.32)	1.79 (0.35, 9.18)	1.03 (0.53, 1.99)	1.33 (0.82, 2.17)	1.34 (0.37, 4.83)	2.58 (1.07, 6.25)
	≥101.6	4.40 (0.81, 23.73)	**6.72 (1.24, 36.37)**	**7.21 (1.60, 32.47)**	0.79 (0.42, 1.48)	1.19 (0.75, 1.87)	1.68 (0.53, 5.34)	0.96(0.36, 2.55)
Vigorous weekly activity	<1	Referent	Referent	Referent	Referent	Referent	Referent	Referent
	≥1	0.22 (0.05, 1.02)	0.72 (0.18, 2.92)	0.57 (0.15, 2.25)	0.93 (0.54, 1.62)	1.24 (0.84, 1.83)	1.02 (0.39, 2.68)	1.26 (0.60, 2.63)

Five azoospermic men were excluded from analysis. Semen parameters dichotomized per WHO 5th edition. Multivariable logistic regression was used for estimating ORs adjusting for age (≤24, 25–29, 30–34, 5 years), college education (yes/no) and serum cotinine (non-smoker/active smoker). Significant ORs and CIs are in boldface.

not appear to alter the relationship between adiposity and sperm parameters, suggesting that exercise does not further impair spermatogenesis. Further investigation of the role of weight loss in fertility is warranted to help determine the optimal approach to correcting obesity related semen impairments.

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Authors' roles

G.M.B.L. oversaw cohort assembly and data collection. All authors assisted in study design and analysis planning. S.K. and Z.C. analyzed the data. M.L.E., G.M.B.L., Z.C. and S.K. drafted the manuscript. All authors provided critical revisions to the manuscript and approved the final version.

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Conflict of interest

None of the authors has any conflict of interest to declare.

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