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# Type of article: Systematic review and meta-analysis

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Title: Male adiposity, sperm parameters and reproductive hormones: An updated systematic 3 review and collaborative meta-analysis 4 5 Running title: Male adiposity, sperm parameters and sex hormones Authors: 6 Albert Salas-Huetos <sup>1,2,3,4,\*</sup>, Leila Maghsoumi-Norouzabad <sup>5,6,†</sup>, Emma R. James <sup>4,7,†</sup>, Douglas T. 7 8 Carrell <sup>4,7</sup>, Kenneth I. Aston <sup>4</sup>, Timothy G. Jenkins <sup>4,8</sup>, Nerea Becerra-Tomás <sup>1,2,3</sup>, Ahmad Zare Javid <sup>5,6</sup>, Reza Abed <sup>9</sup>, Pedro Javier Torres <sup>10,11</sup>, Eugenia Mercedes Luque <sup>10,11</sup>, Nicolás David 9 Ramírez <sup>10,11</sup>, Ana Carolina Martini <sup>10,11,12,‡</sup>, Jordi Salas-Salvadó <sup>1,2,3,13,‡,\*</sup> 10 11 Affiliations: 1. Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició, 12 Reus, Spain. 13 14 2. Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain. 15 3. Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute of Health Carlos III, Madrid, Spain 16 17 4. Andrology and IVF Laboratory, Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA. 18 5. Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University 19

- Department of Nutrition, School of Alled Medical Sciences, Anvaz Jundishapur Oniversity
   of Medical Sciences, Ahvaz, Iran.
- 6. Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of
   Medical Sciences, Ahvaz, Iran.

- 7. Department of Human Genetics, University of Utah School of Medicine, Salt Lake City,
  UT, USA.
- Department of Physiology and Developmental Biology, Brigham Young University, Provo,
   UT, USA.
- 9. Aras Hospital, Iran Social Security Organization, Parsabad, Ardabil, Iran.
- 10. Instituto de Fisiología, Facultad de Ciencias Médicas (FCM), Universidad Nacional de
   Córdoba. Santa Rosa 1085, Córdoba, Argentina.
- 11. Instituto de Investigaciones en Ciencias de la Salud (INICSA), Consejo Nacional de
   Investigaciones Científicas y Tecnológicas (CONICET)-FCM, Argentina.
- 32 12. Established investigator from CONICET, Argentina.
- 13. University Hospital of Sant Joan de Reus, Nutrition Unit, Reus, Spain.
- 1. These authors should be considered similar in author order.
- 35 <sup>‡</sup>. These authors should be considered similar in author order.
- 36 \* Corresponding authors.
- 37
- 38 **Corresponding authors information:**
- 39 Dr. Albert Salas-Huetos
- 40 Address: Andrology and IVF Laboratory, Division of Urology, Department of Surgery, University
- 41 of Utah School of Medicine, 84180 Salt Lake City, UT, USA.
- 42 Contact: +1 (385) 210-5534
- 43
- 44 Dr. Jordi Salas-Salvadó

- 45 Address: Human Nutrition Unit, Biochemistry and Biotechnology Department, Faculty of Medicine
- 46 and Health Sciences, Universitat Rovira i Virgili (URV) and Pere Virgili Institute for Health
- 47 Research (IISPV), 43201 Reus, Spain.
- 48 Contact: +34 977 759 213
- 49
- 50 Authors emails and ORCIDs:
- 51 Albert Salas-Huetos: albert.salas@utah.edu, 0000-0001-5914-6862
- 52 Leila Maghsoumi-Norouzabad: <u>l.maghsumi55@gmail.com</u>, 0000-0002-0674-5025
- 53 Emma R. James: <u>emma.james@utah.edu</u>, 0000-0001-5680-2131
- 54 Douglas T. Carrell: douglas.carrell@hsc.utah.edu, 0000-0002-6471-2803
- 55 Kenneth I. Aston: ki.aston@hsc.utah.edu, 0000-0001-6459-2103
- 56 Timothy G. Jenkins: tim jenkins@byu.edu, 0000-0003-1171-4482
- 57 Nerea Becerra-Tomás: <u>nerea.becerra@urv.cat</u>, 0000-0002-4429-6507
- 58 Ahmad Zare Javid: <u>ahmaddjavid@gmail.com</u>, 0000-0001-7119-7582
- 59 Reza Abed: <u>r.abed55@gmail.com</u>, 0000-0002-1358-5728
- 60 Pedro Javier Torres: pedrojtorres011@hotmail.com.ar, 0000-0002-7825-5623
- 61 Eugenia Mercedes Luque: <u>eugenialu@gmail.com</u>, 0000-0001-9726-9046
- 62 Nicolás David Ramírez: <u>nicoramireznr94@gmail.com</u>, 0000-0001-9762-5637
- Ana Carolina Martini: <u>acmartini2000@yahoo.com</u>, 0000-0003-3063-5640
- 64 Jordi Salas-Salvadó: jordi.salas@urv.cat, 0000-0003-2700-7459

#### 65 ABSTRACT

66 The present updated systematic review and meta-analysis aims to summarize the evidence from published studies with low risk for any important bias (based on methodological quality 67 assessment) investigating the potential associations of adiposity with sperm quality and 68 reproductive hormones. We conducted a systematic search of the literature published in 69 MEDLINE-PubMed and EMBASE through June 2019. Based on the criteria in our review, 169 70 71 eligible publications were used for data abstraction. Finally, 60 articles were included in the 72 qualitative analysis and 28 in the quantitative analysis. Our systematic review results indicated 73 that overweight and/or obesity were associated with low semen quality parameters (i.e. semen 74 volume, sperm count and concentration, sperm vitality and normal morphology) and some specific 75 reproductive hormones (e.g. inhibin B, total testosterone, and sex hormone-binding globulin). 76 Overweight and/or obesity were also positively associated with high estradiol concentrations. Meta-analysis indicated that overweight and/or obesity categories were associated with lower 77 78 sperm quality (i.e. semen volume, sperm count and concentration, sperm vitality, total motility and 79 normal morphology), and underweight category was likewise associated with low sperm normal 80 morphology. In conclusion, our results suggest that maintaining a healthy body weight is important for increasing sperm quality parameters and potentially male fertility. 81

82 **Keywords:** BMI; adiposity; sperm parameters; sex hormones; systematic review; meta-analysis

#### 83 INTRODUCTION

Infertility is defined as the inability to have a child after at least one year of regular unprotected
sexual intercourse. It is reported that about 15 percent of couples across the world are suffering
from infertility <sup>1</sup>.

There are several causes for infertility, however, about half of the causes are attributed to the male partner. Infertility can be caused by a variety of factors, such as anatomical abnormalities including varicocele, ductal obstructions, or ejaculatory disorders. However, more than 25% of infertile men have idiopathic infertility <sup>2,3</sup>, defined as the absence of specific abnormalities in semen parameters <sup>4</sup>. The etiology of suboptimal semen quality is not well understood, but oxidative stress and several genetic, physiological, environmental, and nutritional factors are suggested <sup>5</sup>.

There is increasing evidence showing the important role of nutrition on quality of sperm. Recent studies suggested that nutrition, in terms of both macro- and micro-nutrient intake, plays a key role in normal reproductive function indicating that high energy intake, elevated intake of saturated fatty acids, trans fatty acids, and sodium along with low consumption of antioxidant-rich foods such as fruits and vegetables, may result in an impaired reproductive system, affecting the structure of sperm, as well as fetal and offspring health <sup>6–10</sup>.

100 Underweight and overweight/obesity have been reported to be associated with an increased risk of infertility through sex hormones and seminogram alterations. Because several 101 studies in humans have investigated the links between adiposity (BMI or waist-circumference) 102 and sperm parameters, several systematic reviews and meta-analysis have been conducted <sup>11-</sup> 103 104 <sup>13</sup> suggesting an association between excess of adiposity and several sperm parameters. However, these meta-analyses were conducted some years ago, in some cases in specific 105 106 populations, and frequently included low-quality studies, therefore, the associations are 107 controversial. These controversies are commonly attributed to limitations that are inherent in

human studies such as confounding factors and other limitations that are absent from animalcontrolled studies. In fact, there are a wide variety of studies in animal models indicating detrimental effects of obesity-induced fat-rich diets in spermatogenesis function <sup>14–16</sup>. Importantly, some well-controlled animal studies indicate that a diet-induced reversion to normal weight in not sufficient to reverse the effects of an unhealthy diet on semen parameters <sup>16</sup>. Both types of studies, human observational studies and animal experimental studies highlight the necessity of new, updated systematic reviews and meta-analysis to create a consensus in the topic.

115 The aim of the present systematic review and meta-analysis was to update and 116 summarize the high-quality evidence from published human observational studies investigating 117 the potential associations between adiposity categories (underweight, overweight and obesity), 118 and seminogram parameters or sex-related hormones implicated in male reproductive function.

#### 119 **METHODS**

#### 120 Data Sources and Searches

We followed the Cochrane Handbook of Systematic Reviews guidelines. The protocol has been registered (PROSPERO 2019: CRD42019121920) in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO).

We performed a systematic search of the literature published in MEDLINE-PubMed database (<u>http://www.ncbi.nlm.nih.gov/pubmed</u>), EMBASE database (<u>https://www.embase.com/#search</u>), and a manual search of a reference list of retrieved articles through June 2019, in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) <sup>17,18</sup> and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statements <sup>19</sup>.

For literature searches, a combination of terms as both Medical Subject Headings (MeSH) and 130 131 keywords was used. The search terms for this study included "male (in)fertility" related keywords, and terms related to "weight/obesity" such as: male infertility OR asthenozoospermia OR 132 133 oligozoospermia OR oligoasthenozoospermia OR oligoasthenoteratozoospermia OR teratozoospermia OR spermatogenesis OR semen quality OR sperm DNA damage OR varicocele 134 AND obesity OR abdominal obesity OR metabolic syndrome OR overweight OR body mass index 135 136 OR BMI OR body weight OR fat mass OR body fat. The complete search strategy and filters applied are available in Supplemental Appendix 1. 137

#### 138 Eligibility criteria and study selection

Four authors in the field of male fertility and nutrition screened the titles and abstracts of all articles for eligibility (AS-H, LMN, ERJ, and RA). The accessible case-control, cross-sectional and observational prospective and retrospective studies, in which fertile/infertile men were welldefined with sperm disorders, sperm DNA damage, or idiopathic infertility, were included in this review. In addition, studies were selected with the primary outcomes of semen quality (volume, motility, morphology, sperm count or concentration, sperm DNA damage or chromatin integrity and sex hormonal level). We excluded randomized clinical trials, animal studies, review articles, varicocele studies, and studies of low quality. After primary screening (assessing the scope of study) and evaluating the quality in accordance with inclusion/exclusion criteria, the full text of selected articles was obtained (**Supplemental Table 1**).

#### 149 **Data extraction**

The following information was extracted from each study: author/s, year of publication, location, age (years), infertility status, sample size, study design, exposure, primary and secondary outcomes, and conclusion. After extracting the data, in order to minimize any errors, they were double checked by the authors regarding any discrepancies.

#### 154 **Quality assessment**

155 The quality of selected observational (cross-sectional, retrospective, prospective and casecontrols) studies was assessed and scored on a six-point scale by three authors (AS-H, LMN, 156 and RA) in parallel <sup>20</sup>. The discrepancies were re-evaluated altogether. We assessed the quality 157 of individual studies using the following criteria (0, 0.5 or 1 point per criterion): (i) study 158 participation; (ii) study attrition; (iii) prognostic factor measurement; (iv) confounding 159 160 measurement and account; (v) outcome measurement; and (vi) analysis. Studies with a score between 0 and 3 points were considered low-quality studies (excluded) and studies with a score 161 > 3 were considered as moderate to high quality studies (included for subsequent analysis). 162

#### 163 Statistical analysis (meta-analysis)

Meta-analyses were performed only using the latest World Health Organization <sup>21</sup> BMI categories:
<18.5 (underweight), 18.5-24.9 (normal weight), 25.0-29.9 (overweight, or pre-obesity), 30.0-34.9</li>
(class I obesity), 35-39.9 (class II obesity) and ≥40.0 (morbid obesity, or class III obesity) kg/m<sup>2</sup>.

Participants with a BMI between 18.5-24.9 kg/m<sup>2</sup> were considered as the reference category, 167 except in few cases, where the normal weight was considered 20-24.9 kg/m<sup>2</sup> <sup>22-25</sup>. In the studies 168 with only some categories encompassed in the last WHO-BMI categorization the meta-analysis 169 were done only with these categories (for example: Lugue et al., 2017<sup>22</sup> has WHO categories for 170 171 overweight and obesity but not for underweight). When only one subcategory of obesity was reported in a paper (BMI>30.0), the values where computed in the first obesity category (class I 172 obesity -or more-) (for example: Aggerholm et al., 2008<sup>26</sup>). In a few cases, only two subcategories 173 of obesity were shown (BMI>30-34.9 and BMI>35); in those cases the values in the highest 174 category where computed in the second obesity category (class II obesity -or more-) (for example: 175 Belloc et al., 2014<sup>27</sup>). 176

Meta-analysis was conducted only with the studies included in the qualitative synthesis with seminogram data (semen volume, sperm count and concentration, sperm vitality, sperm total and progressive motility, and/or normal morphology) through the use of Doing Meta-Analysis in R<sup>28</sup> and Meta-Essentials v.1.4<sup>29</sup> platforms in accordance with the Cochrane guidelines <sup>30,31</sup>.

To calculate the effect size (ES) and 95% confidence intervals (95% CIs), the mean and standard 181 deviation (SD) were obtained from patient characteristics data of each study. The ES describes 182 the difference between all aforementioned unhealthy BMI categories (underweight, overweight, 183 184 class I obesity, class II obesity, and morbid obesity, or class III obesity) and healthy-normal weight. Positive values indicated that the specific unhealthy BMI category has better seminogram 185 parameters than normal weight, whereas negative ES indicates poorer seminogram parameters. 186 In the case of prospective studies <sup>32</sup> baseline values were used. In most of the cases, these values 187 were directly obtained from the main data of the article (or supplemental data) and in few cases 188 the values were obtained through a request to the corresponding authors <sup>22,33,34</sup>. When necessary, 189 estimated mean and SD values were calculated with the median and interquartile rank (IQR) <sup>35</sup>. 190 191 The main values for meta-analysis calculations were obtained by the primary author (AS-H) and 192 were checked by three independent authors (PJT, EML, and NDR). Random-effects models were 193 used to obtain summary effects and inter-study variation when ≥5 studies were compared (fixedeffects models were used if number of study comparisons were  $<5^{36}$ ). Statistical significance was 194 set at p-value<0.05 (two-way). Heterogeneity between the studies was evaluated via a chi-square 195 196 test and the  $l^2$  index with the significance level set at p<0.10.  $l^2$  values <50% were deemed moderate, ≥50% to <75% were deemed substantial, and ≥75% were deemed of considerable 197 198 heterogeneity. Tests for funnel plot asymmetry were used only when there were at least 10 studies included in the meta-analysis, as well as, "trim and fill" method, in order to identify and correct for 199 funnel plot asymmetry arising from publication bias <sup>31</sup>. 200

Sensitivity analyses were performed in two different ways when ≥5 studies were included in the
 meta-analysis 1) changing meta-analysis models (random to fixed models) and, 2) systematic
 exclusion of one study at a time and recalculating summary effect sizes.

204 **RESULTS** 

#### 205 Study characteristics

The number of articles identified after a primary search was 2,237 (Figure 1). After analyzing the 206 results, we immediately excluded 565 records because they were duplicated (n=337); they were 207 208 conference papers (n=223), or comments, replies or letters (n=5). The remaining 1,672 records 209 were evaluated based on their title and abstract, and 1,518 articles were excluded based on the scope of the study. One hundred and fifty-four articles (based on the inclusion and exclusion 210 211 criteria) with full texts were selected for quality assessment. Fourteen additional manuscripts were 212 included after a complimentary search of the citation lists. We also included one recently 213 published study obtained by contacting the corresponding authors of all studies included in the meta-analysis, assigned as '(Ramírez et al., 2020)<sup>23'</sup> study. Therefore, the inclusion/exclusion 214 criteria and quality scores were assessed in 169 full-text articles. One hundred nine of these 215 articles were excluded based on inclusion/exclusion criteria (n=24), quality assessment threshold 216 217 (n=13) or other reasons (reviews, n=28; data not found, n=2; no English papers, n=10; conference 218 papers, n=23; comments, replies, or letters, n=5; corrigendums, n=1; or randomized clinical trials, n=3). After considering all eligibility parameters and the PICOS table (Supplemental Table 1), 219 220 60 high-quality articles were used for data abstraction. Finally, 28 articles were included in the 221 quantitative synthesis because seminogram data were displayed and/or subsequently obtained 222 (exclusion reasons: insufficient data, n=18; non-WHO based BMI categories included, n=5; lack 223 of data in normal weight individuals, n=3; lack of BMI data, n=2; and articles with only hormonal data, n=4). 224

225 Qualitative synthesis

The summary of articles analyzing the associations between semen quality, reproductive hormone levels and different exposures related with underweight, normal weight, overweight and obesity data were condensed in **Table 1**.

We identified a total of 54 studies reporting the association between BMI and sperm quality parameters, and 29 studies reporting some associations between BMI and reproductive hormones. The majority of exposure associations are reported with BMI data (58/60), however, some studies also reported other exposures (e.g. body fat, waist circumference, metabolic syndrome, waist-to-height ratio or waist-to-hip ratio).

The articles included subjects from all continents but Antarctica, with 30 countries represented: Argentina, Australia, Austria, Brazil, China, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Georgia, Germany, Hungary, Iceland, India, Iran, Italy, Netherlands, New Zealand, Nigeria, Norway, Pakistan, Saudi Arabia, Sweden, Taiwan, Tunisia, Turkey, United Kingdom, USA. The age of the participants ranged between 16 and 66 years.

Even though all of the studies included in the systematic review have cross-sectional data (reporting baseline characteristics) and these data were used to perform the meta-analysis, when possible, different study types were identified: 8 retrospective, 8 prospective and 44 crosssectional studies. The mean quality assessment score for all included studies was 4.3/6 (range: 3.5-5.5).

244 Globally, our systematic review results indicated that overweight or obesity (based in BMI-WHO) was associated with reduced semen quality parameters (i.e. semen volume, sperm count and 245 246 concentration, sperm vitality and motility, and normal morphology) and disruption of some specific 247 reproductive hormones (i.e inhibin B, total testosterone, and sex hormone-binding globulin). 248 However, overweight and/or obesity were associated with high peripheral concentrations of estradiol. In the case of all other measured parameters (i.e. free testosterone, prolactin, follicle-249 250 stimulating hormone, luteinizing hormone, testosterone/luteinizing hormone ratio, progressive 251 sperm motility, and DNA fragmentation index) the associations are, in some cases, contradictory 252 (Table 1 and Table 2). Even though not all the studies considered possible confounding factors

for the analysis, the vast majority adjusted for age due to age-associated increases in risk of obesity.

## 255 Quantitative synthesis: association between BMI categories and seminogram parameters

The present meta-analysis includes a total of 28 eligible studies with BMI and seminogram data
 <sup>22–27,32–34,37–55</sup>.

Figure 2A-G shows the summary associations (combined effect size) between BMI categories and each seminogram parameter considered.

260 Figure 2A shows the summary associations (combined effect size) between BMI categories and semen volume. The comparisons between each BMI category and semen volume were shown in 261 262 supplemental figures (Supplemental Figures 1-5). Compared to individuals with normal weight, 263 those with class I obesity and class II obesity had a lower semen volume (ES; 95% confidence interval) (-0.31; -0.58 to -0.03; p-value=0.018, and -0.72; -1.07 to -0.36; p<0.001, respectively). 264 265 This association was not observed in the case of class III obesity category, where heterogeneity was moderately high ( $l^2$ <50%, p=0.140). For the other BMI categories there was evidence of 266 267 considerable and significant heterogeneity between the studies ( $l^2$ >85%, p<0.001). The visual evaluation of funnel plot and "trim and fill" test were performed for the meta-analysis with at least 268 10 studies included, and no substantial changes in the ES and heterogeneity (<10% of changes 269 270 in heterogeneity) were detected in semen volume outcomes.

Figure 2B shows the summary associations between BMI categories and sperm count. The comparisons between each BMI category and sperm count are shown in supplemental figures (Supplemental Figures 6-10). Compared to the individuals with normal weight, sperm count was lower in the cases of class II obesity and class III obesity categories (-0.66; -0.91 to -0.42; p<0.001, and -0.20; -0.98 to 0.57; p=0.001, respectively). Except for class III obesity category, where heterogeneity was moderate (I<sup>2</sup>=61%, p=0.110) there was evidence of considerable and

significant heterogeneity between the studies for the other BMI categories ( $I^2>90$ , p<0.001). Funnel plots and "trim and fill" tests indicated that no substantial changes in heterogeneity were detected.

280 Figure 2C shows the summary associations between BMI categories and sperm concentration. The comparisons between each BMI category and sperm concentration were shown in 281 supplemental figures (Supplemental Figures 11-15). Compared to individuals with normal 282 283 weight, only those with class III obesity had decreased sperm concentrations (-0.18; -0.42 to 0.06; p=0.002). In that case, the heterogeneity was classified as substantial ( $I^2$ =71.3%, p=0.015) for 284 class II obesity and moderate ( $I^2 < 50\%$ , p=0.272) for class III obesity. The other categories were 285 286 classified with high heterogeneity (l<sup>2</sup>>90, p<0.001). Funnel plots and "trim and fill" tests indicated 287 that no substantial changes in heterogeneity were detected.

288 Figure 2D shows the summary associations between BMI categories and sperm vitality. The comparisons between each BMI category and sperm vitality were shown in supplemental figures 289 290 (Supplemental Figures 16-19). The meta-analysis comparing individuals with underweight and 291 normal weight could not be performed due to too few studies being identified. We found that, compared to individuals with normal weight, those with overweight, class I obesity and class III 292 293 obesity categories had a decrease in sperm vitality percentages (-0.81; -1.59 to -0.03; p=0.012, -294 0.76; -1.65 to 0.13; p=0.027, and -3.16; -4.82 to -1.51; p<0.001, respectively). Evidence of significant, considerable heterogeneity (12>85%, p<0.001) was observed for all analyzed 295 296 categories. In that outcome, no funnel plots and "trim and fill" tests were applied because fewer than 10 studies were included in the meta-analysis. 297

**Figure 2E** shows the summary associations between BMI categories and total motility. The comparisons between each BMI category and total motility are shown in supplemental figures (**Supplemental Figures 20-24**). We only found a decrease in total sperm motility in individuals with class III obesity as compared with individuals with normal weight (-0.37; -0.61 to -0.12;

p<0.001). This was also the only comparison with moderate heterogeneity ( $l^2<50\%$ , p=0.188). Funnel plots and "trim and fill" tests indicated that no substantial changes in heterogeneity were detected.

305 Figure 2F shows the summary associations between BMI categories and progressive motility. The comparisons between each BMI category and sperm progressive motility are shown in 306 307 supplemental figures (Supplemental Figures 25-28). In the case of progressive motility, no 308 significant associations were found for any adiposity categories analyzed. Except for individuals in underweight category, where heterogeneity was very low ( $l^2=0\%$ , p=0.889), there was evidence 309 310 of considerable and significant heterogeneity between the studies for the other considered BMI 311 categories (I<sup>2</sup>>90, p<0.001). Funnel plots and "trim and fill" tests indicated that no substantial 312 changes in heterogeneity were detected. However, for the overweight category, "trim and fill" tests 313 resulted in a non-significant change of the ES from a negative association without the adjustment (-0.26; -0.57 to 0.05) to a positive association after the adjustment and imputation of six data 314 points (0.02; 0.01 to 0.04) (Supplemental Figure 26). 315

316 Finally, Figure 2G shows the summary associations between BMI categories and normal sperm morphology. The comparisons between each BMI category and morphology are shown in 317 supplemental figures (Supplemental Figures 29-33). We found that individuals with 318 319 underweight, class II obesity and class III obesity were associated with a decrease in spermatozoa with normal morphology (-0.98; -1.40 to -0.56; p<0.001, -0.57; -0.82 to -0.32; 320 321 p<0.001, and -0.31; -0.56 to -0.05; p<0.001, respectively). Except for class III obesity category, where heterogeneity was substantial ( $I^2$ =63%, p=0.068) there was evidence of considerable 322 heterogeneity between the studies for the other BMI categories (I<sup>2</sup>>90, p<0.001). Finally, funnel 323 324 plots and "trim and fill" tests indicated that no substantial changes in heterogeneity were detected.

Figure 2H is a summary of the data and was generated to illustrate significant associations between BMI class and seminogram parameter while considering direction of change. This was

done by plotting statistical significance (-log10 p-value) against combined effect size on the y-axis
 and x-axis, respectively.

#### 329 Sensitivity analyses

#### 330 Fixed models

The use of fixed models (instead of random models), in the meta-analyses with ≥5 studies, 331 substantially modified the significance of some results but maintained the same associations 332 333 described in **Figure 2** with the exception of the sperm volume category (normal vs. underweight) 334 and sperm total motility (normal vs. overweight). In the other cases, the association direction is 335 the same but becomes statistically significant. This is observed in the case of semen volume (overweight), sperm count (underweight, overweight and class I obesity), sperm concentration 336 (underweight, and class I obesity), total and progressive motility (class I obesity) and normal 337 338 morphology (class I obesity), but not in vitality. The results showed that random models are stricter than fixed models, as expected, in meta-analyses with more than 5 studies (see Supplementary 339 Figures 34-50). 340

## 341 Systematic exclusion of one study at time

342 Some changes in results were identified by systematic exclusion of one study at a time in the 343 meta-analyses with ≥5 studies (see Supplementary Table 2). The results showed that the ES of 344 semen volume in the underweight group changed to a significant negative association when we eliminated data from Qin et al., 2007<sup>48</sup>. Removing the study by Qin et al., 2007<sup>48</sup> also explained 345 the heterogeneity in this comparison. Moreover, results showed that the ES of semen volume in 346 347 the group with overweight changed to a significant negative association when we eliminated data from Alshahrani et al., 2016<sup>55</sup>, while the outcome of other groups was not gualitatively changed 348 with or without any study. 349

Removing the study by Qin et al., 2007 <sup>48</sup> explained the heterogeneity for sperm count in underweight group (passing form considerable heterogeneity to moderate). In the same sperm quality variable, the results showed that the ES in the group with overweight changed to a significant negative association when we eliminated data from Qin et al., 2007 <sup>48</sup>. Moreover, the results showed that the ES in the group with obesity (or class I obesity) changed to a significant negative association when we eliminated data from Aggerholm et al., 2008 and/or Shayeb et al., 2011 <sup>26,50</sup>.

Similarly, removing the study by Qin et al., 2007 <sup>48</sup> explained the heterogeneity for sperm concentration in the underweight group (passing form considerable heterogeneity to moderate), while the ES outcome and heterogeneity of other groups was not qualitatively changed with or without any study.

The results showed that the ES of sperm vitality in the group with obesity (or class I obesity) changed to non-significant negative association when we eliminated data from Taha et al., 2016 <sup>51</sup>.

In the case of total motility, neither heterogeneity nor ES associations were qualitatively changed with or without any study. However, in progressive motility the results showed that the ES in the group with overweight changed to a significant negative association when we eliminated data from Bandel et al., 2015; Belloc et al., 2014; Keskin et al., 2017 and/or Ma et al., 2019 <sup>27,34,37,44</sup> and in the group with obesity (or class I obesity) when we eliminated data from Bandel et al., 2015; Hammiche et al., 2012; Keskin et al., 2017; Ma et al., 2019 and/or Taha et al., 2016 <sup>34,37,43,44,51</sup>.

Finally, the results showed that the ES of sperm normal morphology only in the group with obesity (or class I obesity) changed to a significant negative association when we eliminated data from Qin et al., 2007 <sup>48</sup>.

#### 374 **DISCUSSION**

375 The present systematic review and meta-analysis of observational studies provides the most comprehensive analysis to date of the associations between male adiposity and sperm quality or 376 377 sex-related hormones. These data suggest that there is an association between weight status 378 and sperm and hormonal parameters suggesting that weight loss could improve sperm parameters, and therefore, may improve not only assisted reproduction outcomes and live-birth 379 380 rate, but also natural conception. However, it's important to note that well designed studies investigating the impact of weight loss on improving semen parameters and reproductive 381 outcomes are scarce. Our systematic review results indicated that overweight and/or obesity were 382 383 associated with low semen quality parameters (e.g. semen volume, sperm count and 384 concentration, sperm vitality and normal morphology) and the peripheral concentrations of some specific reproductive hormones (e.g. inhibin B, total testosterone, and sex hormone-binding 385 globulin). However, overweight and/or obesity were associated with higher levels of estradiol. Our 386 387 meta-analysis indicated that overweight/obesity categories were associated with lower sperm 388 quality (e.g. semen volume, sperm count and concentration, sperm vitality, total motility and normal morphology) and underweight category was associated with reduced normal sperm 389 morphology. 390

391 There have been several systematic reviews and meta-analyses performed in the last 10 years 392 to investigate the association between adiposity and seminogram parameters but all of them had 393 limitations which restrict their interpretation and/or applicability (see Supplemental Table 3). Aggerholm et al.<sup>26</sup> found no significant relationship between sperm count and BMI. This finding 394 was further confirmed by Pauli et al. study in 2008 56, in which no relationship was observed 395 396 between BMI and semen parameters. In a meta-analysis by MacDonald and collaborators <sup>13</sup>, considering very strict inclusion and exclusion criteria, similarly there was no evidence obtained 397 398 to support the association between BMI and sperm concentration or total sperm count. In several

399 studies, the observed effects on sperm concentration were not significant and the sperm quantity 400 and quality were within the normal range among men with overweight and obesity. There was no 401 association between BMI and semen parameters according to many recent studies. Therefore, 402 although there is some existing support for the suggestion that obesity affects reproductive 403 potential, several studies indicate no connection between BMI and semen parameters.

Although the first systematic review and meta-analysis found no evidence of association between 404 405 BMI and semen parameters <sup>13</sup>, in the next three meta-analyses, a potential association between overweight/obesity and different indices of semen quality was reported <sup>11,12,57</sup>. All of the systematic 406 reviews with meta-analyses analyzing the association between excess of adiposity and 407 seminogram were published in 2017 or before <sup>11–13,57</sup>, with the exception of one that analyzed the 408 association between low BMI and seminogram without sperm morphology analysis <sup>58</sup>. In that 409 410 study, a relationship between low BMI and semen quality was reported, suggesting that low BMI is a harmful factor for male infertility. With the exception of the Campbell et al., study <sup>57</sup>, including 411 412 31 studies in the systematic review and only 5 in the meta-analysis, the other meta-analyses did 413 not evaluate the quality of the studies included in their analysis, therefore the conclusions were 414 weakened. In addition, the majority did not explore heterogeneity due to limited number of studies 415 based upon their entry criteria or did not explore the certainty of the evidence. In addition, new evidence has accumulated since most recent published systematic review and meta-analysis. 416 417 These newer studies were included in the present review. Our search in the MEDLINE-PubMed 418 and EMBASE databases showed that since the most recent meta-analysis was published, at least three new epidemiologic studies have been reported in the case of participants with 419 overweight/obesity and two in the case of underweight. Our study took into consideration all of 420 421 the aforementioned limitations of the already published meta-analyses, being the most 422 comprehensive and updated systematic review and meta-analysis on this topic, including

423 comparisons between individuals with normal weight with those with underweight, overweight and
424 with different types of obesity as measured by BMI.

Obesity may affect male fertility directly or indirectly through several possible mechanisms including alterations in hormonal profiles, increased scrotal temperature due to increased scrotal adiposity, increased production of ROS and inflammatory mediators, and epigenetic changes including methylation of sperm DNA and modification of non-coding RNAs <sup>59–62</sup>.

429 In fact, our qualitative systematic review results indicated that overweight and/or obesity were associated with reduced peripheral levels of some specific reproductive hormones (e.g. inhibin B, 430 total testosterone, and sex hormone-binding globulin) subsequently resulting in hypogonadism. 431 432 Generally, men with obesity present secondary hypogonadism, characterized by abnormal 433 hypothalamic-pituitary levels and difficulties maintaining testicular function due to insufficient levels of gonadotropin <sup>63</sup>, as also has been seen in the results of our qualitative systematic review. 434 Men with obesity also display a marked decrease in SHBG concentrations which is the principal 435 436 reason for the concomitant decrease in total testosterone observed in available studies. Nevertheless, free and total testosterone levels are not always reduced in men with 437 overweight/obesity <sup>63–67</sup>. Despite having low total testosterone concentrations, men with obesity 438 may still have free testosterone within the reference range, and therefore, hypogonadism 439 symptoms are not observed <sup>68</sup>. The ratio of Testosterone/LH may be an important measure to 440 demonstrate the secondary nature of the obesity hypogonadism. Unfortunately, this ratio was 441 measured in only one of the included studies <sup>38</sup> and in this case, an association with overweight 442 or obesity categories was not observed. 443

It has also been suggested that increased scrotal temperatures due to increased scrotal adiposity may impair spermatogenesis impacting semen parameters <sup>69</sup>, and may induce an increase in sperm DNA fragmentation <sup>70</sup>. However, in a recent meta-analysis it was concluded that there is insufficient data to demonstrate a positive association between BMI and sperm DNA

fragmentation <sup>71</sup>. It was suggested that excess levels of leptin in obesity, induced by increased 448 449 secretion from adipose tissue, may have damaging effects on the production of sperm and androgens by Leydig cells <sup>72</sup>, however this has not been confirmed. Moreover, it is suggested that 450 obesity may stimulate sperm abnormalities through the increased production of ROS and 451 452 inflammatory mediators impairing testicular and epididymal tissues directly <sup>73,74</sup>. In fact, elevated 453 levels of inflammatory mediators including TNF- $\alpha$  and IL-6 and decreased levels of vascular endothelial growth factor (VEGF) in the seminal plasma of males with obesity was observed, 454 which may affect semen quality 75. 455

Moreover, our qualitative analysis also indicated that overweight and/or obesity were associated with higher levels of estradiol, and this deserves a special discussion. New data suggested that estradiol levels measured in male serum by immunoassay cannot be considered reliable, and the use of mass spectrometric estradiol measurements are strongly recommended <sup>76,77</sup>. In fact, using mass spectrometric estradiol measurements, it has been shown that peripheral estradiol levels in men with obesity are actually low <sup>78</sup> and increased only upon extreme obesity <sup>79,80</sup>.

Therefore, it is suggested that obesity may alter the systemic and local environment necessary for spermatogenesis and sperm maturation in the epididymis and may result in poor sperm quality including decreased sperm motility, abnormal morphology of sperm, impaired acrosome reaction, altered membrane lipids and increased DNA damage <sup>81</sup>. Furthermore, some recent studies indicate that epigenetic changes including changes in sperm DNA methylation and modification of non-coding RNAs may be a consequence of increased adiposity <sup>59,62</sup>.

In fact, men with obesity are more likely to experience infertility, reduced live birth per ART cycle, and increased absolute risk of non-viable pregnancies <sup>57</sup>. A recent systematic review and metaanalysis including eleven studies revealed that elevated male BMI was associated with a significant reduction in clinical pregnancy rates, and live birth rates per IVF-ICSI treatment cycle,

472 suggesting that male BMI could be an important factor influencing these outcomes potentially
473 through the aforementioned mechanisms <sup>57</sup>.

474 It is possible that weight loss may be an effective treatment approach in obesity linked with male infertility. In fact, it was found that men who reduced their body weight by adhering to a healthy 475 diet and exercise, had increased levels of androgen and inhibin B, improved semen parameters, 476 477 increased sex hormone binding globulin (SHBG) and decreased serum concentrations of insulin 478 and leptin<sup>82</sup>. Moreover, a preliminary prospective double-armed study recently found that large-479 scale weight loss following bariatric surgery was also associated with an improvement in some semen parameters <sup>83</sup>. However, the body of literature for controlled trials on the potential benefits 480 481 of losing weight on sperm parameters, and especially on reproductive potential, is relatively small 482 and controversial <sup>84</sup>. Therefore additional studies are needed to draw strong conclusions in this area <sup>85–87</sup>. It is noteworthy that the extent to which semen parameter improvements associated 483 with weight loss are accompanied by concomitant improvements in reproductive potential need 484 485 to be further studied since most infertile men have normal sperm quality. However, considering 486 the increasing prevalence of obesity and decreasing male fertility, it is suggested that clinicians should have increased awareness of the effects of obesity on fertility and the underlying 487 mechanisms in order to appropriately counsel patients and provide more effective treatments. 488

#### 489 Strengths and limitations

The present study has some strengths that should be highlighted. We used a comprehensive systematic search strategy in multiple databases to identify all available studies published in this field and we only included studies of high quality. Nevertheless, the present systematic review and meta-analysis also has some limitations that need to be addressed. First, the clinical significance of the observed changes in the seminogram is uncertain, and certainty depends on whether the patient has a normal borderline normal (considering WHO 2010 categorization <sup>88</sup>) or abnormal seminogram. Second, we could not perform a publication bias assessment for most of

497 the outcomes because fewer than 10 study comparisons were available. Moreover, in the vast majority of the performed meta-analyses, the inter-study heterogeneity was considerable, and 498 although the exclusion of Qin et al., 2007<sup>48</sup> explained the observed heterogeneity in the semen 499 500 volume, sperm count and sperm concentration analyses, it remained unexplained for the other 501 outcomes. Finally, the possibility for residual confounding and reverse causation inherent to the design of the included studies could not be ruled out. As a consequence, future research in this 502 503 field is critical to better understand the impacts of adiposity on male fertility and the mechanisms underlying adiposity-associated male subfertility. 504

#### 505 CONCLUSIONS

In conclusion, the present systematic review and meta-analysis of observational studies provides 506 507 the most updated and comprehensive analysis to date of the associations between male adiposity 508 and sperm quality and/or sex hormones. The meta-analysis results indicate that overweight/obesity is associated with lower sperm quality (e.g. semen volume, sperm count and 509 510 concentration, sperm vitality, total motility and normal morphology) and underweight is associated 511 with reduced normal sperm morphology. These results suggest that overweight/obesity prevention should be considered at an early age to avoid deleterious effects on reproductive 512 health. Since observational studies can prove associations but not demonstrate causation, the 513 514 associations summarized in the present study need to be confirmed with large prospective cohort 515 studies of high quality, especially in the context of well-designed randomized clinical trials. Additional studies are warranted to elucidate the potential benefits of weight loss for improving 516 reproductive potential in individuals with obesity. 517

## 518 **Contributions**

- 519 Conceptualization: AS-H, and LM-N. Methodology: AS-H, and NB-T. Formal analysis: AS-H, LM-
- 520 N, ERJ, RA, PJT, EML, and NDR. Writing—Original Draft Preparation: AS-H, and JS-S. Writing—
- 521 Review and Editing: LM-N, ERJ, DTC, KIA, TGJ, NBT, AZJ, RA, PJT, EML, NDR, and ACM.
- 522 Visualization: AS-H, and ERJ. Supervision: NB-T, ACM, and JS-S. All authors made substantial
- 523 contributions in writing and editing the manuscript before submission.
- 524

# 525 **Conflict of interest**

- 526 The authors report no financial or commercial conflicts of interest.
- 527

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# TABLES

**Table 1.** Summary of studies reporting the associations between semen quality, hormone levels and different exposures related with adiposity (i.e. BMI, waist circumference, metabolic syndrome, waist-to-height ratio or waist-to-hip ratio). Table is organized in alphabetical order by first author surname.

Reference (First author name/year/loc ation)	Population studied	Age (years)	Study design	Exposur e	Outcomes	Principal conclusion	Adjustm ent variables	Sco re >3	Included in systematic review?	Included in meta- analysis ?
(Aggerholm et al., 2008) <sup>26</sup> /Denm ark	2,139 men	18-66	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, and total motility) and reproductive hormones (T, FSH, LH, SHBG, E2 and Inhibin B)	Men with overweight had a slightly lower adjusted sperm concentration and total sperm count than did men with a normal BMI, but no reduction in sperm count was observed among the men with obesity. The T and inhibin B serum concentrations were 25%-32% lower in men with obesity in comparison with normal- weight men, whereas the E2 concentration was 6% higher in men with obesity.	Age and abstinenc e time	5	Yes	Yes
(Al-Ali et al., 2014) <sup>89</sup> /Austri a and Germany	2,110 men	31.8 (±6.6)	Cross- sectional	BMI	Sperm quality (sperm concentration, total sperm motility, and normal sperm morphology) and reproductive hormones (T, FSH, LH, and PRL)	BMI did not have significant significantly independent association with any of the assessed sperm quality parameters, whereas BMI was significantly associated with LH, T and PRL hormone values.	ND/NA	4	Yes	No. Insufficie nt data
(Al Omrani et al., 2018) <sup>90</sup> /Saudi Arabia	94 couples	23-55	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, total sperm count and concentration, vitality, total motility and, normal sperm morphology), sperm DNA fragmentation, fertilization rate and pregnancy outcome	The BMI was positively correlated with moderate DFI category.	ND/NA	3.5	Yes	No. Insufficie nt data

(Alshahrani et al., 2016) <sup>55</sup> /Saudi Arabia	439 men	≥18	Prospecti ve (cross- sectional data)	BMI	Sperm quality (semen volume, total sperm count and concentration, total motility, and normal morphology)	Sperm concentration was the only semen parameter that was inversely associated with BMI in infertile men.	ND/NA	4	Yes	Yes
(Amjad et al., 2019) <sup>91</sup> /Pakist an	313 (178 infertile and 135 fertile men)	Infertile=3 3.74±5.67 ; Fertile=3 7.65±6.12	Cross- sectional	BMI and BF	Reproductive hormones (T, FSH, LH, SHBG)	FSH, LH, T and SHBG concentrations were significantly lower in obesity as compared to normal weight and overweight categories (BMI).	ND/NA	5	Yes	No. Only hormonal data.
(Andersen et al., 2016) <sup>33</sup> /Norwa y	166 men	22–61	Cross- sectional	BMI	Sperm quality (sperm count and concentration, progressive sperm motility, normal sperm morphology, and vitality), sperm DNA integrity analysis, and reproductive hormones (T, SHBG, inhibin B, and AMH)	BMI was negatively associated with sperm concentration, total sperm count, progressive sperm motility, normal sperm morphology, and percentage of vital spermatozoa. A negative relationship was observed between BMI and T, SHBG, inhibin B and AMH.	Age, abstinenc e time and time to semen analysis	4	Yes	Yes
(Bandel et al., 2015) <sup>37</sup> /Swed en	1,503 men	27.9 (±10.9)	Cross- sectional	BMI	Sperm quality (semen volume, sperm concentration, and total and progressive motility) and sperm DNA fragmentation (SCSA).	High BMI was not associated with impaired sperm DNA integrity as assessed by SCSA.	Age, smoking, and abstinenc e time	5	Yes	Yes
(Belloc et al., 2014) <sup>27</sup> /Franc e	10,665 men	37.1 (±6.1)	Cross- sectional	BMI	Sperm quality (pH, semen volume, sperm count and concentration, total and progressive motility, viability, and normal morphology)	Increased BMI was associated with decreased semen quality, affecting volume, concentration, and motility. The percentage of normal forms was not decreased.	Age and abstinenc e time	5.5	Yes	Yes
(Bieniek et al., 2016) <sup>92</sup> /USA	4,440 men	36.1 (±7.6)	Cross- sectional	ВМІ	Sperm quality (semen volume, sperm concentration, total motility, normal morphology) and reproductive hormones (gonadotropins, T, E2, and PRL)	On multivariate analyses, BMI had weak but significant negative correlations with ejaculate volume, sperm concentration and morphology. Testosterone had a significant negative correlation, whereas E2 conversely demonstrated a positive relationship with these parameters.	Age and study centre	5	Yes	No. Insufficie nt data

(Chavarro et al., 2010) <sup>38</sup> /USA	483 male partners of subfertile couples	36.3 (±5.4)	Cross- sectional	BMI	Sperm quality (semen volume, sperm motility and sperm morphology), sperm DNA fragmentation and reproductive hormones (T, E2, SHBG, inhibin B, T:LH ratio)	BMI was positively related to E2 levels and inversely related to T and SHBG levels. There was a strong inverse relation between BMI and inhibin B levels and a lower T:LH ratio among men with a BMI ≥ 35 kg/m <sup>2</sup> . BMI was unrelated to sperm concentration, motility, or morphology. Ejaculate volume decreased steadily with increasing BMI levels. Men with BMI ≥ 35 kg/m <sup>2</sup> had a lower total sperm count than normal weight men. Sperm with high DNA damage were significantly more numerous in men with obesity than in normal-weight men.	Age, ethnicity, abstinenc e time, smoking history, intakes of alcohol and caffeine, history of undescen ded testes and history of groin injury	5	Yes	Yes
(Christofolini et al., 2014) <sup>93</sup> /Brazil	118 male partners of subfertile couples	35.59 (±7.47)	Cross- sectional	BMI and WC	Sperm quality (semen volume, sperm concentration, progressive sperm motility)	No significant difference was found in the sperm quality relative to the BMI or WC	ND/NA	3.5	Yes	No. Insufficie nt data
(Dubeux et al., 2016) <sup>94</sup> /Brazil	153 men with infertility	ND	Cross- sectional	BMI and WC	Sperm quality (sperm count and concentration, sperm motility and sperm morphology)	No association between obesity and semen alterations in a population of infertile men.	ND/NA	4	Yes	No. Insufficie nt data
(Duits et al., 2010) <sup>95</sup> /The Netherlands	1,401 male partners of subfertile couples	36.4 (±6.5)	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total motility, normal morphology, and total motile sperm count)	Semen quality was not significantly associated with BMI.	ND/NA	5	Yes	No. Insufficie nt data
(Dupont et al., 2013)⁵⁴/Franc e	330 male partners of subfertile couples	37.6±6.2	Cross- sectional	BMI	Sperm quality (total sperm count, sperm motility and sperm morphology) and sperm DNA fragmentation	Using the TUNEL assay, an increased rate of sperm DNA damage in men with obesity was reported.	Age and smoking	4	Yes	Yes
(Ehala- Aleksejev and Punab, 2015) <sup>39</sup> /Estoni a	260 male partners of pregnant women	21–57	Cross- sectional	BMI, BF%, WC and WHtR	Sperm quality (semen volume, sperm count and concentration, total motility, normal morphology), and reproductive hormones (T, FSH, LH, E2, and SHBG)	This study shows that semen quality is affected by central adiposity. Quartile analysis revealed that all adiposity markers were negatively related to SHBG and total testosterone levels. After adjustment for covariates, a high BF%, WC and WHtR	Age, abstinenc e time and alcohol use	5	Yes	Yes

						were negatively associated with total sperm count. The BF% was also negatively related to semen volume. These significant associations occurred in those individuals with a BF% $\geq$ 23.4%, WC > 98 cm and WHtR > 0.54.				
(Ehala- Aleksejev and Punab, 2018) <sup>96</sup> /Estoni a	Fertile=238, male partners of subfertile couples=2,64 2	Fertile 32.0 (±6.1) and male partners of subfertile couples 32.6 (±5.7)	Cross- sectional	MS	Sperm quality (semen volume, sperm concentration, total sperm count, motile spermatozoa, normal morphology), and reproductive hormones (T, FSH, LH, and E2)	Except for testosterone, MS has no independent effect on major fertility parameters in different subgroups of men.	Age, alcohol use, smoking and total testes volume	5	Yes	No. Lack of BMI data
(Eisenberg et al., 2014) <sup>40</sup> /USA	501 male partners of subfertile couples	31.8±4.8	Cross- sectional	BMI, WC	Sperm quality (semen volume, total sperm count and concentration, total motility, vitality, and normal morphology), and DNA fragmentation index	Ejaculate volume showed a linear decline with increasing BMI and WC. Similarly, the total sperm count showed a negative linear association with WC. 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. No relationship between physical activity and semen parameters was identified.	Age, college education and serum cotinine (smoking )	5	Yes	Yes
(Fariello et al., 2012) <sup>41</sup> /Brazil	305 male patients	27-42	Cross- sectional	BMI	Sperm quality (sperm count and concentration, total sperm motility and sperm normal morphology), sperm DNA fragmentation, and sperm mitochondrial activity	Mitochondrial activity was lower in the group with obesity. Compared to the normal weight group, the percentage of sperm with DNA damage was higher in the group with obesity than the other BMI groups.	ND/NA	4	Yes	Yes

(Fejes et al., 2005) <sup>97</sup> /Hunga ry	81 men with infertility	23.7–52.2	Cross- sectional	Weight, WC and HC, WHtR	Sperm quality (semen volume, sperm count and concentration, total and progressive motility) and reproductive hormones (T, FSH, LH, PRL, E2, and SHBG)	The waist/hip ratio was correlated with several reproductive hormone levels. Although both the waist circumference and hip circumference correlated with the semen characteristics, the waist/hip ratio did not.	ND/NA	4	Yes	No. Lack of BMI data
(Ferigolo et al., 2019) <sup>32</sup> /Italy	47 male volunteers	20-50	Prospecti ve (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, progressive motility and normal morphology), sperm DNA fragmentation, acrosome integrity, and mitochondrial activity.	Men with obesity presented decreased non-progressive motility, morphology, acrosome integrity, mitochondrial activity, and increased sperm DNA fragmentation.	ND/NA	5	Yes	Yes
(Foresta et al., 2009) <sup>98</sup> /Italy	31 men with obesity and 64 age- matched men without obesity	22–49, 24–47	Cross- sectional	BMI	Plasma concentrations of INSL3, T, SHBG, E2, LH, FSH, fT	Men with obesity had significantly lower plasma concentrations of T, SHBG, fT and INSL3, and higher levels of E2 with respect to men without obesity. Significant negative correlation between BMI and INSL3, and a positive correlation between INSL3 and T was reported. This study showed for the first time that INSL3 levels decrease with obesity.	ND/NA	3.5	Yes	No. Only hormonal data.
(Hadjkacem Loukil et al., 2015) <sup>42</sup> /Tunisi a	98 men	32.74 (±6.96)	Cross- sectional	BMI	Sperm quality (sperm concentration) and reproductive hormones (T, FSH, LH, and PRL)	Male obesity is not associated with the incidence of sperm concentration.	ND/NA	3.5	Yes	Yes
(Hajshafiha et al., 2013) <sup>99</sup> /Iran	159 male partners in subfertile couples	ND	Cross- sectional	BMI	Sperm quality (sperm concentration, total motility and normal morphology) and reproductive hormones (T, FSH, LH, PRL, E2, and SHBG)	BMI was not associated with sperm count, sperm morphology, and sperm motility. BMI was not significantly correlated with some hormone levels, such as LH, prolactin, and LH/FSH ratio. However, a statistically significant association was observed between BMI and E2, SHBG, and also the T/E2 ratio.	ND/NA	5	Yes	No. Insufficie nt data

(Håkonsen et al., 2011) <sup>87</sup> /Denm ark	43 men	20-59	Prospecti ve (cross- sectional data, pilot cohort)	BMI and weight loss	Sperm quality (sperm count and concentration, total motility and sperm normal morphology), sperm DNA integrity, and reproductive hormones (T, LH, FSH, E2, SHBG, AMH, and inhibin B)	BMI was inversely associated with sperm concentration, total sperm count, sperm morphology and motility, as well as T and Inhibin B and positively associated to E2. 15% total weight loss was associated with an increase in total sperm count, semen volume, testosterone, SHBG and AMH. The group with the largest weight loss had a statistically significant increase in total sperm count and normal sperm morphology.	Age, abstinenc e time, smoking, season, diseases in the reproduct ive organs, spillage at semen sampling, fever, and time to semen analysis	5	Yes	No. Non- WHO based BMI categorie s
(Hammiche et al., 2012) <sup>43</sup> /Nethe rlands	450 men of subfertile couples	22-60	Cross- sectional	BMI, WC	Sperm quality (semen volume ,sperm concentration, progressive motility and total motile sperm count)	Overweight was negatively associated with the percentage of progressive motility type A and positively associated with the percentage of immotility type C. Obesity was negatively associated with ejaculate volume, sperm concentration and total motile sperm count. WC $\geq$ 102 cm, a measure for central adiposity, was inversely associated with sperm concentration and total motile sperm count.	Age, ethnicity, active and passive smoking, alcohol, medicatio n use, and folate status	4.5	Yes	Yes
(Hammoud et al., 2008) <sup>100</sup> /USA	472 men of subfertile couples	32.8 (±0.3)	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (progressive motile sperm count), and oligozoospermia (%)	The incidence of oligozoospermia increased with increasing BMI. The prevalence of a low progressively motile sperm count was also greater with increasing BMI.	ND/NA	4	Yes	No. Insufficie nt data
(Hofny et al., 2010)/ <sup>101</sup> /Egyp t	42 fertile men with obesity and 80 infertile oligozoosper mic men with obesity	Fertile=2 9.79 (±1.1); Infertile=2 9.35 (±0.9)	Prospecti ve (cross- sectional data)	BMI	Sperm quality (sperm count, total motility and normal morphology) and reproductive hormones (T, FSH, LH, PRL, and E2)	The BMI had significant positive correlation with abnormal sperm morphology, LH, serum leptin and significant negative correlation with sperm concentration, sperm motility, serum T.	ND/NA	4	Yes	No. Insufficie nt data
(Hofstra et al., 2008) <sup>102</sup> /Nethe rlands	160 men with obesity	43.3 ± 0.8	Cross- sectional	BMI	Total and calculated free testosterone (T and fT)	T and fT levels were inversely related to BMI. T was subnormal in 57.5% and free	Age	5	Yes	No. Lack of data in normal

						testosterone in 35.6% of the subjects. The group of men with IHH was more obese, had higher HbA1 C levels and had a 2.6 higher risk for cardiovascular disease. Decreased libido and erectile dysfunction were 7.1 and 6.7 times as common in IHH as in eugonadal men with obesity.				weight individual s
(Jensen et al., 2004) <sup>25</sup> /Denm ark	1,558 young men	Mean age=19	Cross- sectional	BMI	Sperm quality (semen volume,sperm concentration and count, sperm motility, and sperm morphology), testis size and reproductive hormones (FSH, LH, SHBG, T, E2 and Inhibin B)	Men with a BMI <20 kg/m <sup>2</sup> had a reduction in sperm concentration and total sperm count of 28.1% and 36.4%, respectively, and men with a BMI >25 kg/m <sup>2</sup> had a reduction in sperm concentration and total sperm count of 21.6% and 23.9%, respectively, compared to men with BMI between 20-25 kg/m <sup>2</sup> . Serum T, SHBG, and inhibin B, all are lower with increasing BMI, whereas free androgen index and E2 increased with increasing BMI. Serum FSH was higher among slim men.	Age, abstinenc e time, smoking, time to semen analysis, research centre, diseases in reproduct ive organs, still in school, and cryptorchi dism	5	Yes	Yes
(Keskin et al., 2017) <sup>44</sup> /Turke y	454 men consulting for infertility	ND	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, sperm concentration, total and progressive motility, total progressive motile sperm count, normal morphology) and reproductive hormones (T, FSH, LH, PRL and E2)	There were no statistically significant differences in all variables between adiposity groups.	ND/NA	3.5	Yes	Yes
(Koloszár et al., 2005) <sup>45</sup> /Hunga ry	274 men with normozoospe rmia	26±4.9	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total motility and normal morphology) and reproductive hormones (T, FSH, LH, PRL, E2, and SHBG)	Sperm concentration was significantly lower in the group with obesity than in the following groups of BMI: 17- 20, 20-25 and 25-30. In the group with obesity, sperm count decreased with aging. It was concluded that obesity is associated with a lower sperm	ND/NA	4	Yes	Yes

						count in case of				
(Kort et al., 2006) <sup>103</sup> /Geor gia	520 men	26–45	Cross- sectional	BMI	Sperm quality (semen volume, sperm concentration, total motility, normal sperm morphology), and DNA fragmentation index	normozoospermia men. Linear regression revealed a significant and negative relationship between BMI and the total number of normal- motile sperm cells. ANOVA revealed a significant difference in the total number of normal-motile sperm cells among the different BMI categories. Linear regression revealed a significant and positive relation between BMI and DFI. Men presenting with a BMI >25 kg/m <sup>2</sup> had fewer chromatin-intact normal-motile	ND/NA	4	Yes	No. Insufficie nt data
(Lu et al., 2015) <sup>104</sup> /China	1,132 men with infertility	29.07 (±4.83)	Cross- sectional	BMI, WC, WHR and WHtR	Sperm quality (sperm count and concentration, total and progressive motility, normal morphology and total normal-progressively motile sperm count), and reproductive hormones (T, LH, FSH, E2 and SHBG)	sperm cells per ejaculate. BMI, WC, WHR and WHtR were positively related to sperm concentration, total sperm count, progressive motility, sperm motility and normal sperm morphology. BMI, WHR, WC and WHtR were negatively related to serum T and SHBG levels.	ND/NA	5	Yes	No. Non- WHO based BMI categorie s
(Luque et al., 2017) <sup>22</sup> /Argen tina	4,860 men of subfertile couples	18-65	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, total motility, vitality and normal morphology), reactive spermatozoa (HOS test) and spermatozoa with mature nuclei, and percentages of oligozoospermia, asthenozoospermia and teratozoospermia.	Sperm concentration, total sperm count, and total motility were significantly lower in the underweight and morbid obesity groups compared with normal weight, overweight and obese groups. Moreover, the percentage of morphologically normal spermatozoa was decreased in the morbid obesity group compared with the other groups. Men in the morbid obesity category had an increased risk (2.3- to 4.9- fold greater) of suffering oligozoospermia and teratozoospermia.	ND/NA	4	Yes	Yes
(Ma et al., 2019 <sup>34</sup> /China	3,966 sperm donors	28.5 (±5.5)	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total and progressive	Underweight was significantly associated with reduction in sperm concentration, total sperm number and total motile	Age, ethnicity, education ,	4	Yes	Yes

					motility, and total motile sperm count)	sperm count. Overweight was significantly associated with reduction in semen volume, total sperm number and total motile sperm count.	smoking, marital status, abstinenc e period and season			
(Macdonald et al., 2013) <sup>105</sup> /New Zealand	511 men attending fertility clinic	36.8	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total sperm motility, normal sperm morphology) and reproductive hormones (T, LH, FSH, E2, and SHBG)	No statistically significant differences or correlation between sperm concentration and total sperm count in relation to BMI were reported. Normal sperm morphology increased with increasing BMI. The multiple linear regression analysis showed that BMI had a marginally significant effect on normal sperm morphology. Statistically significant relationships between BMI and total testosterone, and SHBG were reported. No significant relationships were found for FSH, LH, and E2.	ND/NA	4.5	Yes	No. Insufficie nt data
(Magnusdottir et al., 2005)/ <sup>106</sup> /Icela nd	25 men with poor semen quality, 20 men with normal semen quality and idiopathic subfertility and 27 men with normal semen	30-45	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, progressive motility, and progressively motile sperm count)	Men with poor semen quality were three times more likely to be obese than men with normal semen quality. There was also a significant negative correlation between semen quality parameters and BMI among men with normal semen quality.	ND/NA	4	Yes	No. Insufficie nt data
(Martini et al., 2010) <sup>47</sup> /Argen tina	794 men of subfertile couples	34.9 (±0.2)	Prospecti ve (cross- sectional data)	BMI	Sperm quality (semen volume, sperm concentration, total and progressive motility, normal morphology, and viability), reactive spermatozoa (HOS test), nuclear maturity, and levels of seminal T.	Multivariate analysis showed a negative association between BMI and total and rapid motility. No associations were found between BMI and sperm concentration, semen volume, normal morphology, reactive spermatozoa, nuclear maturity or seminal T levels.	ND/NA	4	Yes	Yes
(Oliveira et al., 2018) <sup>46</sup> /Brazil	1,824 men	37.9 ± 6.6	Cross- sectional	BMI	Sperm quality (semen volume, total sperm count and	High BMI was negatively associated with sperm concentration, vitality, motility	ND/NA	4.5	Yes	Yes

					concentration, vitality, motile sperm, and normal sperm morphology), the percentages of sperm DNA, sperm chromatin packaging/ underprotamination, mitochondrial damage and apoptosis	and morphology. Conversely, high BMI was not associated with impaired sperm DNA integrity, as assessed by DNA fragmentation, nor sperm protamination and sperm apoptosis. Increased BMI was associated with increased spermatozoa mitochondrial damage.				
(Ozdemir et al., 2016) <sup>107</sup> /Turke y	257 men with infertility	22-42	Prospecti ve (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, progressive motility, total progressively motile sperm count, and nomal morphology), and reproductive hormones (T, FSH, LH, E2, PRL, and TSH)	Semen volume was significantly higher in individuals with obesity compared with individuals without obesity. Serum T and T/E2 ratio were statistically significantly lower in the obese group. Serum E2 levels were significantly higher in individuals with obesity compared with individuals without obesity.	ND/NA	4	Yes	No. Lack of data in normal weight individual s
(Pauli et al., 2008) <sup>56</sup> /USA	87 adult men	19–48	Prospecti ve (cross- sectional data)	BMI and skinfold thicknes s	Sperm quality (semen volume, sperm concentration, total motility, and normal morphology) and reproductive hormones (inhibin B, FSH, LH, T, and fT)	There was no correlation between BMI or skinfold thickness and semen parameters. BMI was negatively correlated with T, FSH, and inhibin B levels and were positively correlated with E2 concentrations. Testosterone levels also negatively correlated with skinfold thickness. Inhibin B level correlated significantly with sperm motility.	ND/NA	3.5	Yes	No. Insufficie nt data
(Qin et al., 2007) <sup>48</sup> /China	990 fertile men	38.9(±9.7 )	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total motility and normal morphology), and reproductive hormones (T, LH, FSH, and E2)	Men with underweight had low sperm concentration, total sperm count and percentage of normal sperm forms compared with men with men with normal weight. Reproductive hormones cannot explain the association between BMI and semen quality.	Age, study centre, diseases in reproduct ive organs, smoking, alcohol intake, period of abstinenc e and reproduct	4	Yes	Yes

							ive hormone s			
(Ramaraju et al., 2017) <sup>108</sup> /India	1,285 men attending fertility clinic	34.5 (±4.7)	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, total and progressive motility, and normal morphology), oligozoospermia, teratozoospermia and asthenozoospermia.	Men with obesity had lower semen volume, number, concentration and motility compared with men with men with normal weight.	Age, smoking, and diabetes status	5	Yes	No. Lack of data in normal weight individual s
(Ramírez et al., 2020) <sup>23</sup> /Argen tina	20,563 men of subfertile couples	35.75(±6. 16)	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, total motility and rapid motility, and normal morphology), and HOST test.	Having a BMI below 20 kg/m2 or above 32 kg/m2 might be detrimental for semen quality, and this negative association is more obvious in morbid obesity. They propose a recategorization of the BMI to achieve andrological predictive power. The smallest summatory in sperm abnormalities were found at BMI=27kg/m <sup>2</sup> .	ND/NA	5	Yes	Yes
(Ramlau- Hansen et al., 2010) <sup>109</sup> /Denm ark	347 men	16-19	Retrospe ctive (cross- sectional data)	BMI, birth weight	Sperm quality (semen volume, sperm count and concentration, vitality, total motility, and normal morphology), and reproductive hormones (SHBG, T, FSH, LH, and inhibin B)	Neither childhood BMI, birth weight, nor adulthood BMI was significantly associated with semen quality. Men with the 33% highest childhood BMI had 15% lower SHBG, 8% lower T, and 16% lower FSH than men with the 33% lowest childhood BMI. Men with high adulthood BMI had 14% lower T, 9% lower inhibin B, 31% lower SHBG, and 20% higher E2 than men with low adulthood BMI.	Season, history of diseases of the reproduct ive organs, smoking, maternal smoking during pregnanc y, abstinenc e time, spillage during collection , time to semen analysis	4	Yes	No. Non- WHO based BMI categorie s
(Relwani et al., 2011)/ <sup>110</sup> /USA	530 men attending fertility clinics	18-50	Prospecti ve (cross- sectional data)	BMI	Sperm quality (semen volume, sperm concentration, total motility, normal morphology), and	No consistent relationships were reported between BMI and sperm concentration, motility, or morphology, although the testosterone	ND/NA	4	Yes	No. Non- WHO based BMI

					reproductive hormones (T, FSH, LH, E2, and SHBG)	levels trended downward with increasing BMI.				categorie s
(Rufus et al., 2018) <sup>111</sup> /Niger ia	206 men of subfertile couples	≥20	Cross- sectional	BMI	Sperm quality (sperm concentration and count, total motility, and normal morphology), oligozoospermia, azoospermia, asthenozoospermia, teratozoospermia, and oligoasthenoteratozoo spermia.	There was no statistically significant difference in the semen quality as well as the pattern of semen parameter abnormalities between males with normal and elevated BMI.	ND/NA	4	Yes	No. Insufficie nt data
(Rybar et al., 2011) <sup>49</sup> /Czech Republic	153 men of subfertile couples	31.5 (±6.2)	Cross- sectional	BMI	Sperm quality (semen volume, sperm concentration, total motility and normal morphology) and sperm chromatin integrity	No consistent relationships were observed between BMI and semen parameters or sperm chromatin integrity.	ND/NA	4	Yes	Yes
(Sallmén et al., 2006) <sup>112</sup> /Finla nd	1,329 couples with an attempt at pregnancy	25-54	Cross- sectional	BMI	Prevalence of Infertility	Adjusting for potential confounders, a 3-unit increase in male BMI was associated with infertility risk.	Age, smoking, alcohol, solvent and pesticide exposure , state of residence	4.5	Yes	No. Insufficie nt data
(Sekhavat and Moein, 2010) <sup>113</sup> /Iran	852 normal, healthy men	25-50 y	Cross- sectional	BMI	Sperm quality (sperm count and concentration, total motility, and normal morphology)	Sperm concentration of men with overweight and obesity was lower than subjects with normal BMI. Total sperm count and sperm motility in men with overweight and obesity were significantly lower than men with normal BMI. Sperm morphology in study adiposity groups was similar. The results revealed a significant inverse correlation between BMI and sperm parameters.	ND/NA	4	Yes	No. Insufficie nt data
(Shayeb et al., 2011) <sup>50</sup> /United Kingdom	2,035 men	25-40	Cross- sectional	BMI	Sperm quality (semen volume, sperm concentration, total motility, and normal morphology)	Men with obesity are more likely to have lower semen volume and fewer morphologically normal spermatozoa than men with normal BMI	Age, smoking, alcohol intake, abstinenc e period	5	Yes	Yes

							and social deprivatio n			
(Stewart et al., 2009) <sup>114</sup> /Austr alia	225 men	21–46	Cross- sectional	BMI	Sperm quality (sperm count and concentration) and reproductive hormones (FSH, LH, SHBG, T, and Inhibin B)	Compared with those with BMI < 30, subjects with obesity had significantly lower total sperm count and inhibin B but not FSH.	ND/NA	4	Yes	No. Only hormonal data.
(Taha et al., 2016) <sup>51</sup> /Egypt	165 fertile men	32-44	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, total and progressive motility, normal morphology, and vitality), seminal reactive oxygen species (ROS), and sperm DNA fragmentation	Fertile men with obesity had significantly lower sperm concentration, progressive sperm motility and sperm normal morphology, with significantly higher seminal ROS and sperm DNA fragmentation compared with fertile normal-weight men and overweight men. BMI was negatively correlated with sperm concentration, progressive sperm motility, normal sperm morphology, sperm vitality, but positively correlated with sperm DNA fragmentation percentage and seminal ROS. Increased BMI was found to affect semen parameters negatively even in fertile men.	ND/NA	4	Yes	Yes
(Thomsen et al., 2014) <sup>24</sup> /Swed en	612 men of subfertile couples	32.8 (±5.1)	Cross- sectional	BMI	Sperm quality (sperm count and concentration, progressive and total sperm motility), and sperm DNA fragmentation (SCSA)	No statistically significant effect of male BMI was seen on conventional semen parameters or on SCSA-results.	ND/NA	4	Yes	Yes
(Tsao et al., 2015) <sup>115</sup> /Taiwa n	7630 healthy male individuals	≥18	Cross- sectional	BMI, WC, HC, WHR, WHtR and BF%	Sperm quality (sperm concentration, total and progressive motility, and normal morphology)	Total sperm motility, progressive motility, normal sperm morphology and sperm concentration showed a statistically linear decline with increasing BMI. Sperm concentration showed a significantly negatively linear association with BMI, and normal sperm morphology showed an inverse	Age, triglycerid e, cholester ol, C- Reactive Protein, prolactin and smoking duration	4.5	Yes	No. Non- WHO based BMI categorie s

						association with BMI and waist-to-height ratio. The prevalence of abnormal total sperm motility, progressive motility, and normal sperm concentration increased with increasing age. Lower normal sperm morphology and sperm concentration were associated with increasing body adiposity. No relationship between obesity and sperm motility was identified.				
(Vignera et al., 2012) <sup>52</sup> /Italy	150 men (general population)	20-48	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, progressive motility, vitality and nomal morphology), reproductive hormones (T, FSH, LH, E2, and SHBG), mitochondrial membrane potential, chromatin compactness, and sperm DNA fragmentation.	Men with overweight and obesity had significantly lower sperm progressive motility and normal forms than controls. They also had a significantly higher percentage of spermatozoa with low mitochondrial membrane potential. Men with obesity, but not men with overweight showed a lower percentage of viable spermatozoa. A significant increased percentage of spermatozoa with abnormal chromatin compactness was found in both, men with overweight and men with obesity, whereas only men with obesity had a significantly higher number of spermatozoa with DNA fragmentation compared with controls.	ND/NA	4	Yes	Yes
(Wang et al., 2017) <sup>53</sup> /China	2,384 men	29-36	Retrospe ctive (cross- sectional data)	BMI	Sperm quality (semen volume, sperm count and concentration, total and progressive motility, and normal morphology)	The results clearly indicated lower sperm quality (total sperm count, sperm concentration, motile sperm, relative amounts of type A motility, and progressive motility sperm) in men with overweight and obesity than in those with normal BMI.	ND/NA	4.5	Yes	Yes
(Wen-Hao et al., 2015) <sup>116</sup> /China	617 men with infertility	32.0 (±5.2)	Cross- sectional	BMI	Sperm quality (semen volume, sperm count and concentration, progressive motility,	BMI was negatively correlated with sperm motility, although they did not correlate with semen volume, total sperm	ND/NA	3.5	Yes	No. Insufficie nt data

(Winters et al., 2006) <sup>117</sup> /USA	74 African American and Caucasian young, and 48 African American and Caucasian boys	18-24 and 5-9 (in two different cohorts)	Cross- sectional	BMI	and nomal morphology) Reproductive hormones (T, fT, Inhibin-B, SHBG, E, LH, FSH)	number, concentration, and rate of sperm with normal morphology. Inhibin-B levels declined with increasing obesity in young adult men. Sex hormone– binding globulin and total testosterone, but not free testosterone, were also lower with increasing BMI; serum follicle-stimulating hormone and luteinizing hormone levels were unaffected by obesity. In prepubertal boys, by contrast,	Age	3.5	Yes	No. Only hormonal data.
(Yamaçake et al., 2016) <sup>118</sup> /Brasil	875 men who were screened for prostate cancer	61.0 (±6.0)	Cross- sectional	BMI	Reproductive hormones (T, fT, FSH, LH, and SHBG)	Patients with obesity had lower levels of T, fT, and SHBG compared to underweight or normal weight patients.	ND/NA	3.5	Yes	No. Insufficie nt data

Abbreviations: Anti-Müllerian hormone (AMH), Analysis of variance (ANOVA), Area under the curve (AUC), Assisted reproductive technology (ART), Body fat (BF), Body mass index (BMI), DNA fragmentation index (DFI), estradiol (E2), follicle-stimulating hormone (FSH), free testosterone (fT), Hemoglobin A1c (HbA1c), Hypoosmotic Swelling Test (HOS), human chorionic gonadotropin (hCG), human prolactin (hPRL), Hyaluronan-binding assay (HA), insulin resistance insulin-like factor 3 (INSL3), isolated hypogonadotropic hypogonadism (IHH), luteinizing hormone (LH), Metabolic syndrome (MS), No data/No adjustment (ND/NA), obstructive sleep apnea (OSA), sex hormone-binding globulin (SHBG), testosterone (T), thyroid stimulating hormone (TSH), time to pregnancy (TTP), very-low-energy diet (VLED), waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR).

**Table 2.** Summary of studies reporting associations between BMI and sperm DNA fragmentation and reproductive hormones. Data and measurements are highly heterogeneous, precluding meta-analysis. Table is organized in descending order by year of publication.

	Association bet	tween BMI cate	egories (overwei	ight and obesity	) and sperm Di	NA fragmentat	ion and reprod	uctive hormona	al parameters	
Study	Sperm DNA fragmentation	Inhibin B	Total testosterone	Free testosterone	Sex hormone- binding globulin	Prolactin	Estradiol	Follicle- stimulating hormone	Luteinizing hormone	Testosterone/ Luteinizing hormone ratio
(Jensen et al., 2004) <sup>25</sup>	ND	Negative	Negative	ND	Negative	ND	Positive	None	None	ND
(Fejes et al., 2005) <sup>97</sup>	ND	ND	Negative	ND	Negative	None	ND	ND	ND	ND
(Kort et al., 2006) <sup>103</sup>	Positive	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Winters et al., 2006) <sup>117</sup>	ND	Negative	Negative	None	Negative	ND	None	None	None	ND
(Aggerholm et al., 2008) <sup>26</sup>	ND	Negative	Negative	ND	Negative	ND	None	None	None	ND
(Hofstra et al. 2008) <sup>102</sup>	ND	ND	Negative	Negative	None	ND	None	None	None	ND
(Pauli et al., 2008) <sup>56</sup>	ND	Negative	Negative	None	ND	ND	Positive	Negative	None	ND
(Foresta et al., 2009) 98	ND	ND	Negative	Negative	Negative	ND	Positive	None	None	ND
(Stewart et al., 2009) <sup>114</sup>	ND	Negative	Negative	ND	Negative	ND	ND	None	ND	ND
(Chavarro et al., 2010) <sup>38</sup>	ND	Negative	Negative	ND	Negative	None	Positive	None	None	None
(Hofny et al., 2010) <sup>101</sup>	ND	ND	Negative	ND	ND	Positive	None	None	Positive	ND
(Ramlau- Hansen et al., 2010) <sup>109</sup>	ND	Negative	Negative	ND	Negative	ND	Positive	None	None	ND
(Rybar et al., 2011) <sup>49</sup>	None	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Vignera et al., 2012) <sup>52</sup>	ND	ND	None	ND	Positive	ND	Positive	None	None	ND
(Dupont et al., 2013) <sup>54</sup>	Positive	ND	ND	ND	ND	ND	ND	ND	ND	ND

(Hajshafiha et al., 2013) <sup>99</sup>	ND	ND	Negative	ND	Negative	None	Negative	None	None	ND
(MacDonald et al., 2013) <sup>105</sup>	ND	ND	Negative	Negative	Negative	ND	None	None	None	ND
(Al-Ali et al., 2014) <sup>89</sup>	ND	ND	Negative	ND	ND	None	ND	None	Negative	ND
(Eisenberg et al., 2014) <sup>40</sup>	None	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Thomsen et al., 2014) <sup>24</sup>	None	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Bandel et al., 2015) <sup>37</sup>	Negative	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Ehala- Aleksejev and Punab, 2015) <sup>39</sup>	ND	ND	Negative	ND	Negative	ND	None	None	None	ND
(Hadjkacem Loukil et al., 2015) <sup>42</sup>	ND	ND	None	ND	ND	None	ND	None	None	ND
(Lu et al., 2015) <sup>104</sup>	ND	ND	Negative	ND	Negative	ND	None	None	None	ND
(Alshahrani et al., 2016) <sup>55</sup>	ND	ND	None	ND	ND	None	ND	None	None	ND
(Andersen et al., 2016) <sup>33</sup>	None	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Bieniek et al., 2016) <sup>92</sup>	ND	ND	Negative	ND	ND	None	Positive	ND	None	ND
(Ozdemir et al., 2016) <sup>107</sup>	ND	ND	Negative	ND	ND	ND	Positive	None	None	ND
(Taha et al., 2016) <sup>51</sup>	Positive	ND	ND	ND	ND	ND	ND	ND	ND	ND
(Yamaçake et al., 2016) <sup>118</sup>	ND	ND	Negative	Negative	Negative	ND	ND	None	None	ND
(Keskin et al., 2017) <sup>44</sup>	ND	ND	Positive	ND	ND	Positive	None	None	None	ND
(Amjad et al., 2019) <sup>91</sup>	ND	ND	Negative	ND	Negative	ND	ND	Negative	Negative	ND
(Ferigolo et al., 2019) <sup>32</sup>	Positive	ND	ND	ND	ND	ND	ND	ND	ND	ND

Abbreviations: ND, No data.

## FIGURE CAPTIONS

Figure 1. Flow chart of the literature search and selection process.

**Figure 2**. **A-G.** Summary associations (combined effect size) between BMI categories and each seminogram parameter. **H.** Plot showing seminogram parameters that are associated with BMI class by using statistical significance (-log10 p-value) versus combined effect size on the y-axis and x-axis, respectively. Colored shapes represent significant associations. The horizontal dotted line represents the significance threshold. The vertical dotted line represents an ES of 0, where anything to the left of the line shows a negative change, and anything to the right of the line shows a positive change.

## SUPPLEMENTAL TABLES

Supplemental Table 1. PICOS criteria for inclusion and exclusion of studies.

**Supplemental Table 2.** Sensitivity analysis data by systematic exclusion of one study at a time (only available for analyses of more than 5 studies).

## APPENDIX

**Appendix S1.** Search strategy for the literature published between the earliest available online indexing year and June 2019 in MEDLINE-Pubmed and EMBASE databases.

## SUPPLEMENTAL FIGURE CAPTIONS

**Supplemental Figure 1.** Association between underweight BMI and normal weight in semen volume.

**Supplemental Figure 2.** Association between overweight BMI and normal weight in semen volume and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 3.** Association between obese (or obese I) BMI and normal weight in semen volume and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

Supplemental Figure 4. Association between obese II (or more) BMI and normal weight in semen volume.

Supplemental Figure 5. Association between obese III BMI and normal weight in semen volume.

Supplemental Figure 6. Association between underweight BMI and normal weight in sperm count.

**Supplemental Figure 7.** Association between overweight BMI and normal weight in sperm count and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 8.** Association between obese (or obese I) BMI and normal weight in semen volume and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

Supplemental Figure 9. Association between obese II (or more) BMI and normal weight in sperm count.

Supplemental Figure 10. Association between obese III BMI and normal weight in sperm count.

**Supplemental Figure 11.** Association between underweight BMI and normal weight in sperm concentration.

**Supplemental Figure 12.** Association between overweight BMI and normal weight in sperm concentration and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 13.** Association between obese (or obese I) BMI and normal weight in sperm concentration and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 14.** Association between obese II (or more) BMI and normal weight in sperm concentration.

Supplemental Figure 15. Association between obese III BMI and normal weight in sperm concentration.

Supplemental Figure 16. Association between overweight BMI and normal weight in sperm vitality.

**Supplemental Figure 17.** Association between obese (or obese I) BMI and normal weight in sperm vitality.

**Supplemental Figure 18.** Association between obese II (or more) BMI and normal weight in sperm vitality.

Supplemental Figure 19. Association between obese III BMI and normal weight in sperm vitality.

**Supplemental Figure 20.** Association between underweight BMI and normal weight in sperm total motility.

**Supplemental Figure 21.** Association between overweight BMI and normal weight in sperm total motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 22.** Association between obese (or obese I) BMI and normal weight in sperm total motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 23.** Association between obese II (or more) BMI and normal weight in sperm total motility.

**Supplemental Figure 24.** Association between obese III BMI and normal weight in sperm total motility.

**Supplemental Figure 25.** Association between underweight BMI and normal weight in sperm progressive motility.

**Supplemental Figure 26.** Association between overweight BMI and normal weight in sperm progressive motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 27.** Association between obese (or obese I) BMI and normal weight in sperm progressive motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 28.** Association between obese II (or more) BMI and normal weight in sperm progressive motility.

**Supplemental Figure 29.** Association between underweight BMI and normal weight in sperm normal morphology.

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**Supplemental Figure 30.** Association between overweight BMI and normal weight in sperm normal morphology and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 31.** Association between obese (or obese I) BMI and normal weight in sperm normal morphology and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 32.** Association between obese II (or more) BMI and normal weight in sperm normal morphology.

**Supplemental Figure 33.** Association between obese III BMI and normal weight in sperm normal morphology.

**Supplemental Figure 34.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between underweight BMI and normal weight in semen volume.

**Supplemental Figure 35.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in semen volume and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 36.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in semen volume and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 37.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between underweight BMI and normal weight in sperm count.

**Supplemental Figure 38.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm count and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 39.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm count and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 40.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between underweight BMI and normal weight in sperm concentration.

**Supplemental Figure 41.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm concentration and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 42.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm concentration and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

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**Supplemental Figure 43.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm vitality.

**Supplemental Figure 44.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm vitality.

**Supplemental Figure 45.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm total motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 46.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm total motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

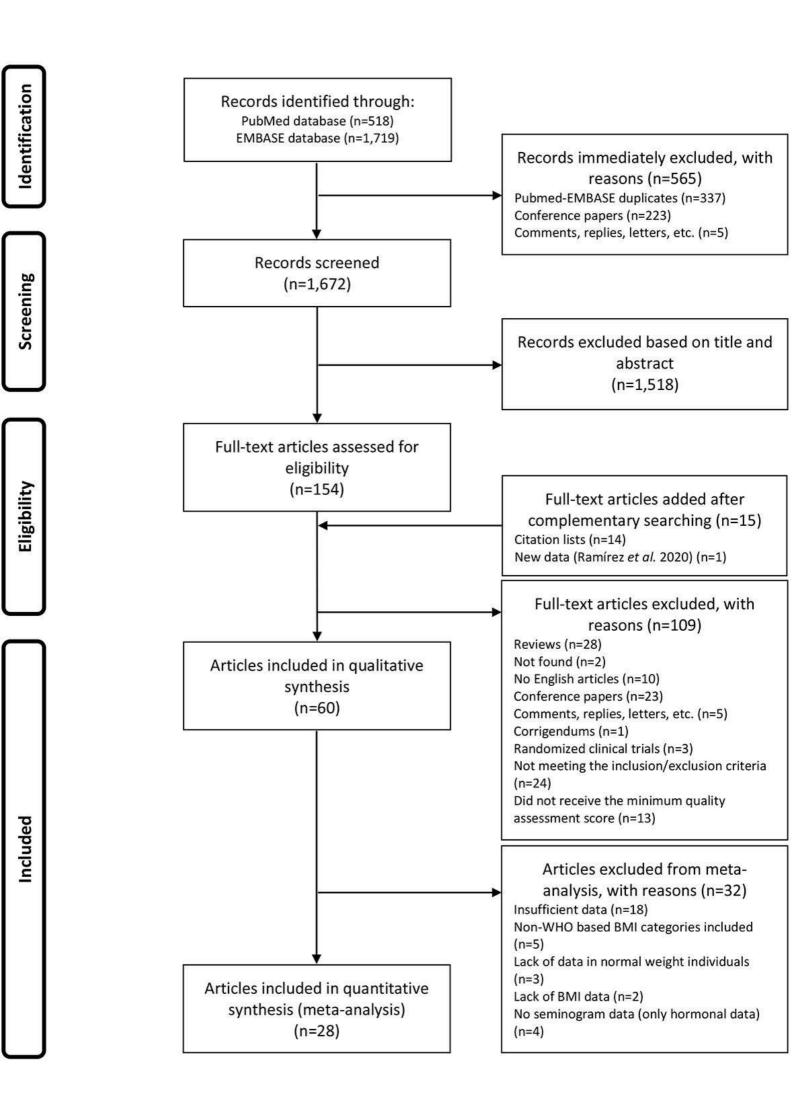
**Supplemental Figure 47.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm progressive motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

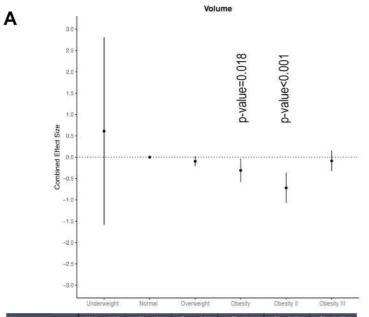
**Supplemental Figure 48.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm progressive motility and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

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**Supplemental Figure 49.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between overweight BMI and normal weight in sperm normal morphology and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

**Supplemental Figure 50.** Sensitivity analysis by changing meta-analysis models (random to fixed models) showing the association between obese (or obese I) BMI and normal weight in sperm normal morphology and corresponding Funnel plot and "trim and fill" test analyzing the heterogeneity of the studies.

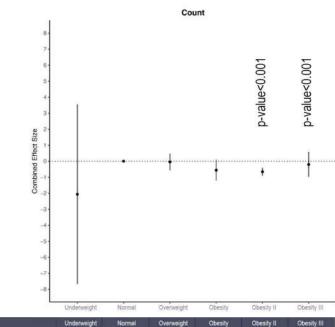




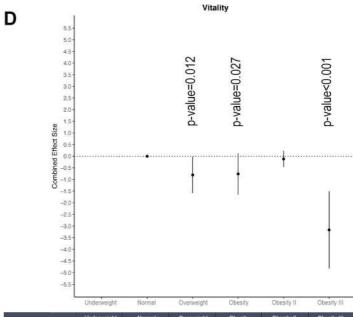
	Underweight	Normal	Overweight	Obesity	Obesity II	Obesity III
Studies	6	REF	20	18	3	3
Individuals	2687	REF	26580	3077	209	334
Model	Random	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	<0.001	REF	<0.001	<0.001	<0.001	0.139988105
Heterogeneity I <sup>2</sup>	99.18%	REF	86.28%	91.83%	97.43%	49.14%

Concentration С 9 8 į p-value=0.002 ł 14.1 Combined Effect Size -2 -3 -4 -5 -6 -7 -8 -9 Obesity III Underweight Overweight Obesity Obesity II Norma

	Underweight	Normal	Overweight	Obesity	Obesity II	Obesity III
Studies	6	REF	26	24	4	3
Individuals	2002	REF	27829	4011	281	334
Model	Random	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	<0.001	REF	<0.001	<0.001	0.014980764	0.271831679
Heterogeneity I <sup>2</sup>	99.59%	REF	98.24%	92.67%	71.34%	23.23%

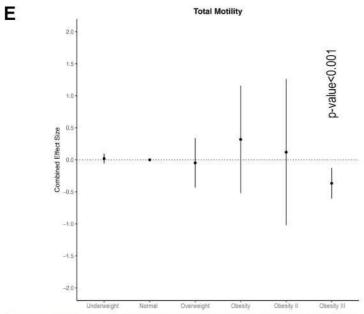


	Underweight	Normal	Overweight	Obesity	Obesity II	Obesity III
Studies	5	REF	16	15	4	2
Individuals	1970	REF	22956	3781	241	277
Model	Random	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	<0.001	REF	<0.001	<0.001	<0.001	0.109787231
Heterogeneity I <sup>2</sup>	99.62%	REF	98.87%	97.77%	94.83%	60.90%



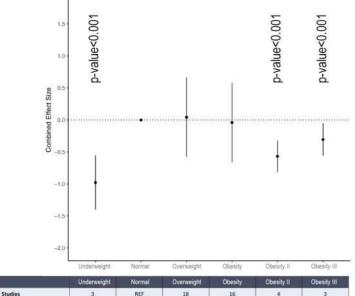
	a reasona pro-	Venerol ten	the cost of the pro-	a warden f	Contraction (1) (1)	Second 10
	Underweight	Normal	Overweight	Obesity	Obesity II	Obesity III
Studies	ND	REF	7	6	3	2
Individuals	ND	REF	7636	1561	201	90
Model	ND	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	ND	REF	<0.001	<0.001	<0.001	<0.001
Heterogeneity I <sup>2</sup>	ND	REF	99.71%	96.76%	85.67%	99.89%

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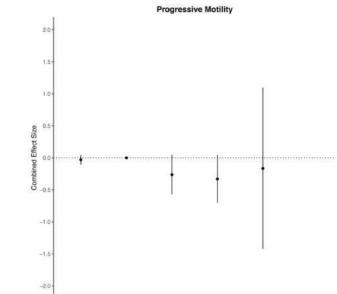


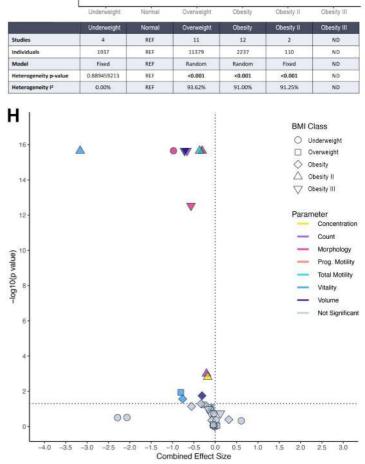
	onderneight	- Conservation	Stattangit	Cocony	D D D D I I I	o oconty in
	Underweight	Normal	Overweight	Obesity	Obesity II	Obesity III
Studies	4	REF	16	13	2	3
Individuals	1902	REF	25943	2943	137	333
Model	Fixed	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	<0.001	REF	<0.001	<0.001	<0.001	0.188021691
Heterogeneity I <sup>2</sup>	99.66%	REF	98.60%	98.56%	93.45%	40.16%

Normal Morphology



	onderweight	Normai	Overweight	Obeany	Obeany in	Obeany in
Studies	3	REF	18	16	4	3
Individuals	137	REF	18310	2229	240	302
Model	Fixed	REF	Random	Random	Fixed	Fixed
Heterogeneity p-value	<0.001	REF	<0.001	<0.001	<0.001	0.068353377
Heterogeneity I <sup>2</sup>	99.78%	REF	98.88%	96.03%	96.42%	62.73%





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Supplemental Table 1. Population, Intervention, Comparator Outcome, Study design

(PICOS) criteria for a systematically searched.

Patients	Well-defined fertile/infertile men.
Interventions	No treatments: Cross-sectional data or baseline data.
Comparators	Control group (fertile males).
Outcomes	Primary outcomes: Semen volume, ejaculate pH, total sperm count or concentration, sperm vitality, sperm motility (progressive or total motility), sperm morphology. Secondary outcomes: Acrosome resistance, sperm DNA fragmentation (SDF) or damage, sperm chromatin integrity (SCI), sperm reactive oxygen species (ROS), sperm aneuploidies, sperm function parameters, or hormonal levels.
Study design	Inclusion: Case-control, cross-sectional, observational prospective or retrospective studies. Exclusion: Animal or <i>in-vitro</i> studies, reviews, editorials, opinions, randomized clinical trial, and case-reports articles.

Removal of	ES	95% CI	P-value*	l² (%)	P-heterogeneity**	Comment				
		Se	emen volume – U	nderweight vs	normal weight					
Overall	0.61	(-1.59, 2.81)	0.47	99.2	<0.001	-				
Bandel et al. 2015 <sup>1</sup>	0.82	(-2.00, 3.64)	0.42	99.3	<0.001	-				
Belloc et al. 2014 <sup>2</sup>	0.81	(-2.02, 3.64)	0.43	99.3	<0.001	-				
Ma et al. 2019 <sup>3</sup>	0.76	(-2.10, 3.63)	0.46	99.3	<0.001	-				
Qin et al. 2007 <sup>4</sup>	-0.16	(-0.25, -0.06)	<0.001	5.2	0.37	Heterogeneity was explained and ES becomes significant				
Shayeb et al. 2011 <sup>5</sup>	0.76	(-2.09, 3.62)	0.46	99.3	<0.001	-				
Wang et al. 2017 <sup>6</sup>	0.75	(-2.12, 3.62)	0.47	99.3	<0.001	-				
Semen volume – Overweight vs normal weight										
Overall	-0.10	(-0.21, 0.02)	0.08	86.3	<0.001	-				
Alshahrani et al. 2016 <sup>7</sup>	-0.11	(-0.22, 0.00)	0.03	85.4	<0.001	Influential study, ES becomes significant				
Bandel et al. 2015 <sup>1</sup>	-0.10	(-0.23, 0.02)	0.08	86.8	<0.001	-				
Belloc et al. 2014 <sup>2</sup>	-0.10	(-0.23, 0.03)	0.10	86.9	<0.001	-				
Chavarro et al. 20108	-0.07	(-0.16, 0.03)	0.13	81.1	<0.001	-				
Ehala-Aleksejev et al. 2015 <sup>9</sup>	-0.10	(-0.22, 0.02)	0.09	87.0	<0.001	-				
Eisenberg et al. 2014 <sup>10</sup>	-0.09	(-0.21, 0.03)	0.11	86.9	<0.001	-				
Fariello et al. 2012 <sup>11</sup>	-0.10	(-0.22, 0.02)	0.09	87.0	<0.001	-				
Hammiche et al. 2012 <sup>12</sup>	-0.06	(-0.15, 0.02)	0.12	78.9	<0.001	-				
Jensen et al. 2004 <sup>13</sup>	-0.10	(-0.23, 0.02)	0.08	86.9	<0.001	-				
Keskin et al. 2017 <sup>14</sup>	-0.10	(-0.22, 0.03)	0.10	87.0	<0.001	-				
Luque et al. 2017 <sup>15</sup>	-0.09	(-0.22, 0.03)	0.12	86.4	<0.001	-				
Ma et al. 2019 <sup>3</sup>	-0.10	(-0.23, 0.03)	0.10	87.0	<0.001	-				
Martini et al. 201016	-0.10	(-0.22, 0.02)	0.09	87.0	<0.001	-				
Oliveira et al. 2018 <sup>17</sup>	-0.11	(-0.23, 0.02)	0.07	86.5	<0.001	-				
Qin et al. 2007 <sup>4</sup>	-0.10	(-0.23, 0.02)	0.08	86.9	<0.001	-				

**Supplemental Table 2.** Sensitivity analysis by systematic exclusion of one study at a time (only available for analyses of  $\geq 5$  studies)<sup>a</sup>.

Ramírez et al. 202018	-0.10	(-0.23, 0.03)	0.11	86.8	<0.001	- I
Rybar et al. 2011 <sup>19</sup>	-0.10	(-0.23, 0.03)	0.11	87.0	<0.001	
Shayeb et al. 2011 <sup>5</sup>	-0.10	(-0.22, 0.03)	0.10	86.7	<0.001	_
Vignera et al. 2012 <sup>20</sup>	-0.10	(-0.22, 0.02)	0.00	87.0	<0.001	
Wang et al. 2017 <sup>6</sup>	-0.10	(-0.22, 0.02) (-0.23, 0.02)	0.09	86.7	<0.001	-
Wally et al. 2017	-0.10	, , ,				-
• "	0.04				) vs normal weight	
Overall	-0.31	(-0.58, -0.03)	0.02	91.8	<0.001	-
Alshahrani et al. 2016 <sup>7</sup>	-0.32	(-0.61, -0.03)	0.02	92.3	<0.001	-
Bandel et al. 2015 <sup>1</sup>	-0.33	(-0.62, -0.03)	0.02	92.3	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.32	(-0.62, -0.03)	0.02	92.3	<0.001	-
Chavarro et al. 2010 <sup>8</sup>	-0.29	(-0.58, 0.00)	0.04	91.9	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	-0.24	(-0.48, 0.00)	0.04	89.8	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.27	(-0.56, 0.01)	0.04	91.3	<0.001	-
Fariello et al. 2012 <sup>11</sup>	-0.31	(-0.60, -0.02)	0.03	92.3	<0.001	-
Ferigolo et al. 2019 <sup>21</sup>	-0.31	(-0.60, -0.02)	0.02	92.3	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	-0.22	(-0.43, 0.00)	0.03	85.3	<0.001	-
Keskin et al. 201714	-0.32	(-0.61, -0.02)	0.02	92.3	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.33	(-0.62, -0.04)	0.02	92.0	<0.001	-
Martini et al. 2010 <sup>16</sup>	-0.32	(-0.62, -0.03)	0.02	92.3	<0.001	-
Oliveira et al. 201817	-0.33	(-0.62, -0.04)	0.02	92.1	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.32	(-0.61, -0.03)	0.02	92.3	<0.001	-
Rybar et al. 2011 <sup>19</sup>	-0.34	(-0.62, -0.06)	0.01	92.2	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	-0.32	(-0.61, -0.02)	0.02	92.3	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.33	(-0.61, -0.04)	0.02	92.3	<0.001	-
Wang et al. 2017 <sup>6</sup>	-0.33	(-0.62, -0.04)	0.02	92.1	<0.001	-
	-	S	perm count – Ur	nderweight vs r	ormal weight	
Overall	-2.07	(-7.68, 3.55)	0.31	99.6	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-2.53	(-10.63, 5.56)	0.32	99.7	<0.001	-
Ma et al. 2019 <sup>3</sup>	-2.56	(-10.66, 5.54)	0.32	99.7	<0.001	-

Qin et al. 2007 <sup>4</sup>	-0.10	(-0.33, 0.13)	0.18	44.0	0.15	Heterogeneity was explained
Shayeb et al. 2011 <sup>5</sup>	-2.61	(-10.62, 5.41)	0.30	99.7	<0.001	-
Wang et al. 2017 <sup>6</sup>	-2.62	(-10.65, 5.41)	0.30	99.7	<0.001	-
		S	Sperm count – O	verweight <i>vs</i> n	ormal weight	
Overall	-0.05	(-0.57, 0.47)	0.84	98.9	<0.001	-
Aggerholm et al. 2008 <sup>22</sup>	-0.02	(-0.59, 0.54)	0.92	98.9	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.03	(-0.58, 0.53)	0.92	98.9	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.05	(-0.61, 0.51)	0.85	98.9	<0.001	-
Chavarro et al. 20108	-0.02	(-0.58, 0.54)	0.94	98.9	<0.001	-
Dupont et al. 2013 <sup>24</sup>	-0.05	(-0.61, 0.51)	0.85	98.9	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	0.01	(-0.53, 0.55)	0.97	98.9	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.04	(-0.60, 0.52)	0.88	98.9	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	0.00	(-0.54, 0.55)	0.99	98.9	<0.001	-
Jensen et al. 2004 <sup>13</sup>	0.00	(-0.56, 0.55)	0.99	98.9	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.05	(-0.61, 0.51)	0.85	98.9	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.26	(-0.45, -0.07)	0.004	95.3	<0.001	Influential study, ES becomes significant
Ramírez et al. 202018	-0.05	(-0.62, 0.51)	0.84	98.9	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	-0.07	(-0.63, 0.49)	0.79	98.9	<0.001	-
Thomsen et al. 2014 <sup>25</sup>	-0.05	(-0.61, 0.51)	0.84	98.9	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.06	(-0.61, 0.50)	0.83	98.9	<0.001	-
Wang et al. 2017 <sup>6</sup>	-0.04	(-0.60, 0.53)	0.89	98.9	<0.001	-
		Spern	n count – Obesit	y (or obesity I)	vs normal weight	
Overall	-0.55	(-1.21, 0.11)	0.07	97.8	<0.001	-
Aggerholm et al. 200822	-0.66	(-1.33, 0.01)	0.03	97.4	<0.001	Influential study, ES becomes significant
Andersen et al. 2016 <sup>23</sup>	-0.58	(-1.29, 0.13)	0.08	97.9	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.59	(-1.31, 0.13)	0.08	97.9	<0.001	-
Chavarro et al. 20108	-0.53	(-1.24, 0.19)	0.11	97.8	<0.001	-
Dupont et al. 2013 <sup>24</sup>	-0.48	(-1.17, 0.21)	0.14	97.7	<0.001	-
Ehala-Aleksejev et al.	-0.49	(-1.18, 0.21)	0.13	97.8	<0.001	-

2015 <sup>9</sup>						
Eisenberg et al. 2014 <sup>10</sup>	-0.57	(-1.29, 0.14)	0.09	97.9	<0.001	-
Ferigolo et al. 2019 <sup>21</sup>	-0.59	(-1.30, 0.12)	0.07	97.9	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	-0.53	(-1.24, 0.18)	0.11	97.8	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.61	(-1.32, 0.11)	0.07	97.9	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.31	(-0.70, 0.09)	0.10	96.6	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	-0.63	(-1.33, 0.06)	0.048	97.6	<0.001	Influential study, ES becomes significant
Thomsen et al. 2014 <sup>25</sup>	-0.60	(-1.31, 0.11)	0.07	97.9	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.59	(-1.30, 0.12)	0.08	97.9	<0.001	-
Wang et al. 2017 <sup>6</sup>	-0.58	(-1.30, 0.14)	0.08	97.9	<0.001	-
		Spern	n concentration	- Underweight	vs normal weight	
Overall	-2.29	(-8.14, 3.56)	0.31	99.6	<0.001	-
Bandel et al. 20151	-2.77	(-10.36, 4.82)	0.31	99.7	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-2.73	(-10.35, 4.88)	0.32	99.7	<0.001	-
Ma et al. 2019 <sup>3</sup>	-2.76	(-10.40, 4.89)	0.32	99.7	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.05	(-0.24, 0.14)	0.45	44.4	0.126	Heterogeneity was explained
Shayeb et al. 2011 <sup>5</sup>	-2.71	(-10.33, 4.90)	0.32	99.7	<0.001	-
Wang et al. 2017 <sup>6</sup>	-2.81	(-10.40, 4.78)	0.30	99.7	<0.001	-
		Sper	m concentration	- Overweight	vs normal weight	
Overall	-0.01	(-0.34, 0.32)	0.96	98.2	<0.001	-
Aggerholm et al. 2008 <sup>22</sup>	0.01	(-0.34, 0.35)	0.98	98.3	<0.001	-
Alshahrani et al. 20167	-0.01	(-0.35, 0.34)	0.97	98.3	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.01	(-0.35, 0.34)	0.97	98.3	<0.001	-
Bandel et al. 2015 <sup>1</sup>	-0.01	(-0.35, 0.34)	0.97	98.3	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.01	(-0.35, 0.34)	0.96	98.3	<0.001	-
Chavarro et al. 20108	-0.02	(-0.36, 033)	0.92	98.3	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	0.03	(-0.30, 0.36)	0.85	98.3	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.04	(-0.38, 0.30)	0.81	98.3	<0.001	-
Fariello et al. 201211	0.00	(-0.34, 0.34)	1.00	98.3	<0.001	-

Hadjkacem-Loukil et al. 2015 <sup>26</sup>	0.01	(-0.33, 0.35)	0.96	98.3	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	0.05	(-0.28, 0.37)	0.77	98.1	<0.001	-
Jensen et al. 200413	0.02	(-0.32, 0.36)	0.89	98.2	<0.001	-
Keskin et al. 201714	-0.01	(-0.35, 0.33)	0.95	98.2	<0.001	-
Koloszar et al. 2005 <sup>27</sup>	0.00	(-0.35, 0.34)	0.99	98.3	<0.001	-
Luque et al. 2017 <sup>15</sup>	-0.01	(-0.36, 0.33)	0.95	98.3	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.01	(-0.36, 0.33)	0.95	98.3	<0.001	-
Martini et al. 201016	-0.01	(-0.35, 0.34)	0.96	98.3	<0.001	-
Oliveira et al. 201817	0.00	(-0.35, 0.34)	0.98	98.3	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.14	(-0.31, 0.02)	0.08	94.3	<0.001	-
Ramírez et al. 202018	-0.01	(-0.36, 0.33)	0.95	98.3	<0.001	-
Rybar et al. 2011 <sup>19</sup>	-0.01	(-0.35, 0.34)	0.96	98.3	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	0.00	(-0.35, 0.34)	0.98	98.3	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.01	(-0.35, 0.33)	0.96	98.3	<0.001	-
Thomsen et al. 2014 <sup>25</sup>	-0.01	(-0.35, 0.34)	0.97	98.3	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.01	(-0.35, 0.33)	0.96	98.3	<0.001	-
Wang et al. 2017 <sup>6</sup>	0.01	(-0.34, 0.35)	0.97	98.3	<0.001	-
		Sperm co	ncentration - Ob	besity (or obesi	ty I) vs normal weig	ht
Overall	-0.08	(-0.30, 0.14)	0.45	92.7	<0.001	-
Aggerholm et al. 2008 <sup>22</sup>	-0.11	(-0.33, 0.12)	0.33	92.2	<0.001	-
Alshahrani et al. 20167	-0.08	(-0.31, 0.15)	0.47	93.0	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.09	(-0.32, 0.14)	0.43	93.0	<0.001	-
Bandel et al. 20151	-0.09	(-0.32, 0.14)	0.44	93.0	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.08	(-0.31, 0.15)	0.48	93.0	<0.001	-
Chavarro et al. 20108	-0.11	(-0.33, 0.11)	0.30	92.5	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	-0.06	(-0.28, 0.17)	0.59	92.8	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.11	(-0.34, 0.11)	0.28	92.4	<0.001	-
Fariello et al. 201211	-0.06	(-0.29, 0.16)	0.56	92.9	<0.001	-
Ferigolo et al. 2019 <sup>21</sup>	-0.08	(-0.31, 0.15)	0.45	93.0	<0.001	-

Hadjkacem-Loukil et al.	0.00	(0.00.0.14)	0.44		0.004	
2015 <sup>26</sup>	-0.09	(-0.32, 0.14)	0.41	93.0	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	-0.01	(-0.18, 0.16)	0.91	89.5	<0.001	-
Keskin et al. 2017 <sup>14</sup>	-0.09	(-0.32, 0.15)	0.45	93.0	<0.001	-
Koloszar et al. 200527	-0.05	(-0.28, 0.17)	0.63	92.6	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.09	(-0.32, 0.14)	0.42	92.8	<0.001	-
Martini et al. 2010 <sup>16</sup>	-0.08	(-0.32, 0.15)	0.45	93.0	<0.001	-
Oliveira et al. 201817	-0.06	(-0.29, 0.17)	0.57	92.1	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.11	(-0.33, 0.11)	0.30	92.8	<0.001	-
Rybar et al. 2011 <sup>19</sup>	-0.09	(-0.32, 0.14)	0.41	93.0	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	-0.10	(-0.33, 0.13)	0.37	92.3	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.06	(-0.29, 0.16)	0.56	92.9	<0.001	-
Thomsen et al. 2014 <sup>25</sup>	-0.09	(-0.32, 0.15)	0.44	93.0	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.08	(-0.31, 0.15)	0.48	93.0	<0.001	-
Wang et al. 2017 <sup>6</sup>	-0.07	(-0.30, 0.16)	0.55	92.4	<0.001	-
		S	perm vitality – C	Overweight <i>vs</i> n	ormal weight	
Overall	-0.81	(-1.59, -0.03)	0.01	99.7	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.89	(-1.82, 0.05)	0.02	99.8	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.94	(-1.82, -0.05)	0.006	99.5	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.69	(-1.60, 0.21)	0.049	99.8	<0.001	-
Luque et al. 2017 <sup>15</sup>	-0.56	(-1.28, 0.15)	0.04	96.8	<0.001	-
Martini et al. 2010 <sup>16</sup>	-0.93	(-1.83, -0.03)	0.008	99.8	<0.001	-
Oliveira et al. 2018 <sup>17</sup>	-0.91	(-1.83, 0.01)	0.01	99.8	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.70	(-1.61, 0.21)	0.049	99.8	<0.001	-
		Sperm	vitality – Obesi	ity (or obesity I)	vs normal weight	
Overall	-0.76	(-1.65, 0.13)	0.03	96.8	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.86	(-1.97, 0.24)	0.03	97.4	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.91	(-2.01, 0.18)	0.02	96.3	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.47	(-1.21, 0.28)	0.08	92.4	<0.001	-
Martini et al. 2010 <sup>16</sup>	-0.89	(-2.00, 022)	0.03	97.4	<0.001	-

Oliveira et al. 201817	-0.84	(-2.01, 0.33)	0.046	97.3	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.59	(-1.58, 0.40)	0.10	96.8	<0.001	Influential study, ES becomes non-significant
		Spei	rm total motility	– Overweight v	s normal weight	
Overall	-0.05	(-0.43, 0.34)	0.79	98.6	<0.001	-
Aggerholm et al. 2008 <sup>22</sup>	-0.12	(-0.50, 0.26)	0.51	98.0	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.05	(-0.47, 0.37)	0.80	98.7	<0.001	-
Chavarro et al. 2010 <sup>8</sup>	-0.11	(-0.50, 0.27)	0.53	98.6	<0.001	-
Dupont et al. 2013 <sup>24</sup>	0.04	(-0.32, 0.40)	0.81	98.5	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	-0.09	(-0.49, 0.31)	0.63	98.7	<0.001	-
Jensen et al. 2004 <sup>13</sup>	-0.05	(-0.47, 0.37)	0.79	98.7	<0.001	-
Keskin et al. 2017 <sup>14</sup>	-0.06	(-0.47, 0.35)	0.76	98.7	<0.001	-
Luque et al. 2017 <sup>15</sup>	-0.05	(-0.47, 0.37)	0.79	98.7	<0.001	-
Ma et al. 2019 <sup>3</sup>	-0.05	(-0.47, 0.36)	0.78	98.7	<0.001	-
Martini et al. 2010 <sup>16</sup>	-0.05	(-0.46, 0.37)	0.81	98.7	<0.001	-
Oliveira et al. 2018 <sup>17</sup>	-0.04	(-0.46, 0.38)	0.84	98.7	<0.001	-
Qin et al. 2007 <sup>4</sup>	0.08	(-0.23, 0.38)	0.59	97.7	<0.001	-
Ramírez et al. 2020 <sup>18</sup>	-0.05	(-0.47, 0.37)	0.80	98.7	<0.001	-
Rybar et al. 2011 <sup>19</sup>	-0.04	(-0.46, 0.37)	0.82	98.7	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	-0.06	(-0.47, 0.36)	0.77	98.7	<0.001	-
Thomsen et al. 2014 <sup>25</sup>	-0.05	(-0.47, 0.37)	0.79	98.7	<0.001	-
		Sperm to	tal motility – Ob	esity (or obesit	y I) vs normal weigh	t
Overall	0.32	(-0.52, 1.16)	0.41	98.6	<0.001	-
Aggerholm et al. 2008 <sup>22</sup>	0.19	(-0.68, 1.06)	0.63	97.8	<0.001	-
Belloc et al. 2014 <sup>2</sup>	0.36	(-0.56, 1.28)	0.39	98.6	<0.001	-
Chavarro et al. 2010 <sup>8</sup>	0.28	(-0.64, 1.20)	0.50	98.7	<0.001	-
Dupont et al. 2013 <sup>24</sup>	0.55	(-0.16, 1.26)	0.09	98.4	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	0.23	(-0.66, 1.13)	0.57	98.6	<0.001	-
Keskin et al. 2017 <sup>14</sup>	0.34	(-0.58, 1.26)	0.42	98.7	<0.001	-

Ma et al. 2019 <sup>3</sup>	0.35	(-0.57, 1.28)	0.40	98.7	<0.001	-
Martini et al. 201016	0.37	(-0.55, 1.28)	0.38	98.7	<0.001	-
Oliveira et al. 201817	0.39	(-0.53, 1.30)	0.35	98.6	<0.001	-
Qin et al. 2007 <sup>4</sup>	0.07	(-0.61, 0.75)	0.82	98.3	<0.001	-
Rybar et al. 2011 <sup>19</sup>	0.35	(-0.57, 1.26)	0.41	98.7	<0.001	-
Shayeb et al. 2011 <sup>5</sup>	0.31	(-0.61, 1.24)	0.46	98.7	<0.001	-
Thomsen et al. 2014 <sup>25</sup>	0.35	(-0.57, 1.27)	0.41	98.7	<0.001	-
		Sperm p	progressive moti	lity – Overweig	ht vs normal weight	
Overall	-0.26	(-0.57, 0.05)	0.06	93.6	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.25	(-0.58, 0.08)	0.09	94.1	<0.001	-
Bandel et al. 20151	-0.31	(-0.65, 0.03)	0.04	94.2	<0.001	Influential study, ES becomes significant
Belloc et al. 2014 <sup>2</sup>	-0.35	(-0.72, 0.02)	0.04	94.3	<0.001	Influential study, ES becomes significant
Fariello et al. 201211	-0.24	(-0.58, 0.10)	0.11	93.8	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	-0.24	(-0.58, 0.10)	0.12	93.5	<0.001	-
Keskin et al. 2017 <sup>14</sup>	-0.30	(-0.64, 0.04)	0.045	94.2	<0.001	Influential study, ES becomes significant
Ma et al. 2019 <sup>3</sup>	-0.35	(-0.71, 0.02)	0.03	93.0	<0.001	Influential study, ES becomes significant
Oliveira et al. 201817	-0.28	(-0.64, 0.07)	0.07	94.1	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.15	(-0.34, 0.04)	0.07	89.3	<0.001	-
Vignera et al. 2012 <sup>20</sup>	-0.22	(-0.53, 0.09)	0.11	93.5	<0.001	-
Wang et al. 20176	-0.27	(-0.63, 0.08)	0.08	93.6	<0.001	-
	·	Sperm progr	essive motility –	Obesity (or ob	esity I) vs normal we	eight
Overall	-0.33	(-0.71, 0.04)	0.051	91.0	<0.001	-
Andersen et al. 2016 <sup>23</sup>	-0.32	(-0.73, 0.08)	0.08	91.8	<0.001	-
Bandel et al. 2015 <sup>1</sup>	-0.39	(-0.77, -0.01)	0.02	89.4	<0.001	Influential study, ES becomes significant
Belloc et al. 2014 <sup>2</sup>	-0.38	(-0.80, 0.05)	0.051	91.8	<0.001	-
Fariello et al. 2012 <sup>11</sup>	-0.30	(-0.71, 0.10)	0.10	91.4	<0.001	-
Ferigolo et al. 2019 <sup>21</sup>	-0.32	(-0.73, 0.08)	0.08	91.8	<0.001	-
Hammiche et al. 2012 <sup>12</sup>	-0.36	(-0.77, 0.04)	0.047	91.7	<0.001	Influential study, ES becomes significant
Keskin et al. 2017 <sup>14</sup>	-0.37	(-0.77, 0.04)	0.046	91.7	<0.001	Influential study, ES becomes significant

Ma et al. 2019 <sup>3</sup>	-0.38	(-0.80, 0.04)	0.04	91.3	<0.001	Influential study, ES becomes significant
Oliveira et al. 201817	-0.32	(-0.74, 0.10)	0.09	90.4	<0.001	-
Taha et al. 2016 <sup>28</sup>	-0.19	(-0.40, 0.01)	0.04	84.5	<0.001	Influential study, ES becomes significant
Vignera et al. 2012 <sup>20</sup>	-0.30	(-0.71, 0.10)	0.10	91.4	<0.001	-
Wang et al. 20176	-0.36	(-0.78, 0.06)	0.06	91.8	<0.001	-
	·	Sperm r	normal morpholo	ogy – Overweig	ht vs normal weight	
Overall	0.04	(-0.58, 0.67)	0.89	98.9	<0.001	-
Andersen et al. 2016 <sup>23</sup>	0.08	(-0.58, 0.73)	0.81	98.9	<0.001	-
Belloc et al. 2014 <sup>2</sup>	0.05	(-0.62, 0.71)	0.88	98.9	<0.001	-
Chavarro et al. 20108	0.05	(-0.62, 0.71)	0.88	98.9	<0.001	-
Dupont et al. 2013 <sup>24</sup>	0.14	(-0.48, 0.77)	0.63	98.8	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	0.01	(-0.65, 0.67)	0.98	98.9	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	0.10	(-0.55, 0.75)	0.75	98.9	<0.001	-
Fariello et al. 2012 <sup>11</sup>	0.05	(-0.61, 0.72)	0.86	98.9	<0.001	-
Jensen et al. 2004 <sup>13</sup>	0.05	(-0.61, 0.71)	0.87	98.9	<0.001	-
Keskin et al. 2017 <sup>14</sup>	0.04	(-0.62, 0.71)	0.89	98.9	<0.001	-
Luque et al. 2017 <sup>15</sup>	0.05	(-0.62, 0.71)	0.88	98.9	<0.001	-
Martini et al. 201016	0.05	(-0.62, 0.71)	0.88	98.9	<0.001	-
Oliveira et al. 2018 <sup>17</sup>	0.05	(-0.61, 0.72)	0.86	98.9	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.19	(-0.45, 0.07)	0.13	93.7	<0.001	-
Ramírez et al. 202018	0.04	(-0.62, 0.71)	0.89	98.9	<0.001	-
Rybar et al. 2011 <sup>19</sup>	0.05	(-0.62, 0.71)	0.88	98.9	<0.001	-
Taha et al. 2016 <sup>28</sup>	0.11	(-0.53, 0.75)	0.71	98.9	<0.001	-
Vignera et al. 2012 <sup>20</sup>	0.05	(-0.61, 0.71)	0.86	98.9	<0.001	-
Wang et al. 2017 <sup>6</sup>	0.04	(-0.62, 0.71)	0.89	98.9	<0.001	-
		Sperm norm	al morphology –	Obesity (or ob	esity I) vs normal we	eight
Overall	-0.04	(-0.66, 0.58)	0.89	96.0	<0.001	-
Andersen et al. 2016 <sup>23</sup>	0.01	(-0.64, 0.66)	0.97	96.2	<0.001	-
Belloc et al. 2014 <sup>2</sup>	-0.03	(-0.71, 0.64)	0.91	96.3	<0.001	-

Chavarro et al. 20108	-0.04	(-0.71, 0.63)	0.89	96.3	<0.001	-
Dupont et al. 2013 <sup>24</sup>	0.01	(-0.65, 0.66)	0.98	96.2	<0.001	-
Ehala-Aleksejev et al. 2015 <sup>9</sup>	-0.05	(-0.72, 0.62)	0.87	96.3	<0.001	-
Eisenberg et al. 2014 <sup>10</sup>	-0.02	(-0.69, 0.65)	0.95	96.3	<0.001	-
Fariello et al. 2012 <sup>11</sup>	-0.04	(-0.70, 0.63)	0.90	96.3	<0.001	-
Ferigolo et al. 2019 <sup>21</sup>	0.00	(-0.66, 0.65)	0.99	96.3	<0.001	-
Keskin et al. 2017 <sup>14</sup>	-0.04	(-0.71, 0.63)	0.91	96.3	<0.001	-
Martini et al. 201016	-0.05	(-0.72, 0.62)	0.88	96.3	<0.001	-
Oliveira et al. 201817	-0.01	(-0.68, 0.66)	0.97	96.0	<0.001	-
Qin et al. 2007 <sup>4</sup>	-0.27	(-0.52, -0.02)	0.02	89.0	<0.001	Influential study, ES becomes significant
Rybar et al. 2011 <sup>19</sup>	-0.05	(-0.71, 0.62)	0.88	96.3	<0.001	-
Taha et al. 2016 <sup>28</sup>	0.04	(-0.59, 0.68)	0.88	96.0	<0.001	-
Vignera et al. 2012 <sup>20</sup>	0.00	(-0.67, 0.66)	0.99	96.2	<0.001	-
Wang et al. 20176	-0.06	(-0.73, 0.61)	0.84	95.9	<0.001	-

<sup>a.</sup> Summary effect size recalculated after the systematical removal of one study at a time. We considered an influential study as the one whose

exclusion changed the significance, direction or magnitude (by >10%) of the pooled estimate or changed the significance of the heterogeneity.

\* p<0.05 considered significant for the pooled effect estimates.

\*\* P-heterogeneity <0.10 is considered significant

Abbreviations: CI, confidence interval; ES, effect size; I<sup>2</sup>, Heterogeneity.

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**Supplemental Table 3.** Characteristics of previous systematic reviews and meta-analysis on adiposity and seminogram parameters.

Author/ Year/ Journal	Included till year	No. of studies in the systematic review	No. of studies in the meta- analysis	Exposure comparison	Outcomes	Subgroup analysis	Quality evaluation of the studies included	Main conclusion	Main differences with our meta- analysis	Limitations
(MacDonald et al., 2009) <sup>1</sup> Human Reproduction Update	2009	31	5	Normal weight versus underweight, overweight and obesity	Semen volume, sperm count, concentration, motility and morphology	No	No	No evidence of an association between increased BMI and semen parameters was found.	OR instead of SE.	Old WHO BMI classification used. Data from most studies could not be aggregated for meta- analysis.
(Sermondade et al., 2013) <sup>2</sup> Human Reproduction Update	2012	44	21 + personal data	Normal weight versus underweight, overweight, obesity and morbid obesity	Sperm count	No	No	Overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia. There was a J- shaped relationship between BMI categories and risk of oligozoospermia or azoospermia.	OR instead of SE.	Studied populations varied, with men recruited from both the general population and infertile couples.
(Campbell et al., 2015) <sup>3</sup> Reproductive BioMedcine Online	2015	30	13	Normal weight versus obesity	Semen volume, sperm concentration, total and progressive motility and	Clinical population and general population	Yes. JBI checklist for descriptive studies	Men with obesity had an increased percentage of sperm with abnormal morphology (in the clinical ART	Only obese population comparison.	Studied populations varied, with men recruited from both the general

					morphology			population) and less progressive motility indexes (in the general population). Clinically significant differences were not found for other conventional semen parameters.		population and clinical population
(Guo et al., 2017)⁴ Oncotarget	2015	24 + personal data	24 + personal data	Normal weight versus underweight, overweight and obesity	Semen volume, sperm concentration, total and progressive motility	Ethnicity	No	SWM differences in sperm concentration did not differ significantly across BMI categories.	No sperm normal morphology analysis.	Methods poor explained. The use of different boundaries for normal, overweight and obese in Chinese studies was different from others, which may affect the final results.
(Guo et al., 2019)⁵ Medicine	2017	13	13	Normal weight versus underweight	Semen volume, sperm concentration, total and progressive motility	Ethnicity	No	There was a relationship between low BMI and semen quality (total sperm count and semen volume), which suggesting low BMI may be a harmful factor of male infertility.	Only underweight population. No morphology analysis.	Yet lacking of the raw data may influence the accuracy of the results. No limitations paragraph.

Abbreviations: ART, assisted reproductive technologies; BMI, body mass index; ES, effect size; OR, odds ratio; SWM, standardized weighted mean.

# REFERENCES

- MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: A systematic review with meta-analysis. *Hum Reprod Update*. 2009;16(3):293-311. doi:10.1093/humupd/dmp047
- 2. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: An updated systematic review and collaborative meta-analysis. *Hum Reprod Update*. 2013;19(3):221-231. doi:10.1093/humupd/dms050
- Campbell JM, Lane M, Owens JA, Bakos HW. Paternal obesity negatively affects male fertility and assisted reproduction outcomes: A systematic review and meta-analysis. *Reprod Biomed Online*. 2015;31(5):593-604. doi:10.1016/j.rbmo.2015.07.012
- 4. Guo D, Wu W, Tang Q, et al. The impact of BMI on sperm parameters and the metabolite changes of seminal plasma concomitantly. *Oncotarget*. 2017;8(30):48619-48634. doi:10.18632/oncotarget.14950
- Guo D, Xu M, Zhou Q, et al. Is low body mass index a risk factor for semen quality? A PRISMA-compliant meta-analysis. Med (United States). 2019;98(32). doi:10.1097/MD.00000000016677

**Supplemental Appendix 1.** Search strategy for the literature published between the earliest available online indexing year and June 2019 in MEDLINE-Pubmed and EMBASE databases.

#### 1. MEDLINE-Pubmed

## 1.1. Search terms:

((((((("infertility, male"[MeSH Terms]) OR asthenozoospermia[Title/Abstract]) OR oligozoospermia[Title/Abstract]) OR oligoasthenozoospermia[Title/Abstract]) OR oligoasthenoteratozoospermia[Title/Abstract]) OR teratozoospermia[Title/Abstract]) OR spermatogenesis[Title/Abstract]) OR semen quality[Title/Abstract]) OR sperm DNA damage[Title/Abstract]) OR varicocele[Title/Abstract])) AND (((((((("obesity"[MeSH Terms]) OR abdominal obesity[Title/Abstract]) OR metabolic syndorme[Title/Abstract]) overweight[Title/Abstract]) index[Title/Abstract]) OR OR Body mass OR BMI[Title/Abstract]) OR body weight[Title/Abstract]) OR Fat mass[Title/Abstract]) OR body fat[Title/Abstract])

# 1.2. Inclusion filters:

Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Corrected and Republished Article, English Abstract, Journal Article, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans, English, Male.

# 2. EMBASE

#### 2.1. Search terms:

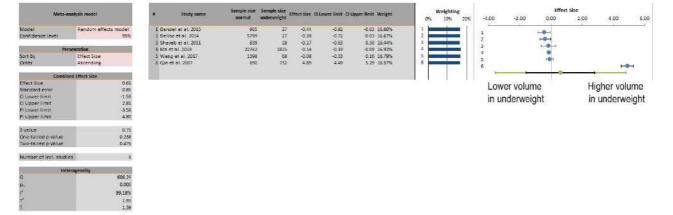
('male infertility' OR asthenozoospermia:ab,ti OR oligozoospermia:ab,ti OR oligoasthenozoospermia:ab,ti OR oligoasthenoteratozoospermia:ab,ti OR teratozoospermia:ab,ti OR spermatogenesis:ab,ti OR 'semen quality':ab,ti OR 'sperm

dna damage':ab,ti OR varicocele:ab,ti) AND (obesity OR 'abdominal obesity':ab,ti OR 'metabolic syndorme':ab,ti OR overweight:ab,ti OR 'body mass index':ab,ti OR bmi:ab,ti OR 'body weight':ab,ti OR 'fat mass':ab,ti OR 'body fat':ab,ti)

## 2.2. Inclusion filters:

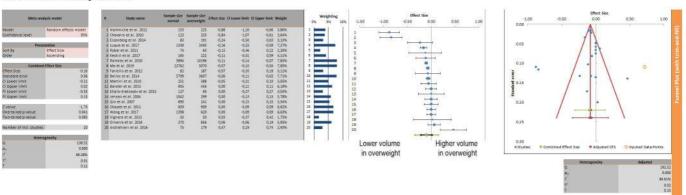
('case control study'/de OR 'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'control group'/de OR 'controlled Clinical trial'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'human'/de OR 'human cell'/de OR 'human experiment'/de OR 'human tissue'/de OR 'in vivo study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'normal human'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized'/it OR 'ra

## Semen volume\_BMI\_Underweight vs. Normal



Semen volume\_BMI\_Overweight vs. Normal

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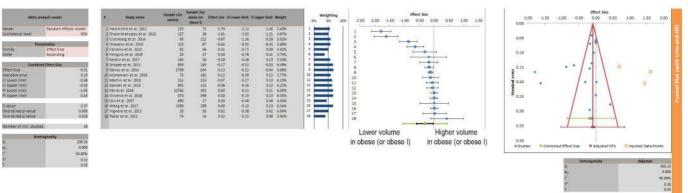
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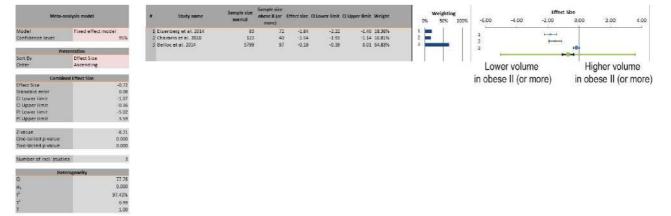
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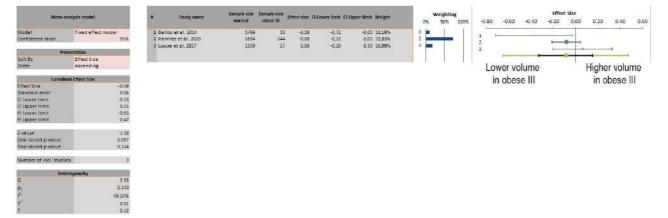
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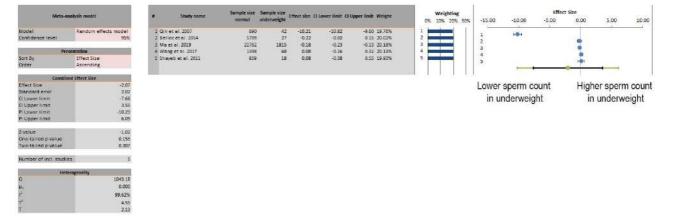
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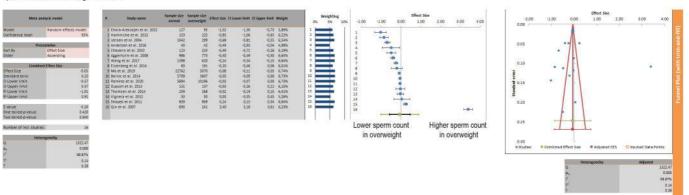
#### Semen volume\_BMI\_Obese III vs. Normal



## Sperm count\_BMI\_Underweight vs. Normal



#### Sperm count\_BMI\_Overweight vs. Normal



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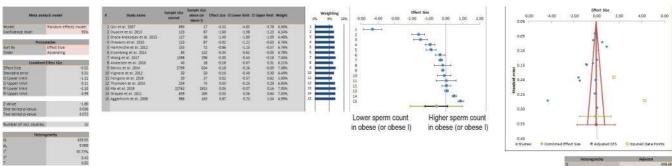
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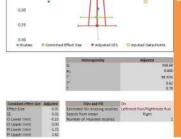
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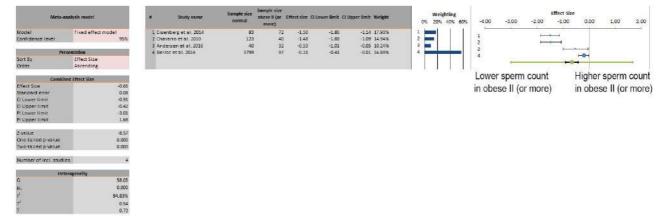
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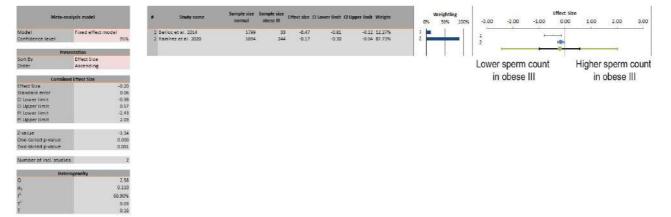




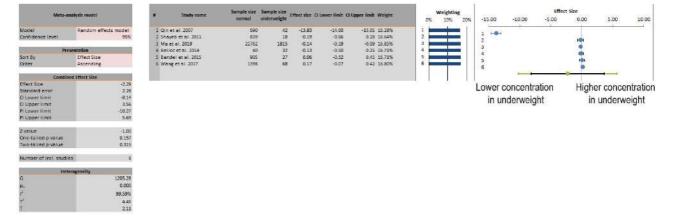
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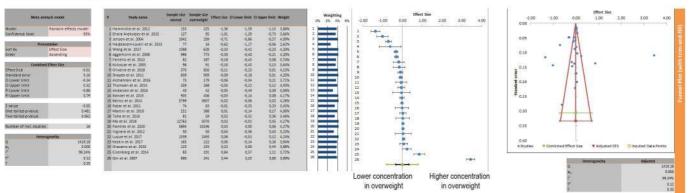
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## Sperm concentration\_BMI\_Underweight vs. Normal



Sperm concentration\_BMI\_Overweight vs. Normal

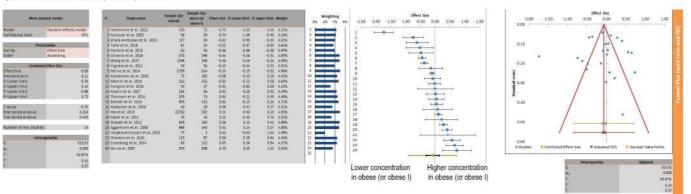


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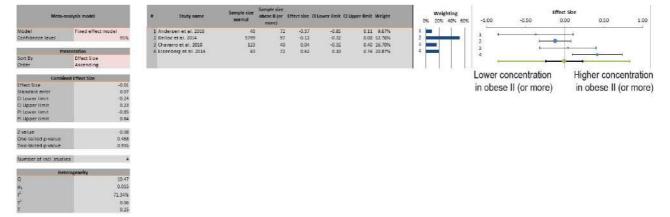


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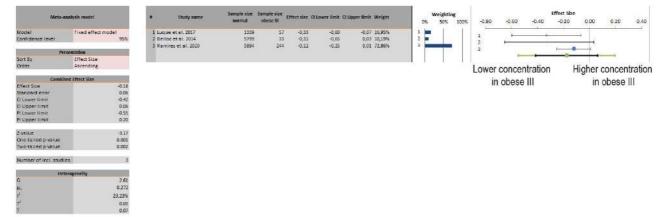
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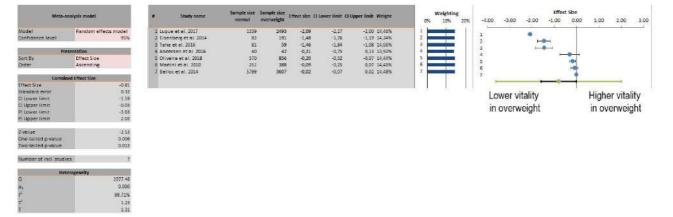
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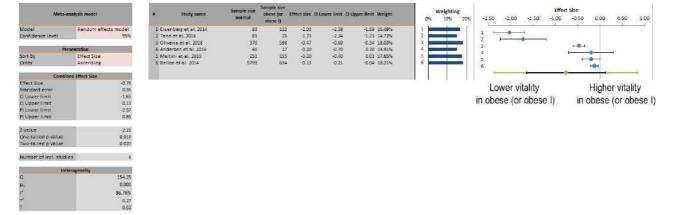
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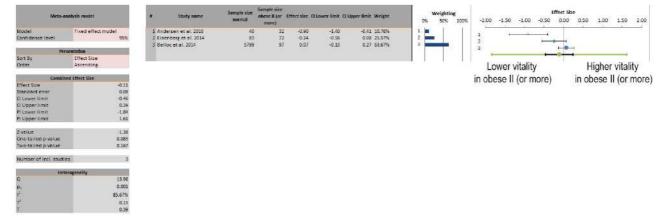
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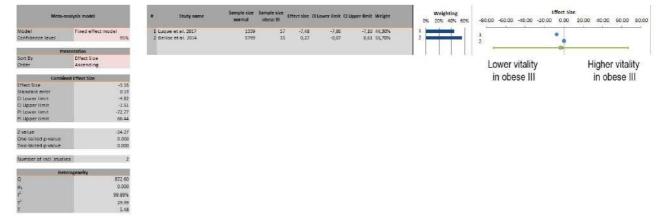
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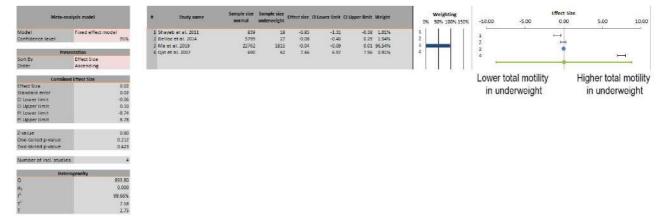
## Sperm vitality\_BMI\_Obese II (or more) vs. Normal



# Sperm vitality\_BMI\_Obese III vs. Normal



## Sperm total motility\_BMI\_Underweight vs. Normal



#### Sperm total motility\_BMI\_Overweight vs. Normal

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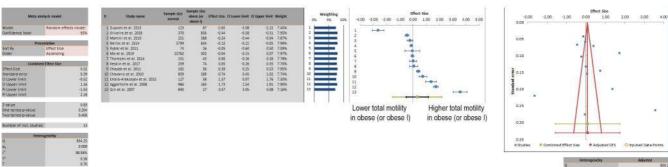
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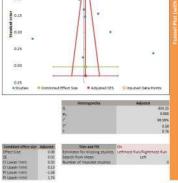
Sperm total motility\_BMI\_Obese (or obese I) vs. Normal

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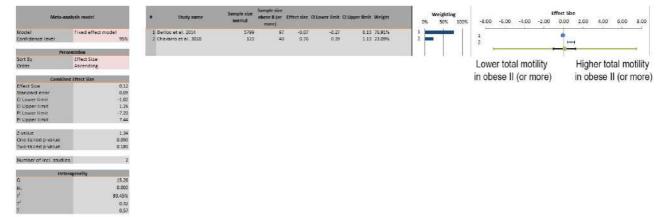
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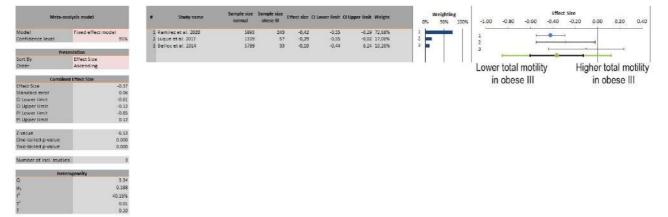




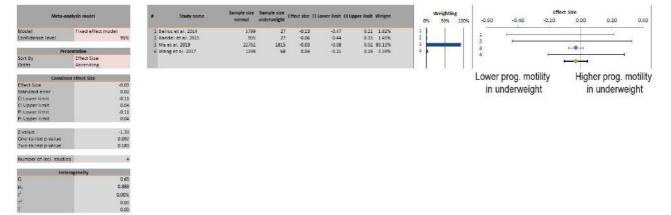
## Sperm total motility\_BMI\_Obese II (or more) vs. Normal



# Sperm total motility\_BMI\_Obese III vs. Normal



# Sperm progressive motility\_BMI\_Underweight vs. Normal



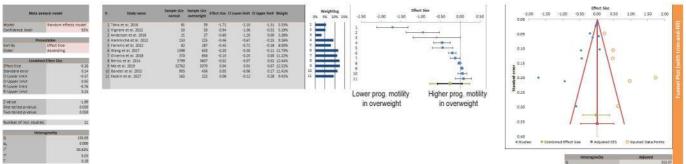
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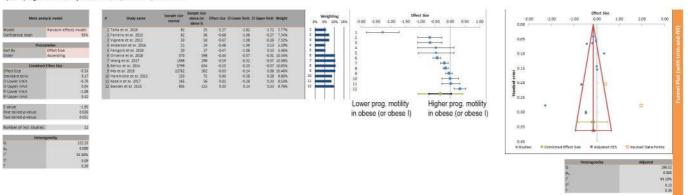
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Sperm progressive motility\_BMI\_Obese (or obese I) vs. Normal

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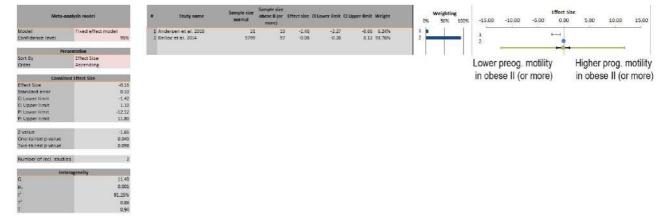
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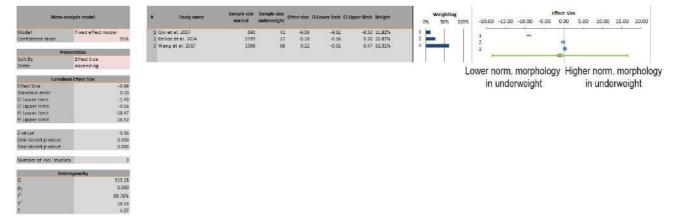
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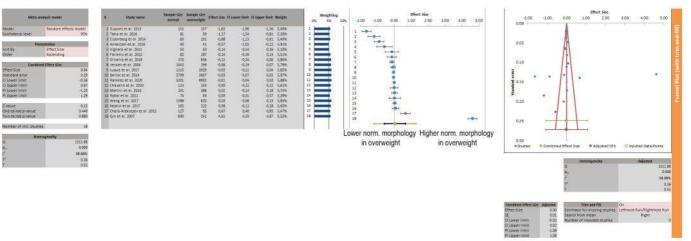
# Sperm progressive motility\_BMI\_Obese II (or more) vs. Normal



# Sperm normal morphology\_BMI\_Underweight vs. Normal

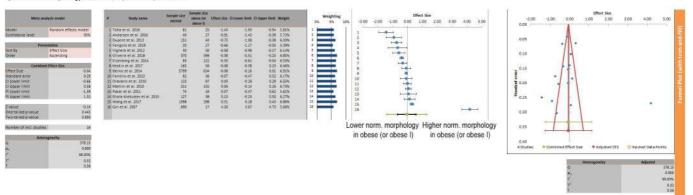


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# Sperm normal morphology\_BMI\_Obese (or obese I) vs. Normal

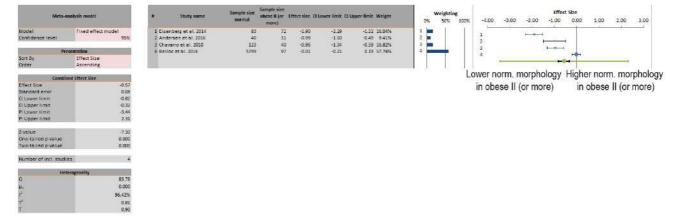


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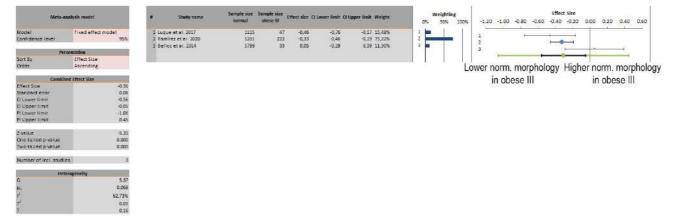
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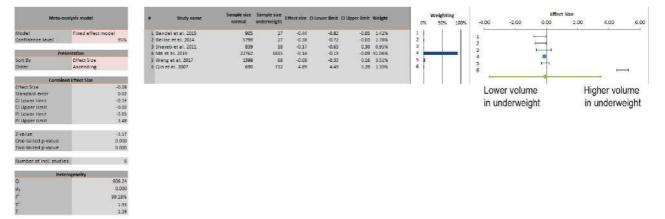
# Sperm normal morphology\_BMI\_Obese II (or more) vs. Normal



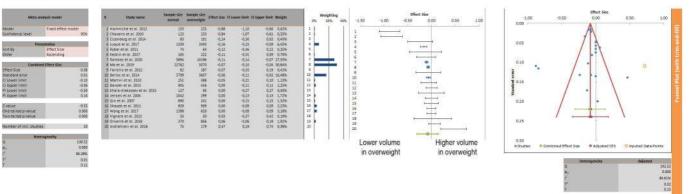
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Semen volume\_BMI\_Underweight vs. Normal\_Sensitivity analysis (fixed model)



Semen volume\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)

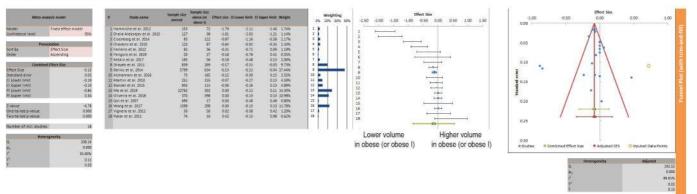


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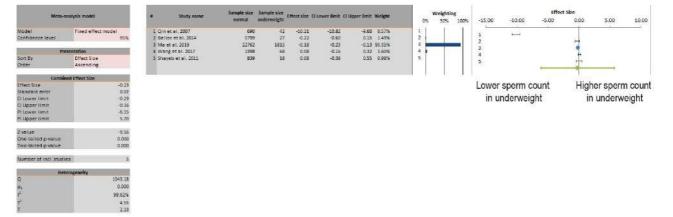
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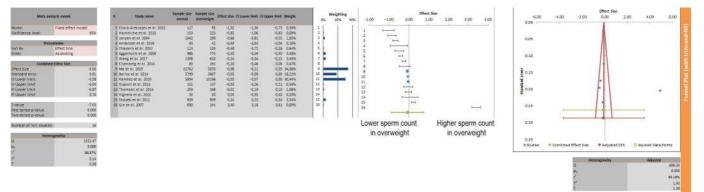
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# Sperm count\_BMI\_Underweight vs. Normal\_Sensitivity analysis (fixed model)



## Sperm count\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)



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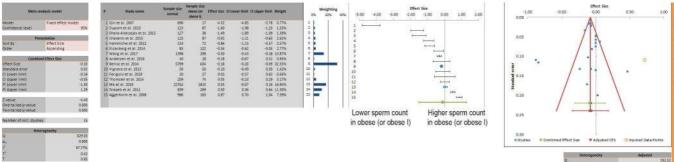
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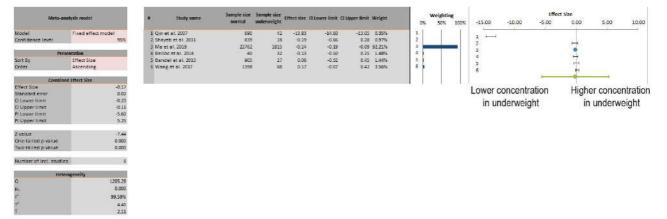
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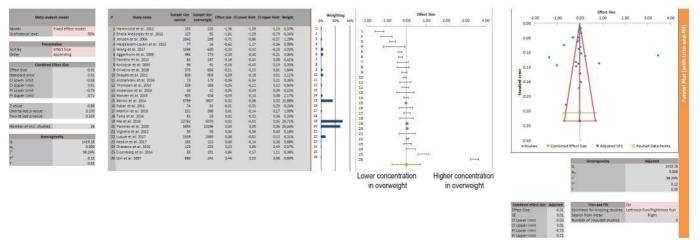




Sperm concentration\_BMI\_Underweight vs. Normal\_Sensitivity analysis (fixed model)



Sperm concentration\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)

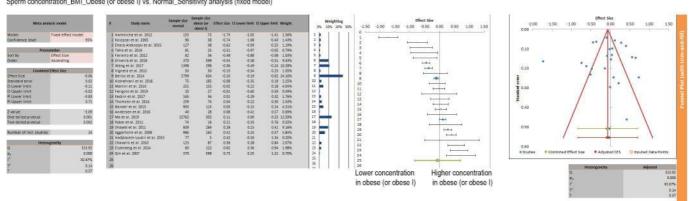


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Sperm concentration\_BMI\_Obese (or obese I) vs. Normal\_Sensitivity analysis (fixed model)

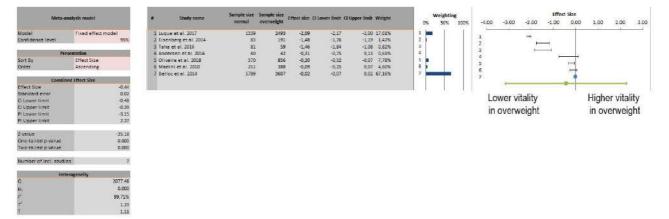


Combined effect Size 40,66 Effect Size 40,66 Effect Size 40,02 O Lover Innit 40,11 O Upper Innit 40,12 P Lover Innit 42,83 P Upper Innit 571

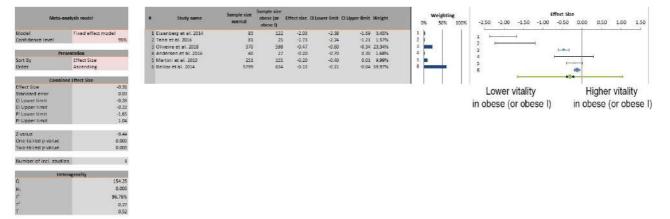
Trim and File Estimator for missing studies Search from mean Number of imputed studies

nun Right

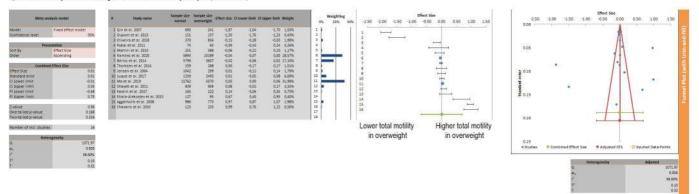
Sperm vitality\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)



Sperm vitality\_BMI\_Obese (or obese I) vs. Normal\_Sensitivity analysis (fixed model)



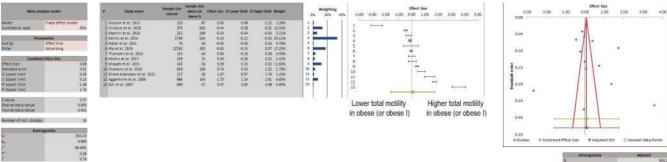
## Sperm total motility\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)

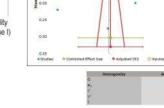


Combined effect size Adjustee Effect Size 0.01 SE 0.01 Ci Lower limit -0.01 Ci Lower limit -0.03 Pi Lower limit -0.68 Pi Lower limit -0.68

Trim and Fill Estimator for missing studies Search from mean Number of imputed studies

## Sperm total motility\_BMI\_Obese (or obese I) vs. Normal\_Sensitivity analysis (fixed model)





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 Execution from mess

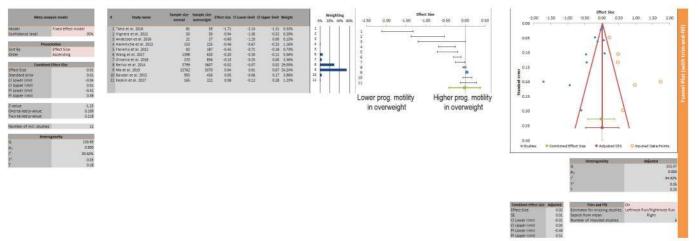
 Oliver Hinit
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 Runner of Imputed studies

 Flower Initit
 -1.36
 Runner of Imputed studies

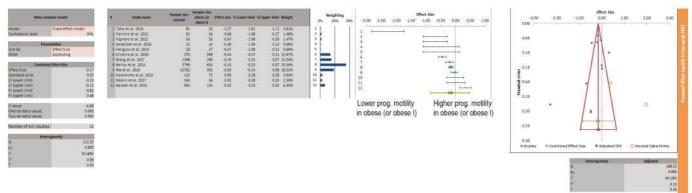
 Flower Initit
 -1.36
 Runner of Imputed studies

834.25 0.000 98.50% 0.58 0.76

## Sperm progressive motility\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)



## Sperm progressive motility\_BMI\_Obese (or obese I) vs. Normal\_Sensitivity analysis (fixed model)



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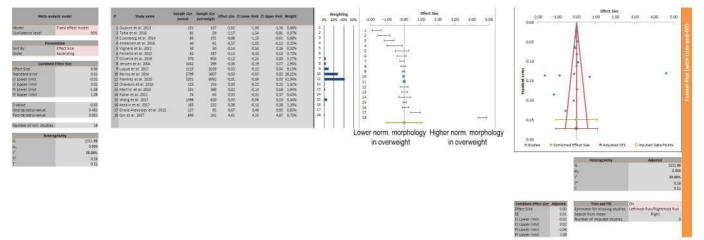
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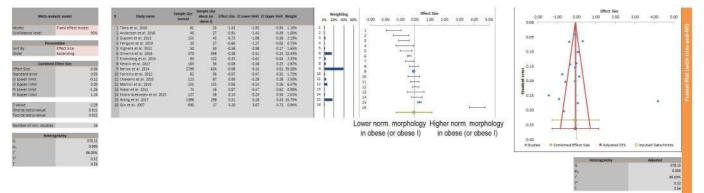
un/Rightmost flun Right

### Sperm normal morphology\_BMI\_Overweight vs. Normal\_Sensitivity analysis (fixed model)



Right

## Sperm normal morphology\_BMI\_Obese (or obese I) vs. Normal\_Sensitivity analysis (fixed model)



Considered effect Size Adjusted Effect Size 0.06 Effect Size 0.03 O Lower Hinit 4.12 O Lower Hinit 4.12 Fi Lower Hinit 1.25 Fi Lower Hinit 1.14

Trim and File Estimator for missing studies Search from mean Number of imputed studies

un/Rightmost Run Right