Received: 5 April 2023 | Revised: 10 May 2023 | Accepted: 16 May 2023

DOI: 10.1111/andr.13460

ANDROLOGY

WILEY

ORIGINAL ARTICLE

Does an increase in adipose tissue 'weight' affect male fertility? A systematic review and meta-analysis based on semen analysis performed using the WHO 2010 criteria

Daniele Santi[1] | Francesco Lotti[2] | Clotilde Sparano[3] | Giulia Rastrelli[2] | Andrea M. Isidori[4] | Rosario Pivonello[5,6] | Arcangelo Barbonetti[7] | Andrea Salonia[8,9] | Suks Minhas[10] | Csilla Krausz[2] | Linda Vignozzi[2] | Mario Maggi[3] | Giovanni Corona[11]

[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Unit of Endocrinology, Department of Medical Specialties, AziendaOspedaliero-Universitaria of Modena, Modena, Italy

[2]Andrology, Women's Endocrinology and Gender Incongruence Unit, Center for Prevention, Diagnosis and Treatment of Infertility, Careggi Hospital, Mario Serio Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

[3]Endocrinology Unit, Mario Serio Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

[4]Department of Experimental Medicine, "Sapienza" University of Rome, Centre for Rare Diseases (Endo-ERN accredited), Policlinico Umberto I Hospital, Rome, Italy

[5]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Diabetologia, Andrologia e Nutrizione, Unità di Andrologia e Medicina della Riproduzione e della Sessualità Maschile e Femminile, Università Federico II di Napoli, Naples, Italy

[6]UNESCO, Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy

[7]Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

[8]Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy

[9]University Vita-Salute San Raffaele, Milan, Italy

[10]Department of Urology, Imperial College NHS Healthcare, London, UK

[11]Endocrinology Unit, Azienda AUSL, Bologna, Italy

Correspondence
Dr. Giovanni Corona, Endocrinology Unit, Azienda Usl Bologna, Largo Nigrisoli, 2-40133 Bologna, Italy.
Email: jocorona@libero.it

Abstract

Introduction: Obesity negatively impact on the metabolism of sex hormones, leading to reduced testosterone serum levels. However, how the obesity could negatively impact on the overall gonadal function, particularly on male fertility, remained unclear so far.

Objective: To systematically review evidences regarding the influence of body weight excess on the sperm production.

Methods: A meta-analysis was conducted, searching all prospective and retrospective observational studies reporting male subjects older than 18 years old, with body weight excess from overweight to severe obesity were considered. Only studies using the V edition of the World Health Organization (WHO) manual for semen analysis interpretation were considered. No specific interventions were considered. Search was focused on studies comparing overweight/obese to normal weight subjects.

Results: Twenty-eight studies were considered. Total sperm count and sperm progressive motility were significantly lower in overweight compared to normal weight

subjects. Meta-regression analyses demonstrated that patients' age impacted on sperm parameters. Similarly, obese men showed lower sperm concentration, total sperm number, progressive and total motilities, and normal morphology lower than normal weight subjects. Reduced sperm concentration in obese men was influenced by age, smoking habit, varicocele, and total testosterone serum levels at meta-regression analyses.

Conclusions: The male potential fertility is reduced in subjects with increased body weight, compared to normal weight men. The higher was the increased body weight, the worst was the sperm quantity/quality. This result comprehensively included obesity among non-communicable risk factor for male infertility, shedding new lights on the negative impact of increased body weight on overall gonadal function.

KEYWORDS
male fertility, obesity, overweight, semen aparameters, sperm concentration and motility

1 | INTRODUCTION

Obesity is a chronic disease characterized by excessive body fat accumulation, defined as a body mass index (BMI) of 30 kg/m^2 or higher.[1] According to data from the World Health Organization (WHO), the prevalence of obesity has tripled since 1975, with a progressive and continued increase since 1990.[2,3] It is estimated that more than 1.9 billion adults are overweight (OW), that is, with a BMI between 25 and 29.9 kg/m^2, with 650 million of people obese.[4]

This growing prevalence is of great concern since obesity is a recognizable modifiable risk factor for many noncommunicable diseases, such as cardiovascular (CV) diseases (CVD), type 2 diabetes mellitus (T2DM), musculoskeletal disorders, and some cancers.[5,6] Obesity-related comorbidities are associated with body fat distribution, in particular with abdominal visceral adiposity, which should be considered an active endocrine organ, secreting many pro-inflammatory molecules and immunomediators, such as adipokines.[7–9] The dysregulated secretion of these molecules can play a crucial role in the obesity-related CV risk.

Alongside obesity-related comorbidities, adipose tissue strongly affects the metabolism of several hormones, including sex hormones, in both men and women.[10–12] Interestingly, the impact of the gonadal function demonstrates a clear sexual dimorphism.[13] In women, obesity could lead to polycystic ovary syndrome and androgens excess disorders or to idiopathic hyperandrogenism.[13] In particular, the prevalence of PCOS in obese populations approaches 30%, with a great impact on ovulation and fertility outcome.[14,15] In men, an increased visceral adiposity leads to androgen deficiency, including male obesity-related secondary hypogonadism.[16–19]

Despite accepted evidence highlighting a strict relationship between obesity and sex hormones homeostasis, the relationship between obesity and human fertility is still unclear. In females, the relationship is more established, with both OW and obesity resulting in a longer time needed to conceive and an increased the risk of adverse pregnancy outcomes.[20] An increased and dysfunctional visceral adiposity activates neuroendocrine mechanisms interfering with physiological ovarian function, affecting ovulation andendometrial, receptivity.[21–23] Accordingly, obesity reduces female fertility and is associated with suboptimal outcomes to assisted reproductive techniques.[24] Obesity can alter the gonadal function leading to adipokines-related LH and testosterone levels reduction or to leptin-related testosterone levels decrease, increases systemic inflammation and reactive oxygen species production, and raises testicular temperature because of body habitus and inactivity.[25] All these mechanisms can potentially impair spermatogenesis. Accordingly, animal studies in which visceral obesity was experimentally induced through a high fat diet (HFD), when meta-analyzed, clearly suggest that there is a reduction of relative testis, seminal vesicle and epididymis volume, along with reduced fertility and sperm parameters (number, motility and morphology).[26] Similar results were obtained in an HFD rabbit model.[27,28] In human, only fragmented and weak clinical evidence is available so far about the detrimental effect of excessive adiposity on male gametogenesis.[29] All available trials, as well as systematic reviews and meta-analyses concluded that multiple interdependent mechanisms could be involved in the harmful effect of visceral obesity on male fertility, but large controlled trials are still needed to better understand this association. In addition, all previous meta-analyses used different laboratory methods (i.e., combination of different WHO, criteria see below) to evaluate sperm parameters and fertility, often resulting in contradictory findings.[29–38]

The aim of the present review and meta-analysis is to scrutinize only prospective or retrospective observational trials reporting sperm data limiting the analysis to 2010 WHO classification.[39]

2 | METHODS

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (Supporting information 1). The protocol of this study

(CRD42022369007) was published on the website of the University of York (Centre for Reviews and Dissemination,https://www.crd.york.ac.uk/PROSPERO/#recordDetailsCRD42022369007).

2.1 | Search strategy

An extensive Medline, Embase and Cochrane search was performed, including the following key words: ((“sperm s”[All Fields] OR “spermatozoa”[MeSH Terms] OR “spermatozoa”[All Fields] OR “sperm”[All Fields] OR “sperms”[All Fields]) AND (“obeses”[All Fields] OR “obesity”[MeSH Terms] OR “obesity”[All Fields] OR “obese”[All Fields] OR “obesities”[All Fields] OR “obesity s”[All Fields])). The search, which accrued data from January 1, 2010 up to September 31, 2022, was restricted to English-language articles including human participants. The identification of relevant studies was performed independently by four of the authors (Daniele Santi, Giulia Rastrelli, Francesco Lotti, Clotilde Sparano), and conflicts were resolved by the last investigator (Giovanni Corona). We did not employ search software but hand-searched bibliographies of retrieved papers for additional references. The main source of information was derived from published articles.

2.2 | Study selection

All prospective and retrospective observational trials reporting data on sperm parameters in patients with OWor obesity compared to normal weight (NW) subjects (BMI 18−24.9 kg/m^2) were included. Only studies reporting sperm data according to the WHO manual[39] were included in the analysis. Case reports were excluded (Figure S1).

2.3 | Outcome and quality assessment

The principal outcome measure was the comparison of conventional sperm parameters between NW and obese individuals (BMI $\geq$ 30 kg/m^2).[1] Secondary outcomes included the comparison of NW subjects to OW individuals (BMI between 25.0 and 29.9 kg/m^2). In addition, comparisons between NW individuals and those with different degree of obesity were performed when available. Other classification proposed to distinguish among NW, OW, and OB were not considered in this study. The quality of trials included was assessed using the Cochrane criteria.[40] Risk of bias was generated with Revman software Version 5.3 (Figure S2) (The Cochrane Collaboration, London, UK).

2.4 | Statistical analysis

Heterogeneity in sperm parameters was assessed using I^2 statistics. Even when low heterogeneity was detected, a random-effect model was applied because the validity of heterogeneity tests can be limited with a small number of component studies. We used funnel plots and the Begg adjusted rank correlation test to estimate possible publication or disclosure bias.[41] However, undetected biases may still be present because these tests have low statistical power when the number of trials is small. Continuous data were compared first between subjects with NW and those with obesity. Then, the analysis was repeated comparing NW with OW men.Meta-regression analyses were performed to test the effect of different variables on the differences between NW and OW/obese subjects. Finally, a linear regression analysis model, weighting each study for the number of subjects enrolled, was performed to verify the independent effect of specific variables on sperm parameter difference after the adjustment for confounders.

All data were calculated using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA). Logistic multivariate analysis was performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows 25.1.

3 | RESULTS

Out of 865 retrieved articles, 29 were included in the study[42–70] (Table 1). The study flow is summarized in Figure S1.

Overall, 60,383 subjects were included with a mean age and BMI of 34.9 years and 26.9 kg/m^2, respectively. According to BMI stratification, 37,819 individuals were NW, 17,187 OW, and 5,377 obese. Data on total sperm count and sperm concentration were available in 21 and 25 studies, respectively, for a total of 29 studies (Table 2). In addition, sperm morphology was available in 20 papers, whereas 12 and 18 studies reported data on total and progressive sperm motility (Table 2). Finally, data on semen volume and DNA fragmentation were included in 23 and 4 studies, respectively (Table 2). Only four studies (13.7%) included in the meta-analysis reported the prevalence of primary/secondary infertility among patients incluced.

3.1 | Normal weight versus overweight

The I^2 in trials assessing total sperm count was 62.89 ($p = 0.002$). A funnel plot and Begg adjusted rank correlation test (Kendall’s τ: 0.17; $p = 0.45$) suggested no publication bias.

OW subjects had significantly lower total sperm count when compared to NW individuals (Figure 1A and Figure S3B). Similar results were observed when semen volume and progressive motility were considered (Figure 1A,B and Figure S3A,F). Moreover, a trend toward a reduced total motility was observed in OW compared to NW, although it did not reach a statistical significance (Figure 1B and Figure S3E). Conversely, no differences between groups were detected when either normal morphology, sperm concentration or DNA fragmentation were analyzed (Figure 1 A,B and Figure S3C,D,G).

Finally, in line to what was observed when continuous parameters were analyzed, OW individuals had a higher risk to show a reduced of progressive motility (defined as < 32%) when compared to NW (1.14[1.01;1.28]; $p = 0.03$) (Figure S4A).

TABLE 1 Characteristics of studies included in the final analysis.

	NW (n)	OW (n)	OB (n)	Age* (years)	Waist circumferences* (cm)	Total testosterone* (nmol/L)	Current smokers* (%)	Varicocele* (%)
Hammiche et al., 2012	153	225	72	34.5	92.3	NR	26.8	NR
MacDonald et al. 2013	139	253	119	NR	NR	14.4	NR	NR
Sermondade et al., 2013	159	120	27	35.5	NR	NR	NR	0
Belloc et al., 2014	5799	3607	764	36.9	NR	NR	NR	NR
Eisenberg et al., 2014	83	191	194	31.8	97.8	NR	NR	NR
Leisegang et al., 2014	19		23	36.6	106.4	NR	NR	NR
Alshahran et al., 2015	75	179	185	36.9	NR	15.1	0	0
Andersen et al., 2015	39		69	38.9	NR	NR	19.1	NR
Luque et al., 2015	747	1304	504	35.6	NR	NR	0	0
Wen-Hao et al., 2015	334	220	63	31.4	NR	NR	NR	NR
Zhu et al., 2015	4241		779	32.0	NR	NR	NR	NR
Andersen et al., 2016	42		60	38.5	NR	NR	NR	NR
Cui et al. 2016	82	74	95	NR	NR	13.3	NR	NR
Taha et al., 2016	81	59	25	33.9	NR	NR	0	0
Oliveira et al. 2017	370	856	598	38.0	NR	NR	10.8	17.4
Wang et al., 2017	1398	620	298	32.3	NR	NR	18.5	NR
Ramaraju et al., 2017	1084		201	34.4	NR	NR	NR	NR
Veron et al., 2018	277		277	35.9	NR	NR	NR	NR
Ferigolo et al., 2019	20		27	NR	NR	NR	NR	NR
Ma et al. 2019	22762	5070	302	28.4	NR	NR	37.9	NR
Samavat et al. 2019	21		47	40.9	128.5	10.8	16.9	NR
Zhang et al., 2019	1803	1161	172	33.0	NR	NR	46.7	NR
Keszthelyi et al., 2020	438	510	221	38.1	100.9	NR	NR	NR
McCray et al., 2020	66		58	40.0	NR	NR	NR	NR
Pini et al., 2020	5		5	39.6	NR	NR	NR	NR
Ramirez et al. 2020	1596	2654	935	35.7	NR	NR	NR	0
Wood et al., 2020	32		42	38.5	NR	11.5	NR	22.1
Antinozzi et al., 2021	34	30	34	36.8	88.9	18.5	NR	0
Ma et al. 2021	103	54	20	30.9	NR	12.8	NR	0

Notes:
*Ponderate means among groups. BMI, body mass index; NR, not reported; NW, normal weight; OB, obese; OW, overweight.

Meta-regression analysis showed that the differences in total sperm count and progressive motility between NW and OW increased as a function of age (Figure S5A,B).

3.2 | Normal weight versus obesity

The I^2 in trials assessing total sperm count in obese subjects versus NW individuals was 87.51 ($p < 0.0001$). A funnel plot and Begg adjusted rank correlation test (Kendall's τ: −0.20; $p = 0.19$) suggested no publication bias.

All conventional semen parameters were significantly lower in obese men when compared to NW, including semen volume, total sperm count, semen concentration, normal morphology, total motility, and progressive motility (Figure 1A,B and Figure S6A–F). Similar results were observed when DNA fragmentation was analyzed (Figure S6G). In line with these data, patients with obesity showed higher risk of reduced sperm concentration ($< 15 \times 10^6$/mL; OR = 1.28[1.13;1.46], $p < 0.0001$) and progressive motility (< 32%; OR = 1.25[1.10;1.42], $p < 0.0001$) (Figure S4B,C).

Similar to what observed for OW, meta-regression analysis showed that age negatively influenced the differences between NW and obesity, with regard to total sperm count and progressive motility (Figure S5C,F). Same results were detected when other sperm parameters, including sperm concentration and total motility, were analyzed (Figure S5D,E). When the influence of other clinical and

TABLE 2 Semen quality parameters available in included studies.

	Semen volume	Sperm concentration	Total sperm count	Sperm morphology	sDF	Total motility	Progressive motility
Hammiche et al., 2012	X	X	X	NR	NR	NR	X
MacDonald et al. 2013	X	X	X	X	NR	X	NR
Sermondade et al., 2013	X	X	NR	X	NR	NR	X
Belloc et al., 2014	X	X	X	X	NR	X	X
Eisenberg et al., 2014	X	X	X	X	X	NR	X
Leisegang et al., 2014	X	X	X	X	X	NR	NR
Alshahrani et al., 2015	X	X	NR	NR	NR	NR	NR
Andersen et al., 2015	NR	NR	X	NR	NR	NR	NR
Tang et al., 2015	X	X	X	X	NR	NR	X
Zhu et al., 2015	NR	NR	NR	NR	NR	NR	NR
Andersen et al., 2016	NR	NR	X	NR	NR	NR	NR
Cui et al. 2016	X	X	NR	X	NR	NR	X
Taha et al., 2016	NR	X	NR	X	X	NR	X
Luque et al., 2017	X	X	X	X	NR	X	NR
Oliveira et al. 2017	X	X	X	X	X	X	X
Wang et al., 2017	NR	X	X	NR	NR	X	X
Ramaraju et al., 2018	X	X	X	X	NR	X	X
Veron et al., 2018	X	X	X	X	NR	X	NR
Ferigolo et al., 2019	X	X	X	X	NR	NR	X
Ma et al. 2019	X	X	X	NR	NR	X	X
Samavat et al. 2019	X	X	X	X	NR	X	X
Zhang et al., 2019	X	X	NR	NR	NR	X	X
Keszthelyi et al., 2020	X	X	X	X	NR	NR	X
Ma et al. 2020	X	NR	NR	NR	NR	NR	NR
McCray et al., 2020	NR	X	X	X	NR	NR	NR
Pini et al., 2020	X	X	NR	X	X	X	NR
Ramirez et al. 2020	X	X	X	X	NR	NR	X
Wood et al., 2020	X	X	X	X	NR	X	X
Antinozzi et al., 2021	X	X	X	X	NR	NR	X

Note: NR, not reported; NW, normal weight; OB, obese; sDF, sperm DNA fragmentation.

biochemical parameters was investigated, as expected, waist circumference increase significantly enhanced the difference between NW and obese men in several sperm parameters, including total sperm count, normal morphology, and progressive motility (Figure 2A–C). In addition, the concomitant presence of other risk factor for male infertility, such as the presence of varicocele, significantly increased the difference between NW and obesity in several seminal parameters including sperm concentration and progressive motility (Figure 3A,B). All the aforementioned associations were confirmed even after the adjustment for age (not shown).

When serum levels of testosterone were taken in consideration, a negative effect on the differences between NW and obesity was detected for sperm concentration, normal morphology and progressive motility (Figure 4A–C). All the latter correlations were confirmed after the adjustment for age (not shown).

Finally, a trend toward reduced sperm motility and semen volume in relation to lower testosterone serum levels was found ($S = 0.012[-0.008;0.213]$, $p = .07$ and $I = -1.568[-3.082;-0.054]$, $p = 0.04$).

3.3 | Obesity classes and sperm parameters

Only few studies provided information subdividing patients according to obesity classes. The majority of results, obtained when overall BMI ≥ 30 kg/m^2 was analyzed, were confirmed when patients were sub-classified according to BMI 30–39.9 kg/m^2 (Figure 1A,B and Figure S7A–F). When BMI ≥40 kg/m^2 was considered, total sperm count, sperm concentration as well as normal morphology were significantly reduced in morbid obesity compared to NW controls

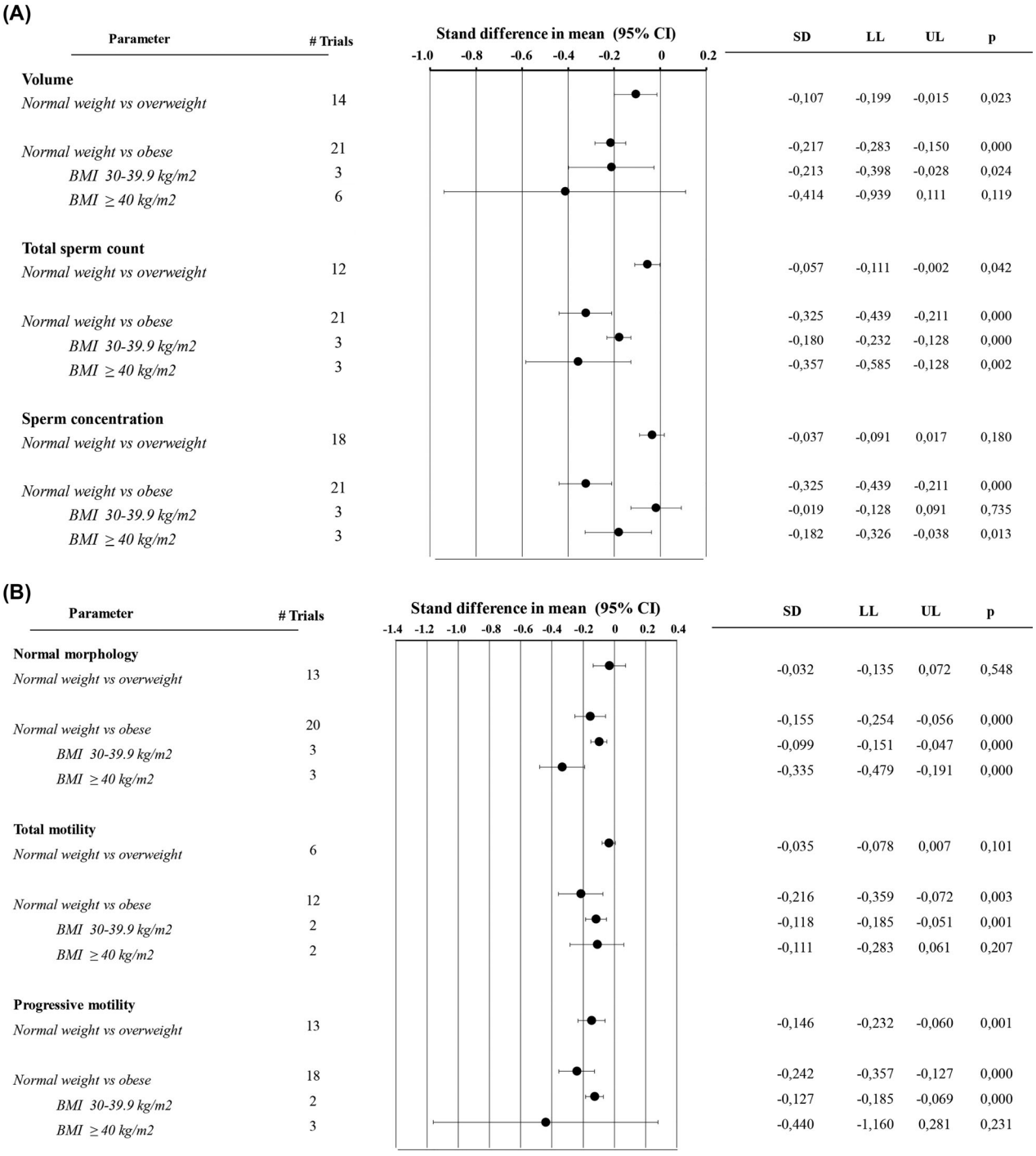

FIGURE 1 Overall effects of overweigh or obesity on different sperm parameters. A) semen volume, total sperm count and sperm concentration; B) normal morphology, total motility and progressive motility. BMI, body mass index; LL, lower levels; UL, upper levels. Data are reported as standardized means for graphical proposal.

(Figure 1A,B and Figure S8B–D). Accordingly, severe obesity was associated with up to a three-fold increased risk of reduced sperm concentration ((< 15 × 10^6/mL) and reduced normal morphology (< 4%) when compared to NW men (OR = 2.47[1.61;3.78] and 1.87[1.13;3.10]; both < 0.05 (Figure S9A,B). Conversely, no association between severe obesity and semen volume as well as total and progressive motility was observed (Figure 1A,B and Figure S8A,E,F).

4 | DISCUSSION

This is the first systematic review and meta-analysis investigating the contribution of excess weight and obesity and semen parameters using comparable and restricted criteria derived from the 5th edition of WHO laboratory manual for the examination and processing of human semen.[39] Our data highlight the negative impact of body weight excess

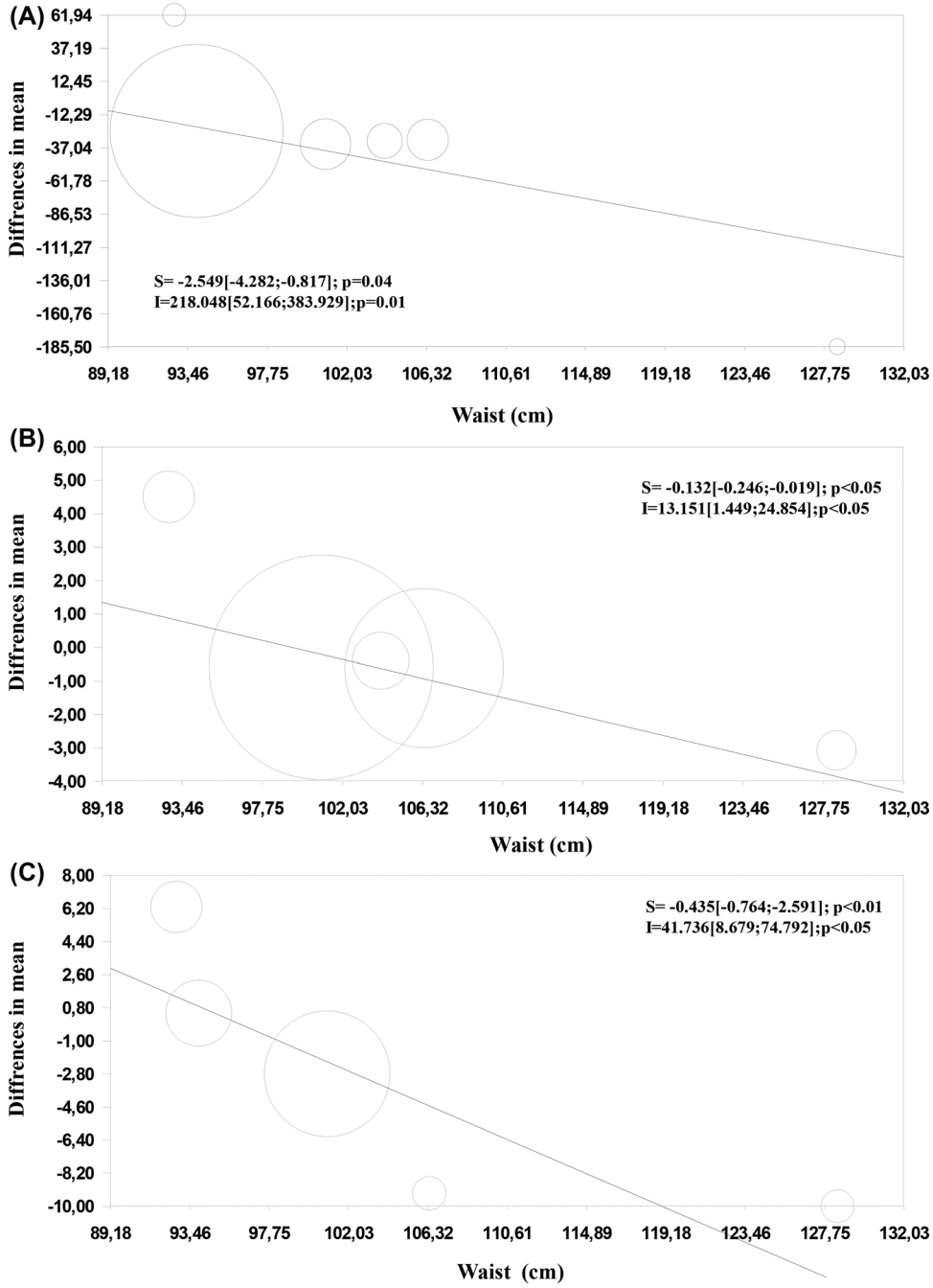

FIGURE 2 Impact of waist circumference on total sperm count (A) and normal morphology (B) and progressive motility (C) between normal weight and subjects with obesity.

on male fertility in terms of the sperm production, as demonstrated by the detected alteration in many conventional semen parameters available in clinical practice. Even just a slight excess of body weight, such as OW, leads to worse semen parameters, with respect to total sperm count and progressive sperm motility. Increasing the degree of body weight excess up to the obesity condition, a more severe alteration is detected considering all semen parameters, such as semen volume, sperm concentration, total sperm count, progressive and total sperm motility, and normal sperm morphology. Thus, the present study provides the most comprehensive analysis to date of the global effect of male adiposity on sperm production, considering a strict methodological subdivision of patients according to body weight excess degree and the same edition of the WHO manual for the interpretation of semen analysis (see below).

Our comprehensive analysis strongly suggests that the body weight excess detrimentally affects semen quantity and quality in a 'dose-dependent' manner. Indeed, when the body weight excess is mild (BMI between 25.0 and 29.9 kg/m^2), supporting the OW definition, only few sperm parameters appear altered. Then, when body weight excess increases (BMI $\geq$ 30 kg/m^2), a 'complete' effect on spermatogenetic

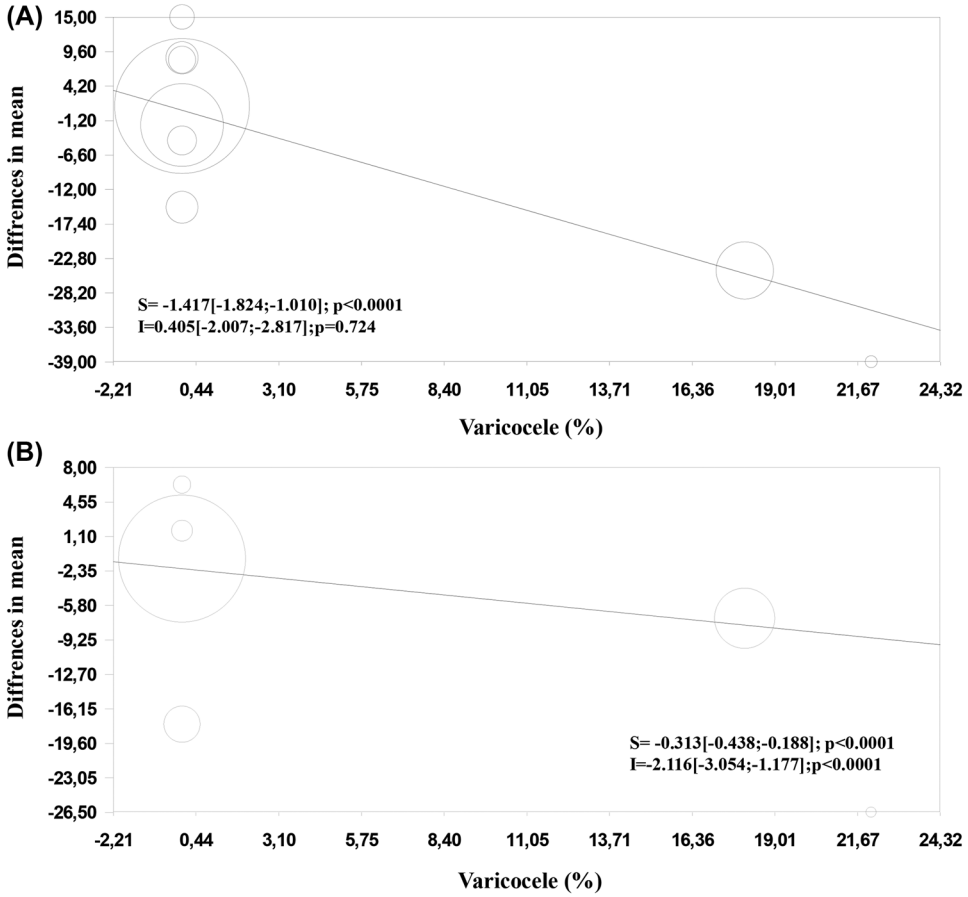

FIGURE 3 Impact of current varicocele on sperm concentration (A), sperm progressive motility (B) between normal weight and subjects with obesity.

damage occurs, with all conventional sperm parameters significantly reduced. Interestingly, this alteration is associated with a decrease of the testosterone serum level in meta-regression analyses. This result is in line with a large body of evidence, suggesting the bi-directional correlation between obesity and hypogonadism in men.[71–73] Although the obesity–hypogonadism connection seems to establish a vicious cycle, in which one condition worsens the other, recent evidence suggested that the effects exerted by obesity on serum testosterone levels are more substantial than those promoted by hypogonadism on fat share.[74] Here, our analysis does not define the 'predominant direction' of this correlation, however we confirm that body weight excess is associated with impaired testicular function. From a pathophysiological perspective, three different mechanisms have been advocated thus far; first, obese men usually have a so-called 'leptin resistance', with high circulating leptin concentrations which positively correlate with total body weight and adiposity.[75] Leptin synthesis and secretion are located in fat cells of white adipose tissue, physiologically mediating a negative feedback mechanism between adipose tissue and the hypothalamus, to regulate appetite.[76] In obese leptin-resistant subjects, this mechanism fails, resulting in over-consumption of food due to a feeling of reduced satiety, contributing to maintain an increased total body mass.[76] Considering hypothalamic–pituitary–gonadal (HPG) axis, while leptin physiologically stimulates gonadotropin releasing hormone (GnRH) secretion throughout kisspeptin production and leptin resistance, typical of obesity, is associated with kisspeptin gene expression reduction.[77] Thus, the obesity-related leptin resistance suppresses the HPG axis, reducing the physiological stimulation on the testis.[75] Another proposed mechanism involves the comprehensive metaflammation status observed in obese patients mediated by increased pro-inflammatory cytokines production.[38] Indeed, the demonstrated reduction in kisspeptin-1 receptor expression in obese patients[38] has been speculated to be due to inflammation at the hypothalamic level, thus impairing the HPG axis functionality. Third, an increased aromatase activity could be expected in case of supernumerary adipocytes, as observed in obese men, causing a higher testosterone conversion to estradiol, which in turns leads to the strongest negative feedback on the HPG axis.[78] This latter mechanism remains the most debated since increasing evidence suggests that obese men have reduced estradiol serum levels compared to NW individuals.[79,80] Overall, despite thrill defined pathophysiological mechanisms, obesity, especially if marked, leads to hypogonadotropic/functional hypogonadism, with a clear effect on serum testosterone levels. However, hypogonadotropic hypogonadism refers to a broader condition, defined as 'gonadal failure associated with reduced gametogenesis and reduced gonadal steroid production due to reduced gonadotropin production or action.' [81] Thus, body weight excess could alter gonadal

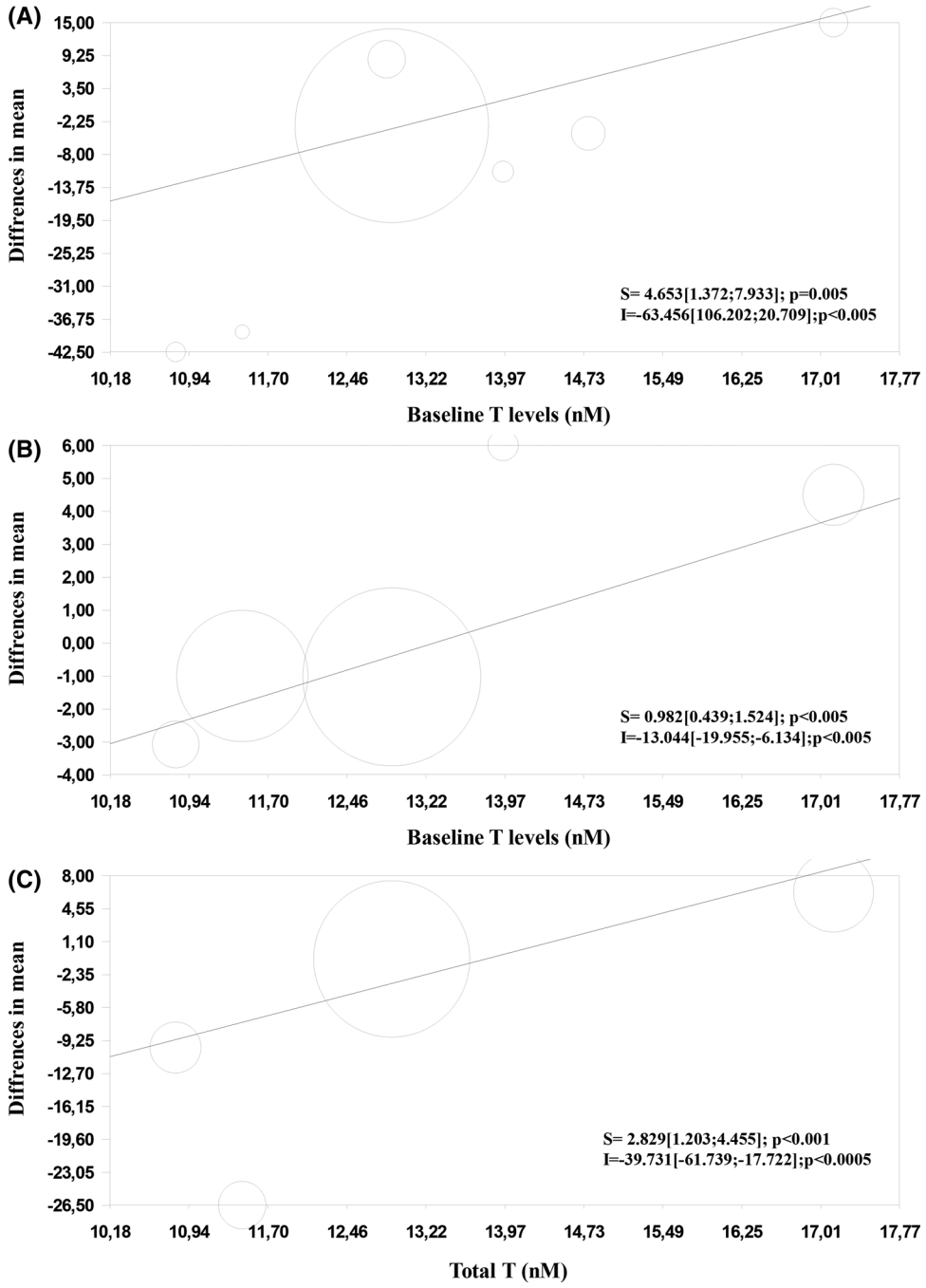

FIGURE 4 Impact of total testosterone levels on sperm concentration (A), sperm normal morphology (B), and progressive motility (C) between normal weight and subjects with obesity.

function beyond the 'simple' interstitial compartment disruption evident through the reduction of serum testosterone levels, but also impairing the spermatogenic compartment, resulting in decreased semen quality. Two different mechanisms could be advocated to explain spermatogenenic impairment occurring in obese men. First, the above discussed HPG axis impairment related to body weight excess could involve both luteinizing hormone (LH) and follicle stimulating hormone (FSH). While reduced LH and testosterone levels have been proven in non-complicated obesity, a clear FSH reduction has never been demonstrated in this setting. Indeed, FSH serum levels are usually low-to-normal in obese men, together with an inhibin B reduction.[82] Despite, this issue remains still open, it is noteworthy that FSH stimulation on Sertoli cells is required for quantitative and qualitative spermatogenesis.[83–85] Thus, it could be speculated that the obesity-related HPG axis disruption could impair the physiological FSH stimulation on Sertoli cells, limiting its role in the first step of sperm maturation during spermatogenesis. In addition, high levels of intratesticular testosterone are fundamental for sperm maturation.[86] Hence, the hypotestosteronemia documented in obese men could be one of the mechanisms by which body weight excess reduces male

fertility. However, low testosterone levels in the serum are not necessarily associated with low testosterone within the testes and if obesity is able to affect intratesticular steroidogenesis remains to be clarified. Comprehensively, we demonstrate that body weight excess impact on gametogenesis in a sort of 'dose-dependent' manner. Indeed, OW men showed a worsening in only two sperm parameters if compared to NW subjects. On the contrary, all available sperm parameters significantly worsened when obesity is considered, with a further deterioration when selecting patients affected by severe obesity. In addition, the observed semen volume reduction in obese men compared to NW subjects could be due at least in part to a more severe hypotestosteronemia experienced by these men. Indeed, the association between semen volume and testosterone serum levels is demonstrated in the general population.[87] In conclusion, our data clearly show that the higher the body weight excess is, the higher is the damage on the testicular functions, in particular on gametogenesis in a dose-dependent manner.

In a non-genomic rabbit model of HFD-induced visceral obesity and MetS we previously demonstrated that indeed in the preoptic region of the hypothalamus of HFD rabbits there is metaflammation, along with increased estrogen signaling, associated with a disruption of the complex network regulating GnRH secretion which was associated with a down-regulation of LH and FSH secretion.[38,88] In the testis, all the genes devoted to androgen signaling were down-regulated and testosterone production from androstenedione was inhibited.[88] This was associated with a testicular and epididymal inflammation and with an impaired spermatogenesis.[27,28] This animal models support a direct effect of obesity on the testicular function, acting at multiple levels of the HPG axis.

Based upon these data, we can speculate that both OW and obesity represent two modifiable risk factors for male infertility. While the evaluation of body weight excess during the diagnostic work-up for hypotestosteronemia has been largely confirmed,[71,73] here we suggest here that this should be considered also in the diagnostic work-up of infertile men.[89] Obviously, other known risk factors for infertility should be considered, as among them the presence of varicocele. Our analysis show that the concomitant presence of varicocele can enhance the body fat excess-related sperm impairment. The association between varicocele and male infertility is well known.[90] However, the role of varicocele repair in the management of a couple infertility is still conflicting.[91–93] Similarly, whether or not obesity can increase the risk of varicocele has not been completely clarified. Accordingly, some studies have found a positive correlation between BMI and an increased varicocele risk,[94–96] other authors have reported no association or even a negative correlation.[97–100] Interestingly, however, Garolla et al.[101] showed that both obesity and varicocele are associated with a significant increase in 24-h mean scrotal temperature when compared to controls. In addition, other authors have reported that obesity negatively affects varicocelectomy outcomes.[102] The latter evidence supports the additive effect of varicocele and obesity on male sperm quality as observed in our study.

Thus, both OW and obesity should be considered within the long list of modifiable risk factors for infertility and appropriate therapeutic approaches aiming at reducing body weight should be considered in infertile men with excess weight.[19] In particular, both diet, metabolic surgery[103] and ketogenic diets[104] have been demonstrated to be effective in reducing body weight and increasing serum testosterone levels.[104] Whether these treatments should be effective also to improve sperm parameters should be addressed by future properly designed clinical trials. Few evidences have been recently published suggesting the potential role of ketogenic diet on infertility in females[105–107] and in vitro studies.[108]

In the literature, several systematic reviews tried to determine the role of obesity on male and human reproduction. Campbell et al. demonstrated that the reproductive potential of obese men was reduced when strong outcomes were considered, such as pregnancy and live birth rates.[109] Although this result could be explained by the obesity-related decrease in normal sperm morphology and increased rates of sperm DNA damage, it is tainted by major biases, such as the selection of the final endpoint. Indeed, the evaluation of pregnancy rate as primary endpoint is not only related to male fertility potential alone, being influenced by many different variables, such as the female factors, for example, ovarian reserve.[31] In order to overcome the latter problem, other systematic reviews tried to consider sperm parameters as endpoints to demonstrate the role of body weight excess on male fertility. However, contrasting results are available so far. MacDonald et al. did not find any significant association between male obesity and sperm count, motility, and semen volume.[33] Although the performed literature search was large, it was not methodologically focused, and many data collected from the majority of studies were not aggregated for meta-analysis.[33] On the contrary, Sermondade et al. demonstrated that OW and obesity were associated with an increased prevalence of azoospermia and oligozoospermia, thus suggesting a weight-related detrimental effect specifically on sperm number.[32] However, this systematic review still classified patients according to categories based on semen analysis alterations. This classification is now clinically obsolete according to the recommendations of the new edition of the WHO manual for the interpretation of semen analysis.[34] Indeed, the new concept of 'decisional limits' instead of 'reference ranges' was proposed for all parameters reported in the semen analysis, pointing out that semen evaluation alone is not able to discriminate between fertile and infertile men. With this in mind, the evaluation of the role of body weight excess on semen parameters grouping patients in strict, clinically not useful categories does not provide clear evidence. Finally, more recently, Salas-Huetos et al. confirmed that male adiposity impaired sperm quality.[29] However, this latter meta-analysis is biased by the study selection, since studies performed before 2010 were included. Thus, different WHO manual editions for semen analysis interpretation were used over the years, increasing the degree of heterogeneity among studies considered. Our meta-analysis for the first time, approached the correlation between obesity and sperm production impairment by applying strict study selection criteria, considering only those studies in which semen analysis was performed by the WHO manual V edition (2010), the longest-running manual. Thus, considering the high variability intrinsic to semen analysis per se, here we considered only those studies in which the same edition of the WHO manual was used reducing potential biases due to the reporting methods applied.

Obviously, our meta-analysis has important limitations. Alongside the limits, intrinsic to a meta-analytic approach, we are not able to demonstrate the real cause–effect correlation between body weight excess and impairment of semen parameters. Similarly, we are not able to investigate other parameters that are potentially altered in obesity and could impact on spermatogenesis, such as the loss of mitochondrial membrane potential and high concentrations of reactive oxygen species within the testes. Indeed, we were able to evaluate only few studies reporting sperm DNA fragmentation index as part of their semen evaluation. Although the number is limited, our meta-analysis confirmed an increased DNA fragmentation in obese versus NW subjects, suggesting indirectly that a possible physio-pathological mechanism connecting obesity and impaired spermatogenesis could be the oxidative stress increase. In addition, due to limited available data the effects of body weight reduction and sperm quality outcomes were not investigated. Similarly, the impact of obesity in primary and secondary infertility was not possible due to limited information. Significant heterogeneity among studies was detected, which reflects the differences observed in population characteristics and degree of obesity detected.

AUTHOR CONTRIBUTIONS

Daniele Santi and Giovanni Corona conceived the studies and extracted data from the literature. Giovanni Corona performed statistical analyses. Daniele Santi, Francesco Lotti, Clotilde Sparano, Giulia Rastrelli, Andrea M. Isidori, Rosario Pivonello, Arcangelo Barbonetti, Andrea Salonia, Suks Minhas, Csilla Krausz, Linda Vignozzi, Mario Maggi, and Giovanni Corona drafted and final approved the manuscript.

FUNDING INFORMATION

No funding was provided for the study's conduction.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Daniele Santi https://orcid.org/0000-0001-6607-7105
Andrea M. Isidori https://orcid.org/0000-0002-9037-5417
Rosario Pivonello https://orcid.org/0000-0002-9632-1348
Andrea Salonia https://orcid.org/0000-0002-0595-7165
Linda Vignozzi https://orcid.org/0000-0003-0907-0630
Mario Maggi https://orcid.org/0000-0003-3267-4221
Giovanni Corona https://orcid.org/0000-0002-9894-2885

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Santi D, Lotti F, Sparano C, et al. Does an increase in adipose tissue 'weight' affect male fertility? A systematic review and meta-analysis based on semen analysis performed using the WHO 2010 criteria. *Andrology*. 2023;1-14. https://doi.org/10.1111/andr.13460