**ASSOCIATIONS BETWEEN BODY MASS INDEX, WAIST CIRCUMFERENCE AND ERECTILE DYSFUNCTION:**

**A SYSTEMATIC REVIEW AND META-ANALYSIS**

**Running head:** BMI and erectile dysfunction

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**ABSTRACT**

**Background** Growing evidence reports that obesity might play a role in erectile dysfunction (ED), but limited knowledge is available. We conducted a meta-analysis to estimate the prevalence of ED in overweight men and men with obesity.

**Methods** We performed a systematic review up to 01/04/2019 to investigate the associations between obesity and ED. Applying a random-effect model, we calculated the prevalence of ED, the odds ratio (OR) for the presence of ED by Body Mass Index (BMI) categories and the mean differences between ED and controls in BMI and Waist Circumference (WC).

**Results** Among 3409 studies, we included 45 articles with 42,489 men (mean age=55 years). Taking normal weight men as reference, the prevalence of ED was significantly higher in overweight (OR=1.31; 95%CI: 1.13-1.51; I2=72%) and in men with obesity (OR=1.60; 95%CI: 1.29-1.98; I2=79%). Adjusting our analyses for potential confounders, the results were confirmed in men with obesity (OR=1.46; 95%CI: 1.24-1.72; I2=72%). ED was associated with significant higher values of BMI (MD=0.769; 95%CI: 0.565-0.973 Kg/m2; I2=78%) and WC (MD=5.251 cm; 95%CI: 1.295-9.208; I2=96%).

**Discussion** Considering the high prevalence of ED among men with obesity, clinicians should screen for this clinical condition in this population. Findings from the present study suggest that reducing adiposity is a crucial approach in patients with ED who are affected by obesity.

**INTRODUCTION**

Overweight and obesity are defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health.[1](#ENREF_1) It is estimated that the worldwide prevalence of obesity nearly tripled between 1975 and 2016. [1](#ENREF_1) In 2016, more than 1.9 billion adults aged 18 years and older were overweight and of these over 650 million were affected by obesity. [1](#ENREF_1)

Obesity is a major public health issue related to several unwanted conditions and diseases. [2-8](#ENREF_2) Growing evidence is reporting that obesity might play a key role in male sexual function, including fertility and erectile dysfunction (ED).[9](#ENREF_9),[10](#ENREF_10) ED, defined as the inability to achieve and/or maintain a sufficient erection to permit satisfactory sexual intercourse, is the most common sexual health issue in men and is associated with a substantial range of physical and psychological adverse effects, including anxiety, low mood and reductions in personal and couple’s quality of life.[11](#ENREF_11)

Although ED is considered an age-related disease, affecting 20% of men aged > 40 years, it can be present across the lifespan from adolescence, especially when risk factors such as diabetes, metabolic syndrome, cardiovascular diseases, physical inactivity and hypertension coexist.[11](#ENREF_11) Interestingly, it has been demonstrated not only that obesity is an independent risk factor for ED, but also that the incidence rate of ED is directly proportional to the level of obesity.[12](#ENREF_12) ED in patients affected by severe obesity has also been linked to a reduced responsiveness to phosphodiesterase 5 (PDE5) inhibitors. Moreover, obesity appears to be a driving factor in decreasing testosterone level since adipose cells secrete leptin, which results in a decrease in testosterone level. 12,13 On the contrary, a reduction in adiposity among men with obesity has been shown to improve erectile function.9

Although these studies provide important information, to date there is no meta-analysis of the synthesized data which would help provide the most reliable estimates of ED prevalence in men with obesity compared with controls. Given this, the aim of this study was to conduct a meta-analysis of existing data to estimate the prevalence of ED in men affected by obesity, compared to other measurements of adiposity.

**METHODS**

This systematic review and meta-analysis is adherent to the PRISMA14 and MOOSE15 statements. The work followed a predetermined, but unpublished protocol.

***Data sources and literature search strategy***

Two investigators (NV and DP) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from database inception until 01st April 2019 for studies investigating the association between BMI and/or waist circumference (WC) and presence of ED. Any inconsistencies were resolved by consensus with a third author (LS).

In PubMed, the following search strategy was used: “("erectile dysfunction" OR "erectile function" OR "sexual dysfunction" OR "sexual function" OR "impotence") AND ("Body Mass Index"[Mesh] OR "Obesity"[Mesh] OR "Overweight"[Mesh] OR "Body Mass Index" OR “Quetelet Index” OR “Quetelet's Index” OR “Quetelets Index” OR “BMI” OR "Obesity" OR “Obesities” OR “obese” OR “adipose tissue hyperplasia” OR “adipositas” OR “adiposity” OR “excess body weight” OR “obesitas” OR “overweight” NOT ("Controlled Clinical Trial"[Publication Type] OR "Randomized Controlled Trial" [Publication Type] "Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase I" [Publication Type])”. Reference lists of included articles were hand-searched to identify any potential additional relevant articles, whilst conference abstracts were excluded.

***Study selection***

Inclusion criteria for this meta-analysis were: i) observational studies (case-control, cross-sectional, prospective) reporting the prevalence of ED across standardized BMI categories16 or reporting data regarding mean BMI values in ED vs. healthy controls or reporting other evaluations of adiposity (e.g. WC) in ED vs. healthy controls; and ii) used a validated tool for the detection of ED (e.g. the International Index of Erectile Function, IIEF-517);

***Data extraction***

Two independent investigators (NV and DP) extracted key data from the included articles in a standardized Excel sheet. A third independent investigator (LS) checked the extracted data. For each article, data were extracted on authors, year of publication, country, number of participants, demographics (mean age), methods of assessment of adiposity (BMI; WC) and of ED; number and type of adjustments.

***Outcomes***

The primary outcome was the prevalence of ED by standardized BMI category (<18.5, 18.5-24.9, 25-29.9, > 30 Kg/m2) and for degree of severity of obesity (30-34.9 and > 35 Kg/m2). In all analyses, normal weight men (18.5-24.9) were taken as the reference. In secondary analyses, odds ratios (ORs) adjusted for potential confounders for the association between BMI categories and ED, where these data were available, were included. Finally, means (with their standard deviations, SDs) for adiposity parameters (BMI, WC) in men with ED vs. healthy controls were reported.

***Assessment of study quality***

Study quality was assessed by two investigators (DP, LS) using the Newcastle-Ottawa Scale (NOS).18, 19 A third reviewer was available for mediation (NV). The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome.

***Data synthesis and statistical analysis***

All analyses were performed using Comprehensive Meta-Analysis (CMA) 2.

The primary analysis reported the prevalence of ED as absolute estimates (in %) with their 95% confidence intervals (CIs) and across standardized BMI categories taking normal weight men as reference. Next, ORs and 95% confidence intervals (CIs) were calculated, applying a random-effect model.20 Moreover, the mean differences (MDs) with their 95% CI in men with ED vs. healthy controls were reported.

Heterogeneity across studies was assessed by the I2 metric and taking as measure of high heterogeneity an I2 >50% and/or p<0.05.21 The mean age of the total sample size as a potential moderator in case of high heterogeneity of the findings was investigated.

Publication bias was assessed by a visual inspection of funnel plots and calculating the Egger bias test.22 In case of publication bias (p<0.10), the trim and fill-analysis23 was applied. For all analyses, a p-value < 0.05 was considered statistically significant.

**RESULTS**

***Search results***

As shown in **Supplementary Figure 1**, the searches produced 3409 non-duplicated articles. After excluding 3263 articles based on title/abstract review, 146 articles were retrieved for full text review and 45 articles were included in the qualitative/quantitative synthesis (the general data of selected studies are reported in **Supplementary Table 1**)24-68.

***Study and patient characteristics***

The 45 studies included a total of 42,489 participants. The majority of the studies (n=18) were conducted in Europe, 8 in Middle East and 8 in North America, 7 in Asia, 3 in Africa and 1 in Oceania. The mean age was 55 years (SD=10.2). The median quality of the studies was 4.8 (range: 3-7), indicating an overall good quality of the studies, according to the NOS (**Supplementary Table 2**).

***Prevalence and odds of ED by BMI categories***

**Table 1** shows the prevalence of ED in normal weight men, overweight and men with obesity. Overall, it was observed that the prevalence of ED in normal weight men was 34.8% (95%CI: 26.4-44.2; n=9428), in overweight was 40.7% (95%CI: 32.5-49.4; n=12173) and in men with obesity 37.4% (95%CI: 27.3-43.0; n=5540). In three studies reporting specific data for categories characterized by obesity, the prevalence of ED in those with a BMI between 30 and 34.9 was 71.5% and in those with a BMI > 35 Kg/m2 was 73.6% (**Table 1**).

**Table 2** reports the prevalence of ED in overweight and in men with obesity, compared to normal weight participants. In 19 studies involving 21,601 participants, the prevalence of ED was significantly higher in overweight vs. normal weight men (OR=1.31; 95%CI: 1.13-1.51; p<0.0001; I2=72%). The mean age of the sample did not significantly moderate the results (beta=0.81; p=0.24). Similarly, in 15 studies reporting data regarding men with obesity, it was observed that the prevalence of ED was significantly higher in men affected by obesity than in the normal weight reference group (OR=1.60; 95%CI: 1.29-1.98; p<0.0001; I2=79%). Again, the mean age of the sample did not significantly moderate these results (beta=0.25; p=0.74). In three studies, a significantly higher presence of ED was found in men affected by obesity with a BMI between 30 and 34.9 Kg/m2 and in those with a BMI > 35 Kg/m2.

**Figure 1** reports the association between overweight and ED (vs. normal weight men) after taking into consideration potential confounders. After adjusting for a mean of 5 (range: 1-14) confounders, no significant association between overweight status and ED in 11 studies was found (OR=1.08; 95%CI: 0.93-1.26; p=0.31; I2=82%). No evidence of publication bias was present for this outcome. After removing an outlier study in a sensitivity analysis (Štulhofer et al., 2006) the re-calculated OR was not significant (OR=1.06; 95%CI:0.91-1.23; p=0.45). **Figure 2** shows the association between obesity and ED, in multivariable analyses. Again, in 11 studies and after adjusting for a mean of 5 potential confounders, the OR was 1.46 (95%CI: 1.24-1.72; p<0.0001; I2=72%). For this outcome the presence of publication bias was observed (Egger’s test: 1.70; p=0.02). After trimming 3 studies at the left of the mean the re-calculated OR was 1.36 (95%CI: 1.15-1.61).

***Mean differences in adiposity parameters between ED and controls***

**Figure 3** reports the mean difference between ED and controls. Overall, 3,304 participants with ED were compared to 4,450 without in 32 studies. The MD was 0.769 (95%CI: 0.565-0.973 Kg/m2; p<0.0001; I2=78%). The presence of publication bias was observed (Egger’s test: 1.22; p=0.003), but the trim and fill analysis did not change results. Mean age did not moderate results (beta=0.21; p=0.84). Similarly, in **Figure 4**, it was found that in 16 studies comparing ED (1,623 participants) vs. controls (2,971 men), ED was significantly associated with higher WC values (MD=5.251 cm; 95%CI: 1.295-9.208; p<0.0001; I2=96%). No evidence for publication bias was present for this outcome and mean age of the sample did not explain any heterogeneity (beta=0.21; p=0.84).

**DISCUSSION**

To our knowledge, this is the first meta-analysis to assess the prevalence of ED among men with obesity, synthesizing a large body of international literature, including 45 studies and 42,489 participants. The main results confirm the very high prevalence of ED in the studies included, ranging from 34.8% in normal weight men to almost 3/4 of participants with grade II-III obesity. Overall, taking normal weight men as reference, the prevalence of ED was significantly higher in overweight (31%) and in men with obesity (60%). After taking into consideration potential confounders, obesity was still independently associated with higher odds of having ED. Finally, men with ED reported significantly higher values of BMI and WC, further confirming that (central) obesity is associated with ED.

Considering that sexual function and penile erection is a bio-psychosocial process that involves the coordination of psychological, endocrine, vascular, and neurological systems69, we can hypothesize that in men affected by obesity at least two mechanisms are probably involved, i.e. vascular and endocrinological pathways. From a vascular point of view, erection is the result of relaxation of the cavernosal smooth muscles, driven by the nitric oxide (NO) released by the endothelium, leading to compression of the subtunical small veins and occluding local venous return70. Indeed, endothelial dysfunction is the common etiologic factor for several vascular risk factors that can lead to arteriogenic ED.71, 72 Thus, considering the well-known detrimental effects of adipose tissue dysfunction and of the associated metabolic abnormalities (including low grade chronic inflammation, high blood pressure, dyslipidemia and oxidative stress) in promoting impaired endothelial function [6](#ENREF_6), we can hypothesize obesity as major risk factor for ED.

From the endocrinological point of view, the role played by androgens (foremost testosterone) in enhancing sexual desire and maintaining adequate sleep-related erections is well established.73 Hence, obesity directly impacts ED due to its action on testosterone. Importantly, adipocytes have high expression of aromatase that enzymatically converts testosterone to estradiol lowering circulating androgens. At the same time, estrogens causes a negative feedback mechanism upon the hypothalamo-pituitary axis suppressing gonadotropin-releasing hormone and, thus, luteinizing hormone, contributing to a reduction in gonadal testosterone release.74 Moreover, testosterone is a key regulator for the expression of NO synthase inside the penis, exacerbating the previous described mechanism.75 Reduction in plasma testosterone contributes to increased arterial stiffness, which in turn has been associated with increased cardiovascular risk.76 The positive interaction between androgens and the vessel wall has been demonstrated both in animal models, where testosterone supplementation inhibits atheroma formation, both in men, where androgen withdrawal has been associated with decreased central arterial compliance and testosterone has been suggested to act as a protective factor against atherosclerosis because of its immunomodulating effects on plaque development and stability.76

Finally, although the role of estradiol is not entirely clear, it is likely that a cycle exists by which the increased estradiol levels in men with obesity, further contribute to the progression of obesity.77 Estradiol is secreted in the testis and adipose tissue trough the irreversible conversion of testosterone by aromatase. Its main negative effect on male gonadal function is due to the suppression of hypothalamic-pituitary-testicular axis, limiting testosterone secretion in the testis.77

Importantly, growing evidence has shown the importance of targeting lifestyle factors commonly associated with ED.78 In particular, exercise and caloric restriction could improve ED by acting both on risk factors of ED and on ED itself.79 Indeed, physical activity has been shown to be inversely associated with ED.80-82 Interestingly, authors showed that frequent vigorous exercise was associated with lower risk for ED.80 Moreover, a small body of literature suggests that men with ED have higher calorie intake due to frequent eating and a Western diet pattern as opposed to a Mediterranean-style dietary pattern.83 This aspect is crucial considering that currently available pharmacological treatments for ED are ineffective in a significant portion of men and only temporarily restore sexual activity with no long-term impact on the underlying vascular dysfunction or risk factors of ED.84 Thus, the implementation of lifestyle changes, alone or in combination with pharmacotherapy, may represent a milestone in the treatment of ED.

Male infertility is a crucial aspect related both with obesity and ED. In fact, in addition to the aforementioned risks for hypogonadism and ED, increasing evidence highlights the negative effects of obesity on semen parameters.85 The possible mechanisms include epigenetic (DNA methylation, histone modification and RNA alteration), hormonal and other factors such as ED, stress, inflammation and sleep apnea.85 Obesity may also play a negative role in assisted reproductive technologies (ART). In fact, although these data are to be confirm by more and larger studies, men affected by obesity undergoing ART have a statistically significant decrease in live birth rate compared with normal-weight and present a higher risk of nonviable pregnancy.85

The present study offers novel insights into the extent of ED among men with obesity. However, some limitations need to be considered. First, due to the small number of primary studies that provide complete clinical and biological (e.g. serum testosterone or estradiol levels) features of the participants, it was not possible to run meta-regression analyses using well-known independent risk factors for ED (such as dyslipidemia, hypertension, diabetes mellitus and depression) as moderators of findings. Importantly, after adjusting for confounders no significant association between overweight BMI category and ED was observed. In a sensitivity analyses, after removing a highly significant study, the present results became not statistically significant and in adjusted analyses no association was present between that BMI category and ED. Second, the data regarding abdominal obesity are limited only to a comparison of means between ED and controls, not taking in consideration potential confounders.[12](#ENREF_12) However, thedata shows that the ED group had, on average, 5 cm more abdominal girth than healthy controls suggesting an important role of abdominal adiposity for ED. Finally, data were mainly derived from cross-sectional and case-control studies that have inherent limitations, such as reverse causation.

In conclusion, the present study provides new insight on the prevalence of ED in men with obesity. Future prospective and longitudinal studies in populations with overweight and obesity are needed to characterize others risk factors such as diabetes, smoking and depression which are involved in the pathogenesis of ED. The findings suggest that clinicians should consider screening for ED in men affected by obesity as part of their routine cardiovascular disease risk assessment. Moreover, because of the common metabolic substrate of these two clinical conditions, managing obesity is a crucial approach in patients with ED who are affected by obesity. Physicians should also promote and stress the importance of lifestyle modifications when providing recommendations to patients regarding effective treatments for ED.

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**Legend to figure**

**Figure 1. Odds ratio (adjusted for potential covariates) of erectile dysfunction in overweight vs. normal weight**

**Abbreviations:** CI = confidence interval

**Figure 2. Odds ratio (adjusted for potential covariates) of erectile dysfunction in men affected by obesity vs. normal weight**

**Abbreviations:** CI = confidence interval

**Figure 3. Mean difference in body mass index between participants with erectile dysfunction and controls**

**Abbreviations:** ED = erectile dysfunction, CI = confidence interval

**Figure 4. Mean difference in waist circumference between participants with erectile dysfunction and controls**

**Abbreviations:** ED = erectile dysfunction, CI = confidence interval