

Semen quality impairment is associated with sexual dysfunction according to its severity

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STUDY QUESTION: Is sexual dysfunction associated with severity of semen quality impairment in men with couple infertility?

SUMMARY ANSWER: In males of infertile couples the prevalence of erectile dysfunction (ED) increases as a function of semen quality impairment severity.

WHAT IS KNOWN ALREADY: Infertile men are at a higher risk for sexual dysfunction, psychopathological and general health disorders. However, it has never been systematically investigated if these problems are associated with severity of semen quality impairment.

STUDY DESIGN, SIZE, DURATION: Cross-sectional analysis of a first-time evaluation of 448 males of infertile couples attending an outpatient clinic from September 2010 to November 2015. In addition, 74 age-matched healthy, fertile men from an ultrasound study on male fertility were studied for comparison.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All subjects underwent a complete physical, biochemical, scrotal and flaccid penile colour-Doppler ultrasound evaluation and semen analysis. Patients had already undergone at least one semen analysis; therefore, the majority were aware of their sperm quality before taking part in the study. Validated tools, such as the International Index of Sexual Function-15 (IIEF-15), Premature Ejaculation Diagnostic Tool (PEDT), Middlesex Hospital Questionnaire (MHQ), National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), International Prostate Symptom Score and Chronic Disease Score (CDS), were used to evaluate, respectively, sexual dysfunction, premature ejaculation (PE), psychopathological traits, prostatitis-like symptoms, lower urinary tract symptoms and general health status.

MAIN RESULTS AND THE ROLE OF CHANCE: Among men with couple infertility, 96 showed azoospermia (Group #1), 245 at least one sperm abnormality (Group #2) and 107 normozoospermia (Group #3). Fertile men were considered as a control group (Group #4). After adjusting for age, we observed a higher prevalence of ED (IIEF-15-erectile function domain score <26) (18.3% versus 0%; $P = 0.006$) and PE (PEDT score >8) (12.9% versus 4.1%; $P = 0.036$) in males of infertile couples compared with fertile men. The ED prevalence increases as a function of semen quality impairment severity ($P < 0.0001$), even after adjusting for confounders (age, CDS, MHQ and NIH-CPSI total score), despite similar hormonal, glyco-metabolic and penile vascular status. Compared to fertile men, all three groups of males with couple infertility showed a poorer erectile function, associated with an overall psychopathological burden (MHQ total score), particularly with somatized anxiety (MHQ-S). Azoospermic men showed the worst erectile function and general health: in this group, erectile function was negatively associated not only with psychopathological disturbances (MHQ total and MHQ-S scores; $P < 0.0001$) but also with a less healthy phenotype (higher CDS; $P = 0.015$). In addition, azoospermic men reported higher PE prevalence and lower sexual desire and orgasmic function when compared to fertile men (all $P < 0.05$), all of which were related to psychopathological symptoms.

[†]F. Lotti and G. Corona contributed equally to this article.

LIMITATIONS, REASONS FOR CAUTION: The cross-sectional nature of the study represents its main limitation. A possible selection bias concerning the control group of healthy, fertile men recruited into an ultrasound study might have occurred. Finally, causality cannot be inferred in this type of study design and hence there should be some caution in interpreting the results.

WIDER IMPLICATIONS OF THE FINDINGS: Investigation of male sexual function, general health and psychological status in infertile couples, especially if azoospermic, is advisable, in order to improve not only reproductive but also general and sexual health.

STUDY FUNDING/COMPETING INTEREST(S): Grants were received from the Ministry of University and Scientific Research (SIR project to F.L., protocol number: RBSI14LFMQ). There are no conflicts of interest.

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Key words: sexual dysfunction / erectile dysfunction / premature ejaculation / infertile men / azoospermic men / fertile men / general health status / psychopathological disturbances

Introduction

Male infertility affects ~7% of all men (Krausz 2011; Giwercman and Giwercman, 2013). Although sexual dysfunctions are rarely the cause of male infertility (Krausz, 2011; Lotti et al., 2012), they are very frequent in the general male population of reproductive age (Corona et al., 2008, 2010a; McCabe et al., 2016).

So far, a few studies investigated erectile dysfunction (ED) and/or premature ejaculation (PE) in infertile men using validated instruments (Lotti et al., 2012; Gao et al., 2013). These studies reported a prevalence of ~18% and ~16% for ED and PE, respectively (Lotti et al., 2012; Gao et al., 2013). Infertile patients with sexual dysfunction have a higher prevalence of mood disturbances, such as anxiety and depressive symptoms, when compared to infertile men without sexual problems or fertile subjects (Ferraresi et al., 2013; Bechoua et al., 2016). However, the relationship between sexual dysfunction and the degree of fertility impairment has never been investigated.

Interestingly, a decreased general health status is associated with impaired male reproductive health (Salonia et al., 2009; Ventimiglia et al., 2015; Eisenberg et al., 2015, 2016a,b). In addition, serious life-threatening conditions such as atherosclerosis, metabolic syndrome and diabetes are associated with testosterone deficiency, which is more prevalent in subfertile males (Giwercman and Giwercman, 2013). Hence, the concept that male infertility might represent an early marker of poor general health is emerging. An early diagnosis of ED and the identification of its risk factors can provide useful information for stratifying cardiovascular risk (Dong et al., 2011; Salonia et al., 2012; Yamada et al., 2012; Vlachopoulos et al., 2013; Eisenberg et al., 2016a,b).

The aim of the present study is to investigate the relationship between severity of semen quality impairment and sexual function in a cohort of males of infertile couples. In addition, the data are compared to those obtained in a healthy control group with proven fertility.

Materials and methods

Patients

We studied a consecutive series of 448 male patients (mean \pm SD age 36.8 ± 7.9 years) attending the outpatient clinic of the Sexual Medicine and Andrology Unit of Florence (Italy) for the first time from September 2010 to November 2015, seeking medical care for couple infertility. All patients studied routinely underwent a standard diagnostic protocol for males of

infertile couples (see below) and were invited to join the study, and the resulting enrolment rate was 100%. Couple infertility was defined according to the World Health Organization (WHO, 2000). Patients were divided into three groups according to their sperm characteristics: azoospermic (Group #1), subjects with at least one abnormality (value $<5^{\circ}$ centile) in sperm concentration, progressive motility or sperm morphology (Group #2) and normozoospermic (Group #3; all the aforementioned sperm parameters $\geq 5^{\circ}$ centile) according to WHO (2010). In Group #1, subjects with sonographic evidence of bilateral absence of vas deferens were considered as patients with obstructive azoospermia (OA).

As a control group (Group #4), we evaluated 74 age-matched (mean \pm SD age 36.2 ± 5.0 years) healthy, fertile men from a Florence spin-off of an ultrasound study on male fertility sponsored by the European Academy of Andrology (EAA; <http://www.andrologyacademy.net/studies.aspx>), defined as healthy partners of a pregnant woman in the second or third trimester of pregnancy or who fathered a child during the last year, following natural conception. In particular, 116 subjects were invited to join the study and the resulting enrolment rate was 64%.

All subjects were evaluated before beginning any treatment. The data reported in this study for patients have been collected according to a 'Day Service' standard protocol for males of infertile couples, encoded by PACC L-99 (D/903/110 Azienda Ospedaliera-Universitaria Careggi [AOUC], Florence, Italy) and approved by the Regional Health Care Service (§DGRT n.1045; n.722; n.867), as previously described (Lotti et al., 2014a). Data reported for the healthy, fertile subjects were collected according to the EAA study protocol, approved by the Florence Ethical Committee (6 June 2013; Prot.2013/0024124) and the AOUC (11 November 2013; Prot.37896/2013, Rubrica n.60/13). All subjects underwent the following routine procedures: medical history, physical, biochemical, scrotal and flaccid penile colour-Doppler ultrasound evaluation and semen analysis. At the time of the first assessment, virtually all patients with infertility problems were aware of their semen quality, which was systematically retested in our center. In addition, all subjects were invited to complete self-administered validated questionnaires to evaluate sexual function, prostatitis-like symptoms and psychological traits. All subjects gave their written informed consent to have their clinical records included in a dedicated database and they were aware that their data, after having been made anonymous, would be used for clinical research purposes.

Physical examination and lifestyle parameters

A complete andrological and physical examination, and self-reported data on smoking, alcohol consumption behavior and physical activity were assessed according to a previous study (Lotti et al., 2015).

Table 1 Clinical, biochemical and seminal parameters of the subjects studied.

| | Males of infertile couples (n = 448) | | | Group 4 (n = 74) | P value |
|--|--------------------------------------|---------------------|---------------------|---------------------|---------|
| | Group 1 (n = 96) | Group 2 (n = 245) | Group 3 (n = 107) | | |
| Clinical and laboratory parameters | | | | | |
| Age (years) | 36.1 ± 7.8 | 37.3 ± 7.8 | 36.3 ± 8.0 | 36.2 ± 5.0 | 0.421 |
| Current smokers (%) | 28.1 | 22.4 | 26.1 | 24.3 | 0.558 |
| Current moderate-severe alcohol consumption (≥4 drinks/day), (%) | 3.8 | 4.8 | 3.0 | 1.4 | 0.570 |
| Current physical activity, (%) | 40.0 | 50.9 | 57.3 | 55.4 | 0.095 |
| Systolic blood pressure (mmHg) | 123.4 ± 11.9 | 124.7 ± 14.8 | 123.7 ± 13.7 | 120.8 ± 10.5 | 0.193 |
| Diastolic blood pressure (mmHg) | 78.1 ± 8.4 | 79.6 ± 8.2 | 78.6 ± 8.3 | 79.3 ± 6.2 | 0.414 |
| Waist circumference(cm) | 97.6 ± 14.0 | 95.7 ± 12.2 | 94.5 ± 13.1 | 93.3 ± 10.1 | 0.137 |
| History of cryptorchidism (%) | 9.8 | 3.3 | 0 | 0 | <0.0001 |
| Mean testis volume (Prader) (ml) | 16.0 ± 6.0 | 19.1 ± 4.4 | 20.9 ± 4.4 | 22.1 ± 4.0 | <0.0001 |
| Clinical varicocele (%) | 28.1 | 35.7 | 36.8 | 24.7 | 0.187 |
| History of genito-urinary infections (%) | 27.6 | 27.7 | 29.6 | 18.9 | 0.415 |
| LH (IU/l) | 3.94 [2.85–6.62] | 3.90 [2.86–5.40] | 3.08 [2.20–4.40] | 3.20 [2.20–4.45] | <0.0001 |
| FSH (IU/l) | 7.30 [3.42–15.30] | 5.32 [3.64–7.82] | 3.38 [2.52–5.00] | 3.35 [2.08–4.23] | <0.0001 |
| Total testosterone (nmol/l) | 14.9 ± 7.1 | 15.4 ± 5.6 | 15.4 ± 6.0 | 16.2 ± 5.3 | 0.594 |
| Calculated free testosterone (nmol/l) | 0.308 ± 0.123 | 0.319 ± 0.103 | 0.324 ± 0.130 | 0.320 ± 0.092 | 0.827 |
| SHBG (nmol/l) | 31.4 ± 14.9 | 31.9 ± 13.7 | 31.9 ± 11.8 | 34.4 ± 14.4 | 0.510 |
| PSA (ng/ml) | 0.67 [0.43–0.93] | 0.77 [0.52–1.06] | 0.63 [0.40–0.95] | 0.77 [0.49–0.99] | 0.118 |
| PRL (pmol/l) | 180.0 [112.0–242.0] | 158.0 [117.0–231.0] | 159.0 [123.8–226.5] | 160.0 [121.0–303.0] | 0.991 |
| TSH (mU/L) | 1.65 [1.15–2.40] | 1.71 [1.17–2.35] | 1.88 [1.23–2.54] | 1.49 [1.15–2.11] | 0.282 |
| Glycaemia (mmol/l) | 5.11 ± 0.94 | 5.06 ± 0.72 | 4.94 ± 0.72 | 5.00 ± 0.61 | 0.400 |
| Insulin levels | 9.7 [6.0–16.2] | 8.0 [6.0–12.1] | 8.3 [5.7–12.8] | 8.2 [5.8–11.9] | 0.293 |
| Total cholesterol (mmol/l) | 4.83 ± 1.14 | 5.14 ± 0.93 | 5.12 ± 1.01 | 4.99 ± 0.90 | 0.110 |
| HDL cholesterol (mmol/l) | 1.25 ± 0.34 | 1.30 ± 0.33 | 1.25 ± 0.31 | 1.26 ± 0.31 | 0.455 |
| LDL cholesterol (mmol/l) | 12.95 ± 0.96 | 3.18 ± 0.81 | 3.17 ± 0.85 | 3.02 ± 0.82 | 0.159 |
| Triglycerides (mmol/l) | 1.17 [0.80–1.59] | 1.19 [0.78–1.67] | 1.26 [0.88–1.78] | 1.20 [0.93–1.82] | 0.646 |
| Seminal parameters | | | | | |
| Genetic abnormalities (%) | 26 | 2.4 | 0.9 | 0 | <0.0001 |
| Sexual abstinence (days) | 4.7 ± 3.4 | 4.3 ± 1.9 | 3.9 ± 1.6 | 4.3 ± 2.5 | 0.128 |
| pH | 7.3 ± 0.5 | 7.6 ± 0.2 | 7.6 ± 0.3 | 7.7 ± 0.2 | <0.0001 |
| Semen volume (ml) | 2.5 ± 1.8 | 3.6 ± 1.8 | 3.2 ± 1.6 | 3.4 ± 1.4 | <0.0001 |
| Sperm concentration, ×10 ⁶ /ml | 0 | 9.0 [3.0–24.8] | 52.0 [28.0–121.0] | 70.0 [40.5–129.1] | <0.0001 |
| Sperm progressive motility (%) | | 30.2 ± 20.2 | 53.9 ± 11.4 | 58.1 ± 15.5 | <0.0001 |
| Sperm normal morphology (%) | | 2.0 [1.0–4.0] | 7.0 [5.0–12.0] | 7.0 [4.0–9.0] | <0.0001 |

Continued

Table 1 Continued

| | Males of infertile couples (n = 448) | | | | P value |
|---|--------------------------------------|-------------------|-------------------|------------------|---------|
| | Group 1 (n = 96) | Group 2 (n = 245) | Group 3 (n = 107) | Group 4 (n = 74) | |
| Leukocytospermia (%) | 5.1 | 9.0 | 9.0 | 8.6 | 0.471 |
| History of infertility | | | | | |
| Duration of infertility (years) | 1.5 [1.0–3.0] | 1.5 [1.0–3.0] | 2.0 [1.0–3.0] | | 0.364 |
| Female partner's age (years) | 33.2 ± 6.2 | 34.9 ± 6.5 | 34.1 ± 7.2 | 33.0 ± 4.3 | 0.178 |
| Colour-Doppler ultrasound | | | | | |
| Mean testis volume (ml) | 12.5 ± 5.6 | 15.1 ± 4.1 | 16.9 ± 4.9 | 19.0 ± 4.6 | <0.0001 |
| Severe varicocele (%) | 22.9 | 23.4 | 19.6 | 20.3 | 0.853 |
| Flaccid penile PSV (cm/s) | 17.6 ± 4.1 | 17.7 ± 4.2 | 18.2 ± 4.1 | 18.4 ± 3.0 | 0.377 |
| Flaccid penile acceleration (m/s ²) | 2.9 ± 0.6 | 2.9 ± 0.6 | 3.0 ± 0.6 | 3.0 ± 0.5 | 0.549 |

Subjects are divided into four groups: #1, azoospermic; #2, males with at least one sperm abnormality; #3, normozoospermic; #4, healthy, fertile men. The right column shows the P value of the unadjusted comparison among groups for different parameters. For continuous parameters, one-way ANOVA or Kruskal–Wallis test were used for comparisons of the four groups, for normally or non-normally distributed variables, respectively. For categorical parameters, chi-squared test was used for comparisons of the four groups. SHBG, sex hormone-binding globulin; PSA, prostate related antigen; PRL, prolactin; TSH, thyroid-stimulating hormone; HDL, high density lipoprotein; LDL, low density lipoprotein; PSV, peak systolic velocity. Data are expressed as mean ± SD when normally distributed, as medians (quartiles) for parameters with non-normal distribution, and as percentages when categorical. Bold characters emphasize significant associations.

Self-reported questionnaires

Patients were invited to complete several self-reported questionnaires, including: International Index of Sexual Function-15 (IIEF-15), Premature Ejaculation Diagnostic Tool (PEDT) National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), International Prostate Symptom Score (IPSS) and Middlesex Hospital Questionnaire (MHQ), according to previous studies (Lotti et al., 2012, 2014b). The Chronic Disease Score (CDS), an index of concomitant morbidities, was calculated as previously described (von Korff et al., 1992).

Colour-Doppler ultrasound

All patients underwent scrotal and flaccid penile colour-Doppler ultrasound using the ultrasonographic console Hitachi H21 (Hitachi Medical System, Tokyo, Japan) and a 7.5 MHz high-frequency linear probe (L54M 6–13 MHz) as previously reported (Corona et al., 2010b; Lotti et al., 2013; Rastrelli et al., 2014; Lotti and Maggi, 2015).

Semen analysis and biochemical evaluation

All patients underwent semen analysis, performed according to the WHO criteria (2010).

Biochemical parameters were assessed as previously reported (Lotti et al., 2016).

Data analysis

Data were expressed as mean ± SD when normally distributed, as medians (quartiles) for parameters with non-normal distribution, and as percentages when categorical.

For continuous parameters, one-way analysis of variance (ANOVA) or Kruskal–Wallis test were used for comparisons of more than two groups, and unpaired two-sided Student's t-tests or Mann–Whitney U-test for comparisons of two groups, for normally or non-normally distributed variables, respectively. Relative risk and 95% CI were calculated for the association of categorical parameters, and chi-squared test was used for comparisons. Subsequent multivariate analyses, adjusted for age along with other confounders when specified, were performed with analysis of covariance (ANCOVA) or binary logistic regression analysis for continuous and categorical parameters, respectively. When distribution of non-normal parameters could be normalized through logarithmic transformation, as in the case of NIH-CPSI total score, the same tests were applied to logarithmically transformed data. A sensitivity analysis was performed with continuity corrections for variables with zero cases.

Moderator analyses were performed to clarify whether the relationship between the IIEF-15-EFD and the CDS, the MHQ score and the NIH-CPSI score changed according to semen quality impairment severity. A moderator is a qualitative or quantitative variable that affects the direction and/or strength of the relationship between an independent or predictor variable and a dependent or criterion variable. General linear model (GLM) was used to examine the moderating role of seminal groups on IIEF-15-EFD and CDS, MHQ or NIH-CPSI score interaction.

Statistical analyses related to the main outcomes of the present study, i.e. ED and PE, were performed both including and excluding subjects with OA or genetic abnormalities.

All statistical analysis was performed on SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows 20.0. A $P < 0.05$ was considered as significant.

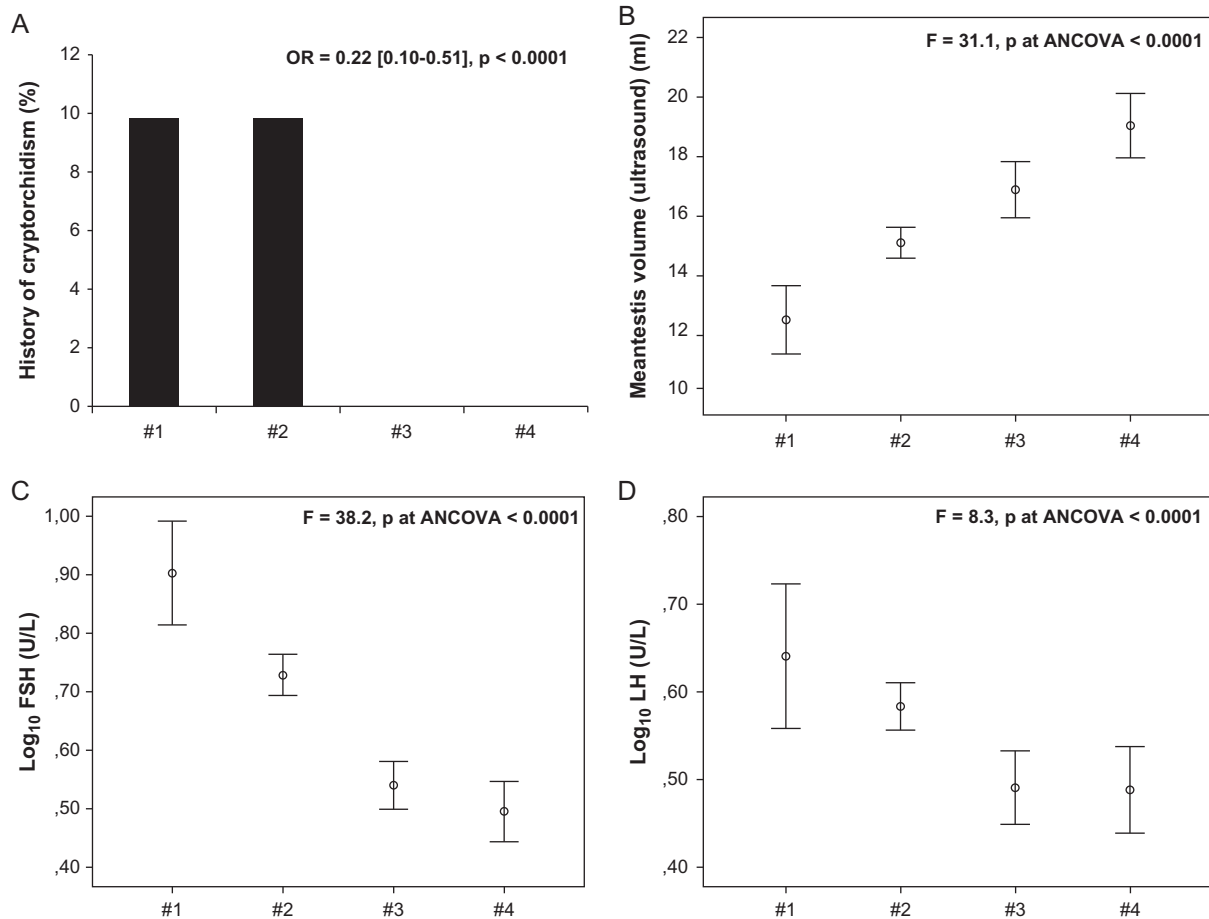


Figure 1 Comparison among groups of men for history of cryptorchidism, (panel A) mean testicular volume, (panel B) FSH (panel C) and LH (panel D) levels. Groups #1–4 indicate: #1–3, males of infertile couples (#1, azoospermic; #2, males with at least one sperm abnormality; #3, normozoospermic); #4, fertile men. The insets show the age-adjusted comparison among groups. In panels A–D, mean \pm 95% CI of the parameters evaluated has been plotted for each group considered (#1–4). OR: odds ratio.

Results

Among 448 consecutive males of infertile couples, 96 showed azoospermia (Group #1), 245 at least one abnormality in sperm parameters (Group #2) and 107 normozoospermia (Group #3). In particular, in Group #1 we found 12 subjects with sonographic evidence of OA (bilateral absence of vas deference). In Group #2, 28 subjects showed isolated oligozoospermia, 19 isolated asthenozoospermia, 51 isolated teratozoospermia, 18 oligo-asthenozoospermia, 31 oligo-teratozoospermia, 20 astheno-teratozoospermia and 78 oligo-astheno-teratozoospermia. A cohort of 74 age-matched healthy, fertile men was considered as a control group (Group #4). Table 1 reports the clinical characteristics of the sample. No differences in the age and duration of infertility for male and female partners, as well as in male lifestyle, were observed in groups #1–3 (Table 1). Genetic abnormalities were detected in 31 men (6.9%), including 5 karyotype abnormalities, 3 Y microdeletions and 23 vas deferens and/or seminal vesicle agenesis. Genetic abnormalities were higher in Group #1 when compared with groups #2 and #3 (Table 1). Statistical analyses related to the main outcomes of the present study, i.e. ED and PE, were

performed both including and excluding subjects with OA or genetic abnormalities (see below).

Considering Group #2, comparing subjects with isolated or multiple sperm abnormalities, only mean testis volume (both at Prader and ultrasound evaluation) was significantly different among subgroups, being lower in oligo-astheno-teratozoospermic men and higher in subjects with isolated asthenospermia as compared to the rest of Group #2 sample (not shown). Conversely, no differences in other clinical, biochemical, psychological and sexual parameters were observed among subgroups (not shown), hence, Group #2 was considered as a single category for statistical analysis.

Clinical and biochemical parameters

The reported frequency of cryptorchidism, at medical history, increased as a function of semen quality impairment severity (Table 1 and Fig. 1, panel A). Accordingly, mean testis volume, as assessed by Prader (Table 1) and ultrasound evaluation (Table 1 and Fig. 1, panel B), decreased and gonadotrophin levels (Table 1 and Fig. 1, panels C–D) increased, as a function of severity of semen quality impairment. In

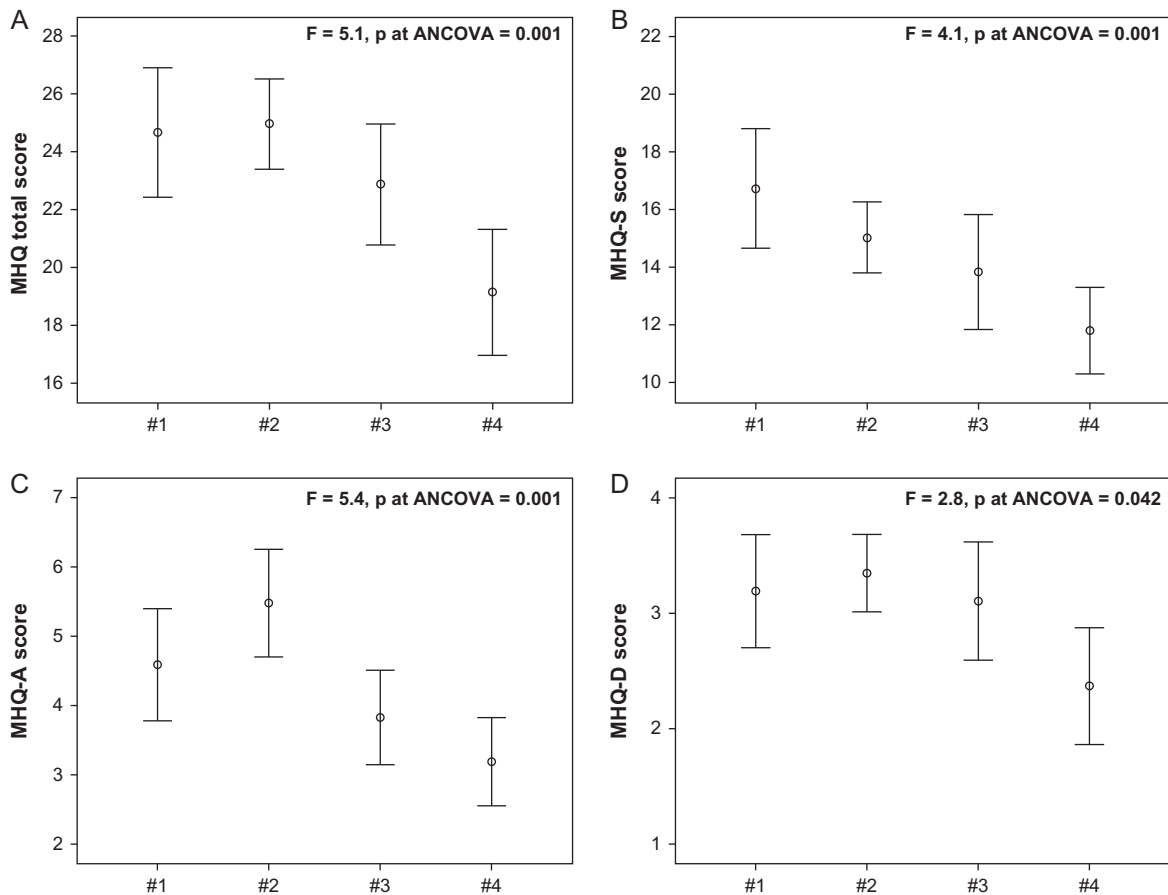


Figure 2 Comparison among groups for psychopathological traits. Comparison among groups for: overall psychopathological traits (MHQ total score) (panel **A**); somatized anxiety (MHQ-S) subdomain score (panel **B**); free-floating anxiety (MHQ-A) subdomain score (panel **C**); depressive symptoms (MHQ-D) subdomain score (panel **D**). Groups #1–4 indicate: #1–3, males of infertile couples (#1, azoospermic; #2, males with at least one sperm abnormality; #3, normozoospermic); #4, fertile men. The insets show the age-adjusted comparison among groups. MHQ, Middlesex Hospital Questionnaire. In panels A–D, mean \pm 95% CI of the parameters evaluated has been plotted for each group considered (#1–4).

particular, Group #1 showed higher prevalence of cryptorchidism, lower mean testicular volume and higher gonadotrophins (all $P < 0.05$), compared to groups #2, #3 and #4. In addition, in Group #1, OA subjects showed higher mean testis volume and lower gonadotrophins (all $P < 0.05$) with respect to the rest of the azoospermic sample, without significant differences in total or calculated free testosterone levels (not shown).

No other significant differences in hormonal, glyco-metabolic and clinical parameters (including flaccid penile peak systolic velocity and acceleration) were observed among the groups (Table 1).

Psychological traits

MHQ results were available for 516 men (98.8%). Overall, MHQ total score, an index of mood and anxious psychopathology, increased as a function of severity of semen quality impairment (Fig. 2, panel A). Accordingly, somatized anxiety (MHQ-S), free-floating anxiety (MHQ-A) and depressive symptoms (MHQ-D) scores decreased from Group #1 to #4 (Fig. 2, panels B–D).

Prostatitis-like symptoms

NIH-CPSI and IPSS results were available for 516 (98.8%) and 510 (97.7%) men, respectively. At ANCOVA, after adjusting for age, NIH-CPSI total or subdomains (pain and quality of life) scores were significantly lower in Group #4 when compared to the rest of the sample (Fig. 3, panels A–C). Conversely, no difference in IPSS total score was observed (not shown).

Chronic disease score

CDS was significantly different among the groups (Fig. 3, panel D), being higher in Group #1 when compared to the rest of the sample, even after adjusting for age (Group #1 = 0.9 ± 2.5 versus groups #2–4 = 0.3 ± 1.1 ; $F = 13.5$, $P < 0.0001$). Accordingly, Group #4 showed the lowest prevalence of men with CDS > 0 when compared to the rest of the sample (Group #4 = 6.8% versus #1–3 = 16.1%, $P = 0.022$), even after adjusting for age (odds ratio (OR) = 0.39 [0.15–0.99], $P = 0.049$).

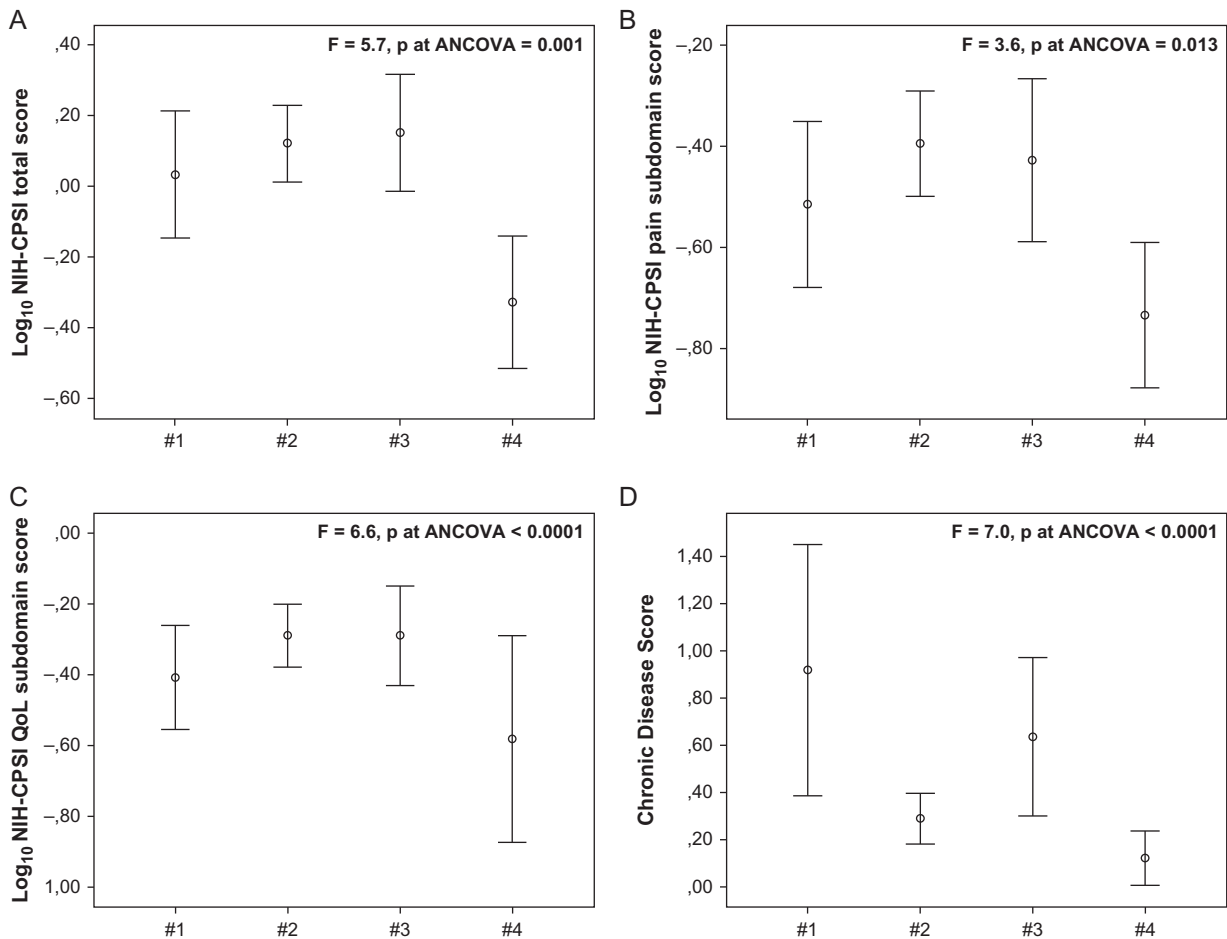


Figure 3 Comparison among groups for prostatitis-like symptoms and Chronic Disease Score. Comparison among groups for: NIH-CPSI total score (panel **A**); NIH-CPSI pain subdomain score (panel **B**); NIH-CPSI quality of life subdomain score (panel **C**); Chronic Disease Score (CDS) (panel **D**). Groups #1–4 indicate: #1–3, males of infertile couples (#1, azoospermic; #2, males with at least one sperm abnormality; #3, normozoospermic); #4, fertile men. The insets show the age-adjusted comparison among groups. NIH-CPSI, National Institute of Health-Chronic Prostatitis Symptom Index. In panels A–D, mean \pm 95% CI of the parameters evaluated has been plotted for each group considered (#1–4).

Sexual function

IIEF-15 results were available for all the subjects studied. Among males of infertile couples, 82 (18.3%) reported ED (IIEF-15-EFD score <26). In particular, 53 patients (11.8%) had mild, 16 (3.6%) mild to moderate, 8 (1.8%) moderate and 5 (1.1%) severe ED. Conversely, none of the fertile subjects had ED. After adjusting for age, the prevalence of any ED was higher in males of infertile couples compared with fertile men (OR = 0.06 [0.01–0.46], $P = 0.006$).

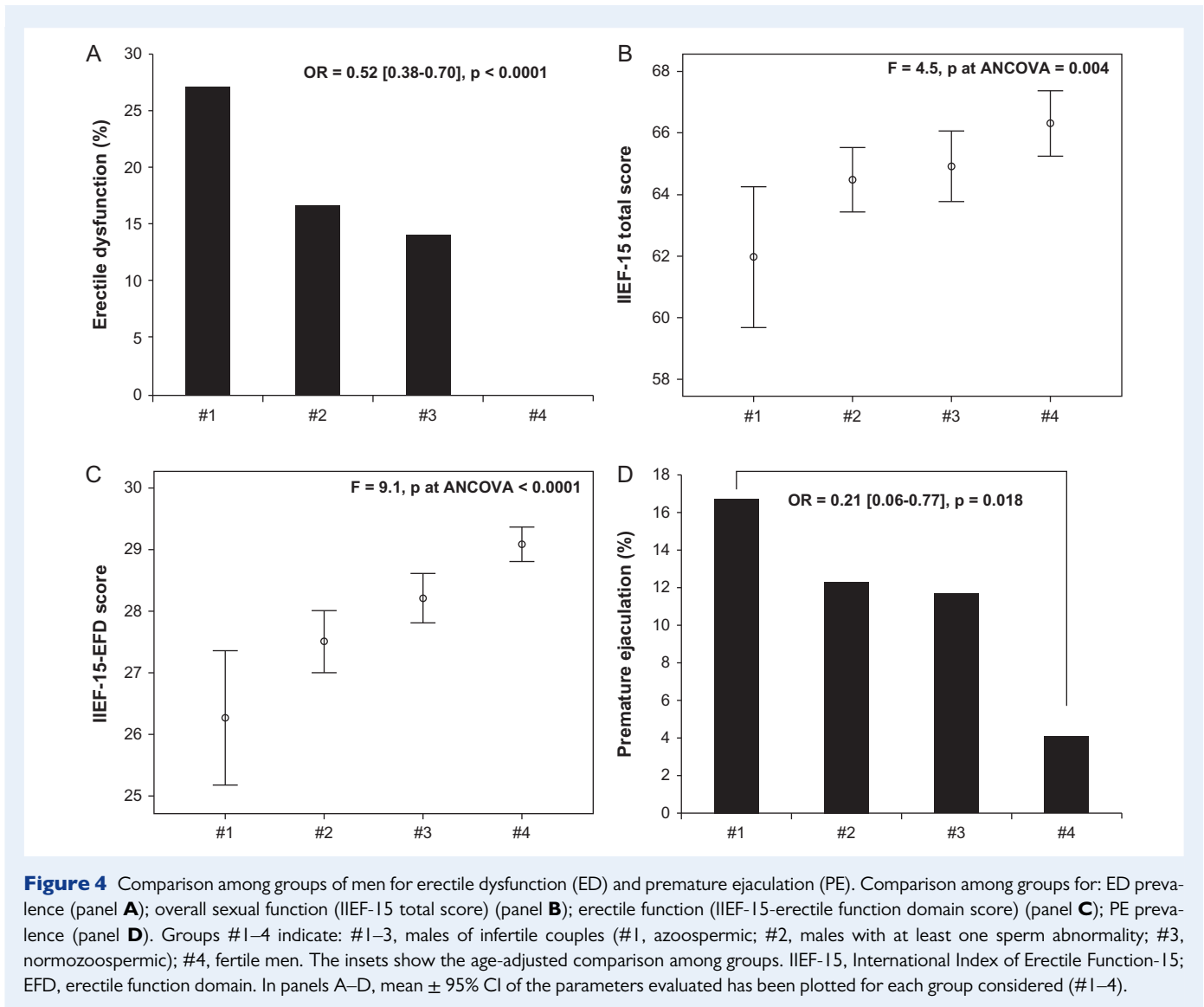
A significant difference in the prevalence of any kind of ED was observed among groups (Fig. 4, panel A). In particular, Group #1 showed the highest and Group #4 the lowest prevalence of ED, even after adjustment for age (not shown). Similar results were observed when subjects with IIEF-15-EFD score <22 were considered (OR = 0.30 [0.17–0.56], $P < 0.0001$). Accordingly, IIEF-15 total and EFD scores decreased as a function of semen quality impairment severity (Fig. 4, panels B–C), with EFD score being the lowest in Group #1 and highest in Group #4 (not shown). The differences in

ED and IIEF-15-EFD score among groups were confirmed after adjustment for age, CDS, MHQ and NIH-CPSI total score (OR = 0.55 [0.39–0.77], $P < 0.0001$ and $F = 5.5$, $P = 0.001$, respectively). Similar results were observed when subjects with OA (OR = 0.57 [0.40–0.81], $P = 0.002$ and $F = 3.87$, $P < 0.01$, for ED prevalence and IIEF-15-EFD score, respectively) or genetic abnormalities (OR = 0.58 [0.41–0.84], $P = 0.003$ and $F = 3.69$, $P < 0.02$, for ED prevalence and IIEF-15-EFD score, respectively) were excluded from the analysis.

After adjusting for age, Group #1 showed lower scores in sexual desire (7.4 ± 1.4 versus 7.9 ± 1.4 ; $F = 4.20$, $P < 0.05$) and orgasmic function (8.9 ± 2.1 versus 9.5 ± 1.1 ; $F = 4.67$, $P < 0.05$) IIEF-15 subdomains when compared to Group #4. No differences in intercourse and overall sexual satisfaction were observed among groups (not shown).

Ejaculatory function

PEDT results were available for 519 men (99.4%). According to PEDT score, 58 males of infertile couples (12.9%) reported PE: 26 (5.8%)



'probable PE' (PEDT score 9–10) and 32 (7.1%) 'overt PE' (PEDT score \geq 11). Among fertile subjects, three reported PE: 1 (1.4%) probable PE and 2 (2.7%) overt PE. After adjusting for age, the prevalence of any PE was lower in fertile men than in patients of infertile couples (OR = 0.28 [0.09–0.92], $P = 0.036$). The highest prevalence of any PE was observed in Group #1, which was significantly different from Group #4 (Fig. 4, panel D). Similar results were observed when subjects with OA or genetic abnormalities were excluded from the analysis (not shown).

Moderator analysis

We evaluated whether the relationship among IIEF-15-EFD score and CDS, MHQ and NIH-CPSI scores would change as a function of severity of semen quality impairment. Accordingly we estimated the moderation effect of being in the different seminal groups on the interaction of IIEF-15-EFD with other variables, including CDS, MHQ and NIH-CPSI (GLM). We used the moderator analysis, which allows for the identification of subpopulations of subjects in whom a specific

relationship between two variables is more likely. IIEF-15-EFD score was negatively associated with CDS ($r = -0.158$, $P < 0.0001$), MHQ ($r = -0.300$, $P < 0.0001$) and NIH-CPSI total score ($r = -0.174$, $P < 0.0001$) as well as with age ($r = -0.152$, $P = 0.001$). The relationship between IIEF-15-EFD score and CDS or MHQ, but not NIH-CPSI, score, was differentially moderated by different seminal groups, according to the GLM (Fig. 5, panels A–D). IIEF-15-EFD was found to be associated with MHQ total score in groups #1, #2 and #3, but not in #4 (Fig. 5, panel A). Considering MHQ subdomains, similar associations were verified only for MHQ-S (Fig. 5, panel B). In addition, GLM revealed significant interactions between CDS and categorization into seminal groups on IIEF-15-EFD score. IIEF-15-EFD was found to be associated with CDS in Group #1, but not in the other groups (Fig. 5, panel C). Conversely, the relationship between IIEF-15-EFD and NIH-CPSI total score was not moderated by different seminal groups (Fig. 5, panel D; data not shown). Similar results were observed when subjects with OA were excluded from the analyses (not shown).

In addition, GLM revealed significant interactions between MHQ-D score and categorization into seminal groups (MHQ-D score * Group

#1 versus #4: $F = 4.3$, $P = 0.015$, adjusted for age, CDS, NIH-CPSI total score, MHQ-A and MHQ-S scores) on sexual desire subdomain score, as sexual desire was found to be associated with MHQ-D score in Group #1 ($\beta = -0.314$, $P = 0.016$), but not in Group #4 ($\beta = -0.186$, $P = 0.166$). In a similar model, GLM revealed significant interactions between MHQ-S score and categorization into seminal groups (MHQ-S score * Group #1 versus #4: $F = 7.1$, $P = 0.01$, adjusted for age, CDS, NIH-CPSI total score, MHQ-A and MHQ-D scores) on orgasmic function subdomain score, as orgasmic function was found to be associated with MHQ-S in Group #1 ($\beta = -0.354$, $P = 0.009$), but not in Group #4 ($\beta = -0.209$, $P = 0.150$).

Finally, GLM revealed a significant interaction between MHQ total score and categorization into seminal groups (MHQ total score * Group #1 versus #4: $F = 7.4$, $P = 0.001$, adjusted for age, CDS and NIH-CPSI total score) on PE, as PE was found to be associated with

MHQ total score in Group #1 (OR = 1.09 [1.02–1.16], $P = 0.013$), but not in #4 (OR = 1.04 [0.94–1.15], $P = 0.473$).

Similar associations were observed when subjects with OA or genetic abnormalities were excluded from the analysis (not shown).

Discussion

This is the first study investigating the association between the severity of the infertility condition and sexual dysfunction in males of infertile couples, comparing results with those of a control group of healthy, fertile subjects of similar age. We essentially found that having semen impairment exerts a negative effect not only on fathering but also on male sexuality. In particular, ED prevalence increases as a function of severity of semen quality impairment, despite similar hormonal (including testosterone), glyco-metabolic and penile vascular status of the

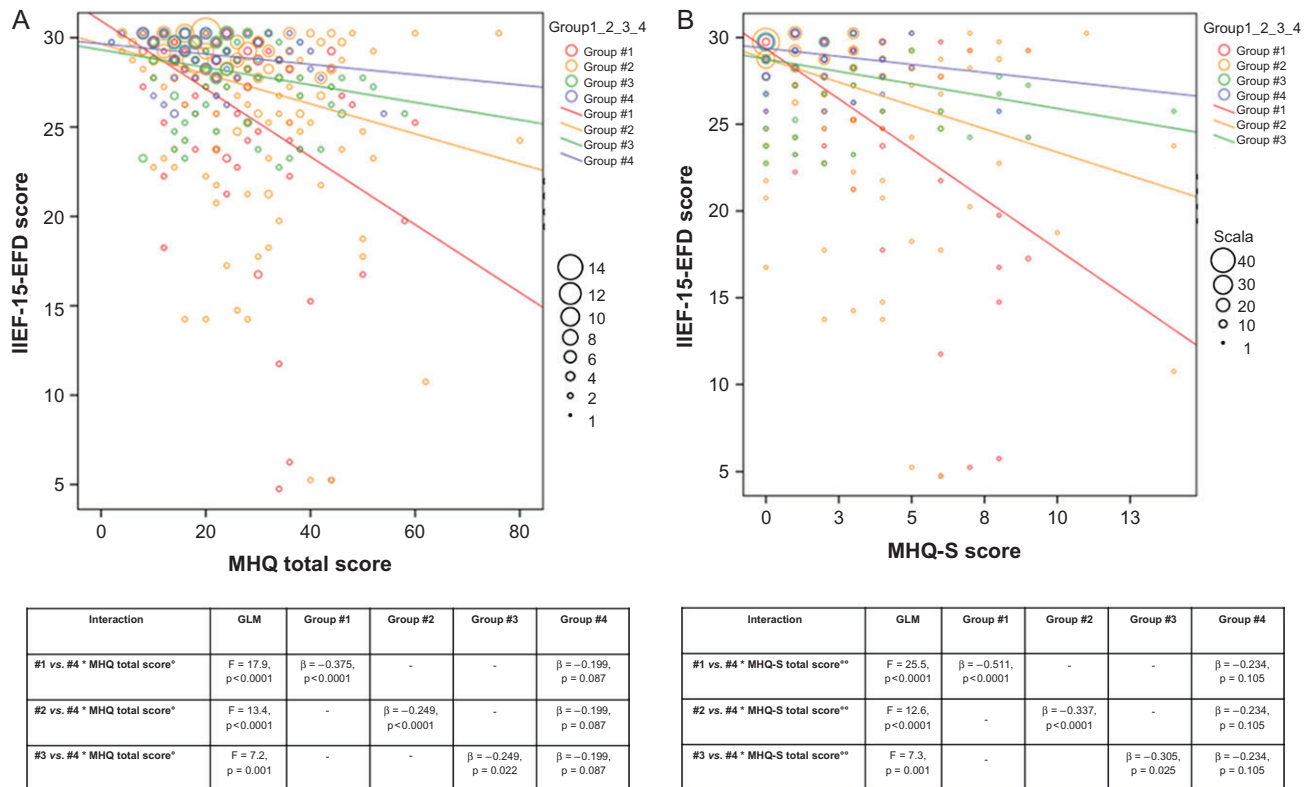


Figure 5 Associations between IIEF-15-erectile function domain (EFD) score and psychopathological traits, CDS or prostatitis-like symptoms in groups of men with different severity of semen quality impairment, according to moderator analysis. Associations, in groups with different severity of semen quality impairment, of erectile function (IIEF-15-EFD score) with: overall psychopathological symptoms (MHQ total score) (panel **A**); somatized anxiety (MHQ-S) subdomain score (panel **B**); CDS (panel **C**); NIH-CPSI total score (panel **D**). Tables show F and p value of the interactions between moderator variables (comparison between groups with different severity of semen quality impairment) and MHQ total score, MHQ-S subdomain score and CDS, in a moderator analysis adjusted for confounders considering as dependent variable the IIEF-15-EFD score. Accordingly, associations between IIEF-15-EFD score and the aforementioned parameters in different seminal groups are shown. Because the relationship between IIEF-15-EFD and NIH-CPSI total score was not moderated by different seminal groups, no Table is reported in panel **D**. ° adjusted for age, NIH-CPSI total score and CDS; °° adjusted for age, NIH-CPSI total score, CDS, MHQ-A and MHQ-D scores; °°° adjusted for age, NIH-CPSI and MHQ total scores. MHQ, Middlesex Hospital Questionnaire; A, free-floating anxiety; S, somatized anxiety; D, depressive traits; IIEF-15, International Index of Erectile Function-15; NIH-CPSI, National Institute of Health-Chronic Prostatitis Symptom Index; GLM, general linear model. Groups #1–4 indicate: #1–3, males of infertile couples (#1, azoospermic, red circles and lines; #2, males with at least one sperm abnormality, orange circles and lines; #3, normozoospermic, green circles and lines); #4, fertile men (blue circles and lines). The circle size reflects the number of observations.

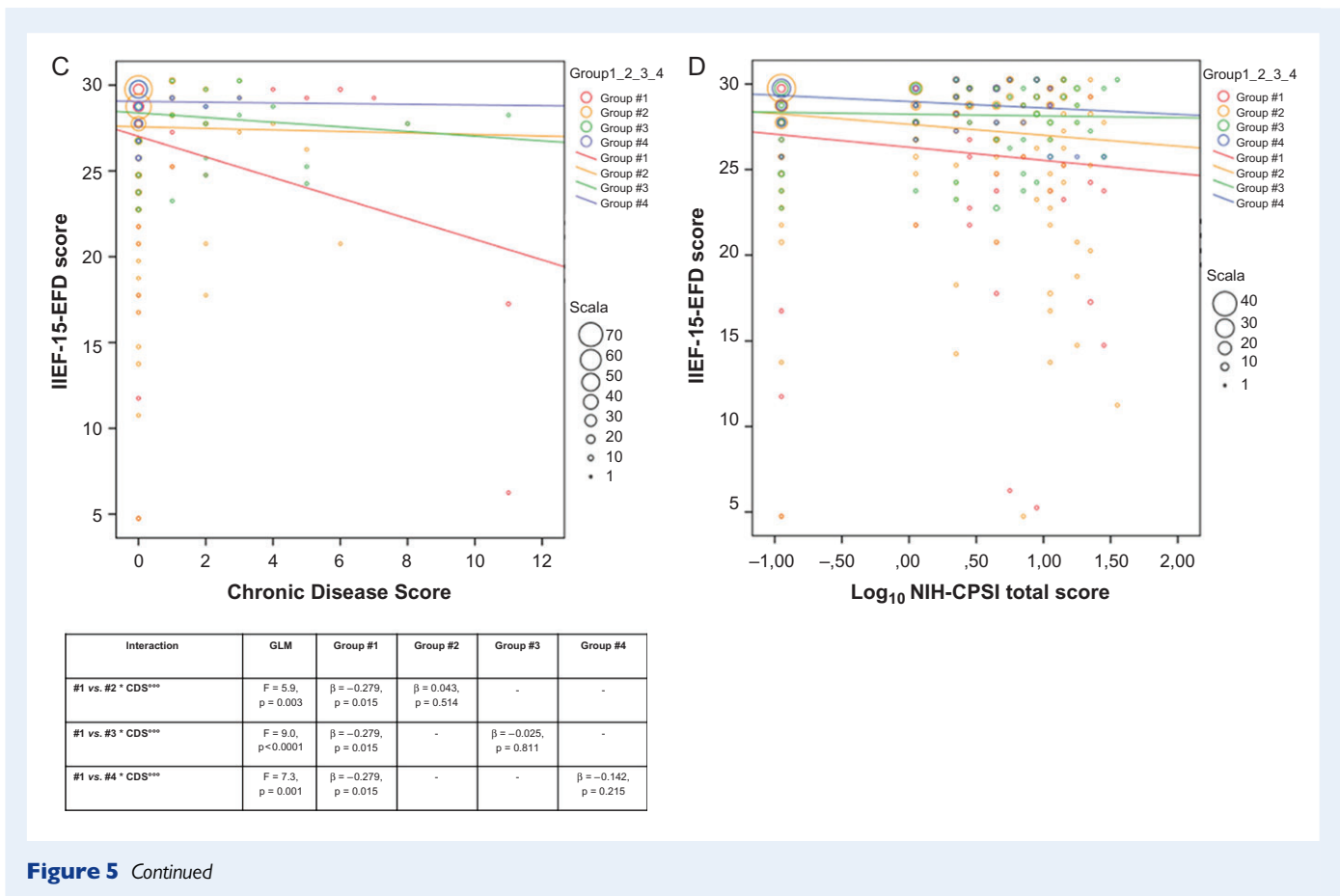


Figure 5 Continued

different groups. Compared to fertile subjects, all males with couple infertility showed a poorer erectile function closely associated with an increased psychopathological burden, particularly with somatized anxiety. Azoospermic men showed the worst sexual function and general health, with psychopathological traits and a less healthy phenotype being the most important factors underlying ED. In this group, ejaculatory latency, sexual desire and orgasmic function were reduced with respect to fertile men, and mainly associated with mood disturbances.

In our cohort, ED prevalence is in agreement with previous reports on infertile men (Lotti et al., 2012; Gao et al., 2013). Erectile function decreased in a stepwise fashion as a function of severity of semen quality impairment, although ED-related hormonal, glyco-metabolic and penile vascular parameters were not different among seminal groups. Despite this evidence, a less healthy phenotype, as assessed by CDS, was observed in infertile men, being the worst in the azoospermic group. In addition, only in the azoospermic group was CDS associated with ED. It can be speculated that the relatively young age of our cohort, with a limited duration of any underlying diseases, might explain the lack of difference observed in ED-related parameters despite a stepwise increase in CDS as a function of semen quality impairment. Accordingly, men with couple infertility have a higher rate of cancerous (Raman et al., 2005; Walsh et al., 2010; Eisenberg et al., 2013) and noncancerous (Salonia et al., 2009) conditions than age-matched males of the general population or fertile men. In addition, in line with our data, a relationship between a decreased general

health and sperm abnormalities has been previously reported (Eisenberg et al., 2015; Ventimiglia et al., 2015). Our data add new insights to this field. ED is a well-known risk factor for cardiovascular diseases in the general population (Dong et al., 2011; Yamada et al., 2012; Vlachopoulos et al., 2013). We suggest that the presence of ED in infertile—particularly in azoospermic—men, might alert physicians to evaluate possible subclinical underlying morbidities. Whether or not ED in infertile subjects might represent an earlier marker of forthcoming cardiovascular diseases would need further studies.

As expected, azoospermic men had a higher prevalence of cryptorchidism, lower mean testicular volume and higher gonadotrophins, compared to the other groups of patients (#2 and #3) and controls (#4), but testosterone levels were similar. Of note, we observed a slightly decreased testis volume and only moderately increased gonadotrophin levels with normal testosterone, while other studies reported different clinical or hormonal characteristics in azoospermic men (Wosnitzer et al., 2014; Bobjer et al., 2016). This may depend on the patient characteristics of the cohort investigated. For example, a higher prevalence of OA patients (without sonographic evidence of bilateral absence of vas deferens) or of subjects with maturation arrest might explain the different results (Wosnitzer et al., 2014). Hormonal findings indicate a frequent condition of compensated hypogonadism in azoospermic men. It has been hypothesized that compensated male hypogonadism represents a milder form of hypogonadism potentially

associated with neurological, psychological and cardiovascular disturbances, including alterations of bone metabolism and glycolipid profile (Giannetta *et al.*, 2012; Bobjer *et al.*, 2016). In subjects with sexual dysfunction (Corona *et al.*, 2014) and in the general population (Tajar *et al.*, 2010), those with compensated hypogonadism more often report mood impairment, including higher somatized anxiety and depressive symptoms, when compared to eugonadal patients. A possible explanation is that the testosterone threshold to maintain adequate mood level is lower than for other testosterone-dependent functions (Corona *et al.*, 2014).

In our cohort, psychopathological traits increase in a stepwise fashion as a function of semen impairment. We found, for the first time, that erectile function is negatively associated with somatized anxiety, which was highest in azoospermic men. Somatized anxiety is the unconscious process by which psychological distress is expressed as physical symptoms (APA, 2013). It is well known that infertile men may develop feelings of inadequacy, guilt, depression, distress, anxiety (Ferraresi *et al.*, 2013; Bechoua *et al.*, 2016), low virility, low self-esteem (Owens, 1982; Gannon *et al.*, 2004) and psychological pressure resulting from sex aimed at conception (Monga *et al.*, 2004; Song *et al.*, 2015). Accordingly, the announcement of azoospermia has been described as 'the worst news ever received' (Johansson *et al.*, 2011). Infertility *per se* and related psychological problems, including anxiety, are associated with sexual dysfunction, including ED (Berger, 1980; Marci *et al.*, 2012; Ferraresi *et al.*, 2013; Bechoua *et al.*, 2016).

The prevalence of PE observed in the present study is similar to what has been reported in the general population (McCabe *et al.*, 2016). Azoospermic men showed a higher PE frequency when compared to fertile men, associated with psychopathological alterations, in line with a previous study (Gao *et al.*, 2013). The relationship between anxiety (Lotti *et al.*, 2012; Zhang *et al.*, 2013a; Gao *et al.*, 2014) or depression (Son *et al.*, 2011; Gao *et al.*, 2013; Zhang *et al.*, 2013a,b; Gao *et al.*, 2014) and PE has been previously reported.

Azoospermic men also showed lower sexual desire and orgasmic function when compared to fertile men. Previous studies reported that hypoactive sexual desire is more prevalent in infertile men (Ramezanzadeh *et al.*, 2006; Smith *et al.*, 2009) than in the general population (Laumann *et al.*, 1999; Corona *et al.*, 2013, 2016). This has been related to the loss of spontaneity of sexual intercourse, deprived of its recreative value and subordinated to pregnancy (Cousineau and Domar, 2007). It could be speculated that azoospermic men, aware that the sexual act cannot lead to pregnancy ('firing blanks'), experience both depressive symptoms and somatic anxiety, related to decreased sexual desire and orgasmic function, respectively, along with ED.

Our study has some limitations. First, due to the cross-sectional nature of the study, no causality hypothesis can be inferred. In addition, a possible selection bias concerning the control group of healthy, fertile men might have occurred. Hence, caution is advisable in interpreting the results. Furthermore, in the CDS, some of the agents described are no longer commonly prescribed, while newer agents for treating the conditions are not listed, and chronic infections are not represented. Of note, the trend of CDS in different seminal groups is more heterogeneous than those observed for other endpoints. Hence, results derived from CDS must be considered with caution.

Another limitation is that the results obtained can be considered biased by the participants knowing their fertility status. Considering

that our unit represents a second-level fertility center, patients consulting for couple infertility for the first time usually had already undergone at least one semen analysis. Hence, the majority of patients evaluated in our study were aware of their sperm quality. Even fertile subjects were aware of their fertile status, by definition. Although responses to inventories could be systematically biased by knowing their fertility status, they reflect the real emotions and feelings of subjects.

Finally, data observed in azoospermic men were confirmed after excluding subjects with genetic abnormalities from the statistical analysis. Hence, psychological symptoms and sexual dysfunctions seem to be related to the diagnosis of azoospermia, rather than a consequence of the underlying genetic diseases (Corona *et al.*, 2010c; Towns, 2010; Quittner *et al.*, 2016).

Conclusions

ED increases as a function of severity of semen quality impairment, independently of physical, biochemical and vascular parameters, and is associated with mood disturbances. Azoospermic men reported the worst erectile function and general health status, closely related to somatized anxiety. In addition, they also had higher PE, lower sexual desire and poorer orgasmic function, all of which were related to psychopathological symptoms. Investigation of sexual function, general health and psychological status of males of infertile couples, especially if azoospermic, is advisable, to improve not only reproductive but also general and sexual health.

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Authors' roles

F.L., G.C. and M.M. made substantial contributions to the conception and design of the manuscript, analysis and interpretation of data and drafting the manuscript. G.C. was involved in analysis and interpretation of data. F.L., G.C. and M.M. revised the manuscript for intellectual content. F.L. and E.M. performed scrotal and penile colour-Doppler ultrasound evaluation. F.L., E.M. and M.C. were involved in acquisition and inclusion of data in a dedicated database. M.G.F. performed seminal analyses. All the authors gave final approval of the submitted version of the manuscript.

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Conflict of interest

None declared.

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