BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis


1Service d’Histologie-Embryologie-Cytogénétique-CECOS, Hôpital Jean Verdier (AP-HP), 93143 Bondy, France 2Unité de Recherche en Épidémiologie Nutritionnelle, UMR US57 Inserm; U1125 Inria; Cnam; Université Paris 13, CRNH IdF, 93017 Bobigny, France 3University Hospital of Wales, Heath Park, Cardiff CF 14 4XW, UK 4Department of Occupational and Environmental Medicine, Bispebjerg Hospital of Copenhagen University, Bispebjerg Bakke, 2400 Copenhagen NV, Denmark 5University Department of Growth and Reproduction, GR 5064, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark 6Centre for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Centre, Meibergdreef 9, H4-205, 1105 AZ Amsterdam, The Netherlands 7Department of Preventive Medicine, Third Military Medical University, No. 30 Gaoyan Road, Shapingba District, Chongqing 400038, China 8Instituto de Fisiologia, Facultad de Ciencias Medicas, Universidad Nacional de Cordoba, Santa Rosa 1085, X5000ESU Cordoba, Argentina 9Department of Obstetrics and Gynaecology, College of Medicine, King Khalid University, PO Box 641, Abha, Saudi Arabia 10Department of Nutrition and Epidemiology, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115, USA 11Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115, USA 12Department of Obstetrics and Gynaecology, University of Szeged, 6725 Szeged, Semmelweis u.1., Hungary 13Departments of Obstetrics and Gynaecology, Room Ee22.71a, Erasmus MC, University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands 14Department of Public Health, Section of Epidemiology, Aarhus University, 8000 Aarhus C, Denmark 15Fertility-Assisted Fertilization Center, Av. Brig. Luis Antonio, 4545 Sao Paulo, Brazil 16Sexual Medicine and Andrology Unit, Department of Clinical Biophysics, University of Florence, Viale Pieraccini 6, I-50139 Florence, Italy 17Andrology Center, Department of Obstetrics and Gynecology, University Medical Center Ljubljana, Ljubljana, Slovenia 18Department of Obstetrics and Gynecology, University of Colorado Denver, 12631 East 17th Avenue, Mail Stop B198-3, Academic Office 1, Room 4515, Aurora, CO 80045, USA 19University of Catania, Section of Andrology, Endocrinology and Internal Medicine, Policlinico ‘G. Rodolico’, Via S. Sofia 78, 95123 Catania, Italy 20Center for Environmental Research and Children’s Health, UC Berkeley School of Public Health, 1995 University Avenue, Suite 265, Berkeley, CA 94704, USA 21Remapped, 180 Fullarton Road, Dulwich, Adelaide & School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia 22Department of Pharmacology and Toxicology, University of Iceland, Hofsvegata 53, IS-107 Reykjavik, Iceland 23Department of Ophthalmology, University of Szeged, H6720 Szeged, Koranyi for 10-11, Hungary 24Département de Santé Publique, Hôpital Avicenne (AP-HP), 93017 Bobigny, France 25Department of Nutrition, Ambroise Paré Hospital (AP-HP); University of Versailles Saint Quentin en Yvelines, 9 avenue Charles-de-Gaulle, 92100 Boulogne-Billancourt, France 26INSERM, U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France

*Correspondence address. Tel: +33-1-49-09-47-66; Fax: +33-1-49-09-45-18; E-mail: sebastien.czernichow@apr.aphp.fr

Submitted on August 21, 2012; resubmitted on September 27, 2012; accepted on October 2, 2012

TABLE OF CONTENTS

- Introduction
- Methods
- Literature search
- Study selection and data extraction
- Data synthesis and analysis
- Results
- Study characteristics

1 Both authors equally contributed to the manuscript.

© The Author 2012. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology. All rights reserved.
For Permissions, please email: journals.permissions@oup.com
BACKGROUND: The global obesity epidemic has paralleled a decrease in semen quality. Yet, the association between obesity and sperm parameters remains controversial. The purpose of this report was to update the evidence on the association between BMI and sperm count through a systematic review with meta-analysis.

METHODS: A systematic review of available literature (with no language restriction) was performed to investigate the impact of BMI on sperm count. Relevant studies published until June 2012 were identified from a PubMed and EMBASE search. We also included unpublished data (n = 717 men) obtained from the Infertility Center of Bondy, France. Abstracts of relevant articles were examined and studies that could be included in this review were retrieved. Authors of relevant studies for the meta-analysis were contacted by email and asked to provide standardized data.

RESULTS: A total of 21 studies were included in the meta-analysis, resulting in a sample of 13,077 men from the general population and attending fertility clinics. Data were stratified according to the total sperm count as normozoospermia, oligozoospermia, and azoospermia. Standardized weighted mean differences in sperm concentration did not differ significantly across BMI categories. There was a J-shaped relationship between BMI categories and risk of oligozoospermia or azoospermia. Compared with men of normal weight, the odds ratio (95% confidence interval) for oligozoospermia or azoospermia was 1.15 (0.93–1.43) for underweight, 1.11 (1.01–1.21) for overweight, 1.28 (1.06–1.55) for obese and 2.04 (1.59–2.62) for morbidly obese men.

CONCLUSIONS: Overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia. The main limitation of this report is that studied populations varied, with men recruited from both the general population and infertile couples. Whether weight normalization could improve sperm parameters should be evaluated further.

Key words: obesity / BMI / sperm concentration / total sperm count / meta-analysis

Introduction

Subfertility affects ~15% of couples who seek to obtain a pregnancy and a male contribution is identified in 20–50% of the cases (Thonneau et al., 1991). A gradual decrease in sperm quality since the 1970s, particularly of sperm count, has been suggested by two meta-analyses (Carlsen et al., 1992; Swan and Elkin, 1999). This reported secular trend has traditionally been attributed to various methodological (standardization of the techniques, abstinence delay) or environmental (geography, season, genetic, ethnic group, tobacco, toxins) factors (Jouannet et al., 2001) but has also coincided with a worldwide increase in the prevalence of overweight and obesity (Finucane et al., 2011).

The association between high adiposity and subfertility has not been clearly demonstrated in men. Data from three large-scale epidemiological studies suggest an elevated risk for infertility among couples when the male partner is overweight or obese (Sallmen et al., 2006; Nguyen et al., 2007; Ramlau-Hansen et al., 2007). Results of studies investigating the links between BMI and sperm parameters, the gold standard for evaluation of male fertility potential, remain controversial. Several reports have shown an inverse correlation between BMI and sperm concentration or total sperm count (TSC) (Jensen et al., 2004; Paasch et al., 2010) but others have failed to document this association (Aggerholm et al., 2008; Duits et al., 2010). A previous meta-analysis published in 2010 concluded that there was no evidence of an association between BMI and sperm concentration or TSC (MacDonald et al., 2010). However, data from most studies could not be aggregated for the meta-analysis and the conclusion was based on five publications only (Jensen et al., 2004; Koloszar et al., 2005; Fejes et al., 2006; Qin et al., 2007; Aggerholm et al., 2008). Moreover, ~30 original studies have been published since then. In a preliminary report, we showed that overweight and obesity were associated with an increased risk of presenting with oligozoospermia or azoospermia, compared with normal weight (Serondade et al., 2012a).

The purpose of the current study is to update the systematic review on the relationship between BMI and sperm count and to perform a meta-analysis.

Methods

Literature search

A systematic review of available literature was performed to investigate the impact of BMI on sperm parameters in human males according to the PRISMA statement (Liberati et al., 2009). Relevant studies published until June 2012 were identified from PubMed and EMBASE using a combined free text and the following MeSH search strategy: (‘overweight’ OR ‘weight’ OR ‘obesity’ OR ‘BMI’ OR ‘body fat’ OR ‘body weight’ OR ‘body mass index’ OR ‘adiposity’) AND (‘sperm’ OR ‘ semen’ OR ‘ spermatozoa’ OR ‘ sperm count’ OR ‘ sperm concentration’ OR ‘ semen quality’ OR ‘ semen parameters’ OR ‘ sperm quantity’ OR ‘ total sperm count’ OR ‘ oligozoospermia’ OR ‘ azoospermia’). References from these studies were also scrutinized to identify other relevant studies. No language restriction was applied.

Study selection and data extraction

Titles of all articles retrieved from the database searches were screened. We excluded studies without results on the relationship between BMI and sperm parameters, case reports, reviews, experimental or...
interventional studies, studies restricted to men with a particular pathology (such as a varicocele) and studies comparing exposed/non-exposed men. The abstracts of relevant articles investigating the relationship between BMI and sperm parameters were examined and all studies that could potentially be included in this review were retrieved, regardless of population size, origin or age. References from these studies and previous reviews were also scanned for any other relevant articles. Two reviewers independently extracted data (N.S. and C.F.) and there was no disagreement over eligibility of studies.

Owing to the wide variety of statistical methods and outcomes used in published studies (different BMI categories, mean or median, sperm concentration or TSC), authors of studies selected to be included in the present meta-analysis were contacted by email and asked to complete a standardized data extraction form indicating TSCs according to BMI categories, as specified by the World Health Organization (WHO: World Health Organization, 2000). We also included previously unpublished data obtained from all patients seen at the Infertility Center of Jean Verdier Hospital, Bondy, France, between January 2007 and December 2010, assigned as ‘Levy et al. (unpublished)’ study in the following text, table and figures.

Data synthesis and analysis
Analyses were performed using the following BMI categories: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), 30.0–39.9 (obesity) and ≥40.0 (morbid obesity) kg/m² (World Health Organization, 2000). Participants with a BMI between 18.5 and 24.9 kg/m² were considered as the reference group. Random effects models were used to obtain summary estimates in order to account for inter-study variation. Studies were weighted according to an estimate of statistical power.

A J-shaped association was found between BMI and abnormal sperm count according to WHO guidelines (Shayeb et al., 1999). We tested whether the association between BMI and sperm parameters could not be analyzed (Strain et al., 1982; Parazzini et al., 1993; Corti et al., 2006; Gao et al., 2007; Qin et al., 2007; Hammoud et al., 2008, 2010; Paal et al., 2008; Robeva et al., 2008; Nicopoulou et al., 2009; Stewart et al., 2009; Bak et al., 2010; Hofny et al., 2010; Paasch et al., 2010; Sekhavat and Moein, 2010; Wegner et al., 2010; Egwurugwu et al., 2011; Rybar et al., 2011; Fariello et al., 2012)

The present meta-analysis included a total of 21 eligible studies. All were cross-sectional studies, except two prospective cohort studies (Vujkovic et al., 2009; Hammiche et al., 2011, 2012). The study sample sizes ranged from 72 (Magnusdottir et al., 2005) to 1966 (Shayeb et al., 2011) and totaled 13 077 individuals, including men from Jean Verdier Hospital Infertility Center (n = 717) (Table I).

Study characteristics
The search strategy identified a total of 10 400 articles, including duplicates and articles that had no relevance to the primary research questions. After review of 287 abstracts, 64 articles providing BMI and sperm data were selected. Among them, 44 articles investigating the relationship between BMI and sperm parameters seemed potentially appropriate to be included in the meta-analysis (Fig. 1). We were able to contact 43 of the 44 authors by email (one email address was not available), allowing us to obtain original and complete data for 20 studies corresponding to 25 published articles (Eskenazi et al., 2003; Jensen et al., 2004; Fejes et al., 2005, 2006; Koloszar et al., 2005; Magnusdottir et al., 2005; Zorn et al., 2007, 2012; Aggerholm et al., 2008; Li et al., 2009; Vujkovic et al., 2009; Chavarro et al., 2010; Duits et al., 2010; Keltz et al., 2010; Martinet et al., 2010; Ramlau-Hansen et al., 2010; Hammiche et al., 2011, 2012; Lotti et al., 2011; Relwani et al., 2011; Shayeb et al., 2011; Tunc et al., 2011; Braga et al., 2012; Eskandar et al., 2012; La Vignera et al., 2012). Three authors could not contribute to the meta-analysis because of incomplete data (Strain et al., 1982; Nicopoulou et al., 2009; Paasch et al., 2010).

We included previously unpublished data obtained from Jean Verdier Infertility Center, Bondy, France. Data from 19 articles, totaling 8359 men, which addressed the association between BMI and sperm parameters could not be analyzed (Strain et al., 1982; Parazzini et al., 1993; Corti et al., 2006; Gao et al., 2007; Qin et al., 2007; Hammoud et al., 2008, 2010; Paal et al., 2008; Robeva et al., 2008; Nicopoulou et al., 2009; Stewart et al., 2009; Bak et al., 2010; Hofny et al., 2010; Paasch et al., 2010; Sekhavat and Moein, 2010; Wegner et al., 2010; Egwurugwu et al., 2011; Rybar et al., 2011; Fariello et al., 2012).

Association between BMI and sperm count abnormality
With azoospermia and oligozoospermia considered as a single outcome, a J-shaped association was found between BMI and abnormal sperm count (<40 M/ ejaculate) (Fig. 2; n = 13 077 men analyzed). Compared with normal weight men, the ORs (95% CI) for oligozoospermia or azoospermia were 1.15 (0.93–1.43) for underweight men,
1.11 (1.01–1.21) for overweight men, 1.28 (1.06–1.55) for obese men and 2.04 (1.59–2.62) for morbidly obese men (see also Supplementary data, Figs S1–IV).

A similar J-shaped association was observed between BMI and abnormal sperm concentration ($<15$ M/ml; $n = 13,453$ men analyzed). Compared with normal weight men, the ORs (95% CI) for oligozoospermia or azoospermia were 1.46 (1.14–1.88) for underweight men, 1.06 (0.95–1.18) for overweight men, 1.31 (1.07–1.61) for obese men and 1.97 (1.27–3.07) for morbidly obese men.

**Sensitivity analyses**

Using fixed effects models did not substantially modify the results (underweight: 1.03, 0.83–1.28; overweight: 1.12, 1.05–1.19; obese: 1.26, 1.15–1.38; morbidly obese: 2.36, 1.93–2.89). Also, excluding data from Levy et al. (unpublished) did not influence the results: when this study was excluded, the ORs (95% CI) for abnormal sperm count were 1.10 (0.89–1.37) for underweight, 1.10 (1.00–1.22) for overweight, 1.31 (1.08–1.60) for obesity and 2.11 (1.59–2.80) for morbid obesity.

Possible sources of heterogeneity were investigated by stratifying the studies according to study population type (general population or clinical population, see Supplementary data, Fig. SV).

**Assessment of publication bias**

The Egger test provided no evidence of publication bias when analyses were performed for underweight ($P = 0.92$), overweight ($P = 0.66$) or obesity ($P = 0.79$) using ‘oligozoospermia or azoospermia’ as abnormal sperm count. Similar results were obtained for oligozoospermia or azoospermia analyzed separately.

**Discussion**

This meta-analysis based on 13,077 men showed a J-shaped association between BMI and abnormal sperm count: underweight was associated with an increased but non-significant risk of abnormal sperm count, whereas overweight and obese men had a significantly elevated risk of abnormal sperm count compared with normal weight men.

The relationship between obesity and alteration of sperm parameters or male subfertility is likely to be multifactorial, and different pathophysiological hypotheses have been raised. First, alterations of the hypothalamic–pituitary–gonadal axis have been suggested to be involved in this process. Indeed, aromatization of steroids to estrogens in peripheral tissues leads to the hypogonadotropic hyperestrogenic hypogonadism previously described in obese men (Schneider et al., 1979), with a significant decrease in total and free testosterone levels and increase in estradiol ($E_2$), both leading to deleterious effects on spermatogenesis. Moreover, studies showed a decrease of sex hormone-binding globulin among obese men, notably mediated by hyperinsulinemia, emphasizing the negative feedback effect of elevated total $E_2$ levels (Stellato et al., 2000). Obesity is also associated with an increase of endorphins leading to a both lower LH pulse amplitude and GnRH production (Blank et al., 1994). Some authors have also suggested that obesity may directly alter spermatogenesis and...
<table>
<thead>
<tr>
<th>Study</th>
<th>Population*</th>
<th>Ascertainment of BMI</th>
<th>Repeated semen collection</th>
<th>Age (years, mean ± SD)</th>
<th>Percentage by BMI category (kg/m²)</th>
<th>Percentage by TSC category</th>
<th>Normozoospermia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggerholm et al. (2008), Denmark</td>
<td>1669 male volunteers from general population</td>
<td>Self-reported</td>
<td>Once</td>
<td>33.9 ± 8.8</td>
<td>0.5% 52.0 39.4 8.1 0 1.2%</td>
<td>11.1</td>
<td>87.7</td>
</tr>
<tr>
<td>Jensen et al. (2004), Denmark</td>
<td>1558 young male military recruits</td>
<td>Measured on site</td>
<td>Once</td>
<td>19.5 ± 1.3</td>
<td>3.5% 77.3 15.4 3.7 0.1 0.3%</td>
<td>45.2</td>
<td></td>
</tr>
<tr>
<td>Li et al. (2009), China</td>
<td>1338 healthy male volunteers</td>
<td>Measured on site</td>
<td>Once</td>
<td>32.4 ± 5.5</td>
<td>6.9% 74.1 17.8 1.2 0 0%</td>
<td>8.4</td>
<td>91.6</td>
</tr>
<tr>
<td>Ramlay-Hansen et al. (2010), Denmark</td>
<td>259 sons of mothers recruited during their pregnancy in 1984–1987</td>
<td>Self-reported</td>
<td>Once</td>
<td>20.1 ± 0.8</td>
<td>3.9% 72.2 17.8 6.1 0 0.8%</td>
<td>20.5</td>
<td>78.7</td>
</tr>
<tr>
<td>La Vignera et al. (2012), Italy</td>
<td>150 healthy non-smoking male volunteers</td>
<td>Self-reported</td>
<td>Twice</td>
<td>31.4 ± 2.3</td>
<td>0% 33.3 33.3 26.7 6.7 2.7%</td>
<td>41.3</td>
<td>56.0</td>
</tr>
<tr>
<td>Eskenazi et al. (2003), USA</td>
<td>97 non-smoking male volunteers without known fertility problems</td>
<td>Self-reported</td>
<td>Once</td>
<td>46.4 ± 15.9</td>
<td>0% 50.5 42.3 7.2 0 4.1%</td>
<td>12.4</td>
<td>83.5</td>
</tr>
<tr>
<td>Shayeb et al. (2011), UK</td>
<td>1966 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Once</td>
<td>33.1 ± 6.0</td>
<td>0.9% 40.8 44.9 12.5 0.9 EXC</td>
<td>18.2</td>
<td>81.8</td>
</tr>
<tr>
<td>Duits et al. (2010), The Netherlands</td>
<td>1401 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>Twice</td>
<td>36.4 ± 6.5</td>
<td>0.4% 47.3 41.9 9.7 0.7 6.3%</td>
<td>17.5</td>
<td>76.2</td>
</tr>
<tr>
<td>Martini et al. (2010), Argentina</td>
<td>793 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Once</td>
<td>34.9 ± 6.2</td>
<td>EXC 31.0 49.4 18.5 1.1 1.9%</td>
<td>52.7</td>
<td>45.4</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Population*</th>
<th>Ascertainment of BMI</th>
<th>Repeated semen collection</th>
<th>Age (years, mean ± SD)</th>
<th>Percentage by BMI category (kg/m²)</th>
<th>Percentage by TSC category</th>
<th>Normozoospermia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy et al. (unpublished data), France</td>
<td>717 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>Once</td>
<td>37.4 ± 7.5</td>
<td>0.4% 45.5 38.9 13.5 1.7</td>
<td>8.2% 27.6</td>
<td>64.2</td>
</tr>
<tr>
<td>Eskandar et al. (2012), Saudi Arabia</td>
<td>500 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Twice</td>
<td>34.8 ± 7.7</td>
<td>11.0% 13.4 24.0 26.4 25.2 1.4%</td>
<td>29.0</td>
<td>69.6</td>
</tr>
<tr>
<td>Chavarro et al. (2010), USA</td>
<td>483 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Once</td>
<td>36.3 ± 5.4</td>
<td>EXC 25.5 48.2 23.8 2.5 EXC</td>
<td>10.8</td>
<td>89.2</td>
</tr>
<tr>
<td>Koloszar et al. (2005) and Fejes et al. (2005, 2006), Hungary</td>
<td>473 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Twice</td>
<td>29.5 ± 3.6</td>
<td>6.3% 33.6 32.4 22.0 5.7 4.4%</td>
<td>30.0</td>
<td>65.6</td>
</tr>
<tr>
<td>Hammiche et al. (2012), The Netherland</td>
<td>449 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>Once</td>
<td>35.4 ± 6.5</td>
<td>1.1% 34.1 49.2 15.2 0.4 5.8%</td>
<td>35.2</td>
<td>59.0</td>
</tr>
<tr>
<td>Braga et al. (2012), Brazil</td>
<td>250 male partners from subfertile couples during IVF/ICSI cycles</td>
<td>Measured on site</td>
<td>Once</td>
<td>38.4 ± 9.3</td>
<td>2.0% 50.0 40.0 4.0 4.0 EXC</td>
<td>34.4</td>
<td>65.6</td>
</tr>
<tr>
<td>Vujkovic et al. (2009) and Hammiche et al. (2011), The Netherland</td>
<td>225 male partners from subfertile couples during IVF/ICSI cycles</td>
<td>Self-reported</td>
<td>Once</td>
<td>37.4 ± 5.3</td>
<td>0.9% 45.3 45.3 8.5 0 EXC</td>
<td>40.9</td>
<td>59.1</td>
</tr>
<tr>
<td>Study</td>
<td>Population Details</td>
<td>Methodology</td>
<td>BMI (Mean ± SD)</td>
<td>Underweight (%)</td>
<td>Normal Weight (%)</td>
<td>Overweight (%)</td>
<td>Obese (%)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Lotti et al. (2011), Italy</td>
<td>222 male partners from subfertile couples presenting in fertility center</td>
<td>Measured on site</td>
<td>35.3 ± 7.0</td>
<td>0%</td>
<td>59.0</td>
<td>32.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Zorn et al. (2007), Slovenia</td>
<td>189 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>34.4 ± 5.8</td>
<td>0%</td>
<td>43.9</td>
<td>41.8</td>
<td>14.3</td>
</tr>
<tr>
<td>Keltz et al. (2010) and Relwani et al.</td>
<td>185 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>37.5 ± 8.0</td>
<td>0.5%</td>
<td>22.2</td>
<td>47.0</td>
<td>29.2</td>
</tr>
<tr>
<td>Tunc et al. (2011), Australia</td>
<td>81 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>36.8 ± 5.2</td>
<td>0%</td>
<td>25.9</td>
<td>45.7</td>
<td>28.4</td>
</tr>
<tr>
<td>Magnusdottir et al. (2005), Iceland</td>
<td>72 male partners from subfertile couples presenting in fertility center</td>
<td>Self-reported</td>
<td>37.0 ± 5.4</td>
<td>0%</td>
<td>36.1</td>
<td>44.4</td>
<td>15.3</td>
</tr>
</tbody>
</table>

EXC, excluded; TSC, total sperm count.

*Size of the population corresponds to the size used for the main studied outcome.
Sertoli cell function (Winters et al., 2006), as indicated by the more severe decrease of inhibin B levels compared with the decrease of FSH. Another hypothesis is the increase of scrotal temperature caused by hip and abdominal fat tissue accumulation, or even scrotal fat deposition (Shafik and Olfat, 1981), which would involve spermatogenesis disturbances. Preferential accumulation in fatty tissue of toxic substances and liposoluble endocrine disruptors would amplify those alterations, as indicated by serum organochlorine levels being correlated with BMI (Magnusdottir et al., 2005).

When mean sperm concentrations were compared using SMD across BMI categories, no significant difference was observed (data not shown) in agreement with a previous meta-analysis (MacDonald et al., 2010). Our analysis based on dichotomized sperm count or concentration, however, is in sharp contrast with the previous meta-analysis. We believe the current meta-analysis overcomes many of the limitations of previous attempts to summarize the association between BMI and semen quality. First, because sperm count has a highly skewed distribution, it is not unexpected that our analyses comparing means across BMI categories or previous analyses based on correlation statistics suggested no association between BMI and sperm count. We believe our alternative approach of dichotomizing on correlation statistics suggested no association between BMI and semen quality. Secondly, study populations varied, with men recruited from the general population or infertile couples. However, this variability also suggests that both the clinical population and the general population would benefit from our findings. Thirdly, BMI and conventional semen parameters suffer from high uncertainty of measurement and only provide partial information about sperm functions. For example, functional tests, such as the hemizona assay or zona-binding test, have been suggested to be more relevant to predict fertilization outcome (Sifer et al., 2005). Cutoff values for sperm parameters have also been blamed to be of insufficient clinical relevance because of

Our study has several limitations. First, despite our efforts, incomplete data or absence of response from contacted authors led to the exclusion of 19 studies (Strain et al., 1982; Parazzini et al., 1993; Kort et al., 2006; Gao et al., 2007; Qin et al., 2007; Hammoud et al., 2010; Pauli et al., 2008; Robeva et al., 2008; Nicopoulou et al., 2009; Stewart et al., 2009; Bak et al., 2010; Hofny et al., 2010; Paasch et al., 2010; Sekhavat and Moein, 2010; Wegner et al., 2010; Egwurugwu et al., 2011; Rybar et al., 2011; Fariello et al., 2012). Among them, 10 studies corresponding to 4809 men (Kort et al., 2006; Hammoud et al., 2008, 2010; Robeva et al., 2008; Stewart et al., 2009; Bak et al., 2010; Hofny et al., 2010; Paasch et al., 2010; Sekhavat and Moein, 2010; Egwurugwu et al., 2011) argued for a relationship between BMI and sperm parameters, whereas 9 studies investigating 3550 men (Strain et al., 1982; Parazzini et al., 1993; Gao et al., 2007; Qin et al., 2007; Pauli et al., 2008; Nicopoulou et al., 2009; Wegner et al., 2010; Rybar et al., 2011; Fariello et al., 2012) did not. A selective outcome reporting can then probably be rejected and, owing to the high number of excluded studies showing an inverse association between BMI and sperm parameters, it is likely that this exclusion led to an underestimation of the computed ORs. Secondly, study populations varied, with men recruited from the general population or infertile couples. However, this variability also suggests that both the clinical population and the general population would benefit from our findings. Thirdly, BMI and conventional semen parameters were considered relevant enough to estimate body fat content and assess male fertility. BMI may not be the best indicator, as suggested by the questions about thresholds (Prentice and Jebb, 2001) and its inability to distinguish body fat composition or distribution, such as with waist circumference or waist-to-hip ratio (Fejes et al., 2005; Akpinar et al., 2007; Hammiche et al., 2012). Nevertheless, our findings will prove easy to apply, as BMI is a marker widely used in clinical and research settings. Similarly, conventional semen parameters suffer from high uncertainty of measurement and only provide partial information about sperm functions. For example, functional tests, such as the hemizona assay or zona-binding test, have been suggested to be more relevant to predict fertilization outcome (Sifer et al., 2005). Cutoff values for sperm parameters have also been blamed to be of insufficient clinical relevance because of
variations in semen analysis results, related to both physiological variations and limitations of the techniques used (Björmdahl, 2011). However, conventional semen parameters remain the gold standard for primary clinical evaluation of male fertility. Notably sperm count is a relatively consensual and objective semen parameter (Auger et al., 2000; Eustache and Auger, 2003) and TSC is a readily available parameter that most laboratories would assess fairly consistently with a WHO cutoff that can be used. We believe that, beyond controversies about reference limits, our meta-analysis offers several strengths, including the largest sample size ever published and the original use of standardized aggregated data.

In conclusion, a J-shaped association was found between BMI and the risk of abnormal sperm count, defined as oligozoospermia or azoospermia. Our systematic review with meta-analysis is in contradiction with a previous one that did not find associations of overweight and obesity with sperm concentration and TSC. Several methodological issues and updates in the literature have helped in understanding such a discrepancy. Although the risk may remain moderate at an individual level, our data indicate that high BMI affects sperm production. It is currently unclear whether weight loss can reverse this effect. Whereas weight loss was associated with an increase in TSC in a recent pilot cohort study (Hakonsen et al., 2011), others reported a severe worsening of semen parameters during the months after bariatric surgery (Sermontade et al., 2012b). Longitudinal studies and randomized controlled trials will then be required to evaluate whether weight normalization through diet modification and physical activity or bariatric surgery could improve sperm parameters and therefore male fertility.

Supplementary data
Supplementary data are available at http://humupd.oxfordjournals.org/.

Acknowledgements
Niels Jorgensen, Rigshospitalet, Copenhagen, Denmark; Yafei Li, Third Military Medical University, Chongqing, China; Zhihong Cui, Third Military Medical University, Chongqing, China; Rosa Molina, Laboratorio de Andrologia y Reproduccion, Cordoba, Argentina; Ruben Daniel Ruiz, Facultad de Ciencias Medicas, Universidad Nacional de Cordoba, Argentina; Thomas L. Toth, Harvard Medical School, Boston MA, USA; Russ Hauser, Harvard School of Public Health, Boston MA, USA; Janos Szoilos, University of Szeged, Hungary; Ane Marie Thulstrup, Aarhus University Hospital, Aarhus, Denmark; Daniela Braga, Fertility-Assisted Fertilization Centre, Sao Paulo, Brazil; Gabriela Halpern, Fertility-Assisted Fertilization Centre, Sao Paulo, Brazil; Mario Maggi, University of Florence, Italy; Joop Laven, Erasmus University Medical Center, Rotterdam, The Netherlands; Marijana Vujkovic, Erasmus University Medical Center, Rotterdam, The Netherlands; Fatima Hammiche, Erasmus University Medical Center, Rotterdam, The Netherlands; Gregor Majdic, Center for Animal Genomics, Veterinary Faculty, University of Ljubljana, Slovenia; Sangita Jindal, Albert Einstein College of Medicine And Montefiore Medical Center, Bronx, NY, USA; Rosita A. Condorelli, University of Catania, Catania, Italy; Rosana Hernandez Weldon, UC Berkeley School of Public Health, Berkeley CA, USA; Andrew J. Wyrobek, Lawrence Berkeley National Laboratory, Berkeley CA, USA; Ozlem Tunc, Repromed, Adelaide, South Australia; Tanja Thorsteinsson, Department of Assisted Reproduction, Landspitali University Hospital (current address: Art Medica), Iceland; Zoltan Zavaczki, Landstinget Gavleborg, Hudiksvall, Sweden.

Authors’ roles

Funding
J.E.C. was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases grant SP30DK046200-19 and B.E. was supported in part by National Institutes of Health grant P42ES04705.

Conflicts of interest
None declared.

References


