

1 **TITLE: Psycho-biological correlates of delayed ejaculation in male patients with sexual**
2 **dysfunctions.**

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4 **SHORT TITLE: Delayed ejaculation and sexual dysfunctions**

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30 **ABSTRACT**

31 Pathogenesis of delayed ejaculation (DE) is rather unknown, although the contribution of various
32 psychological, marital, hormonal and neurological factors has been advocated. In this study we
33 systematically investigated the relative relevance of the aforementioned factors in 1632 men,
34 seeking medical help for sexual dysfunction. The severity of DE was classified according to Kaplan
35 criteria. Mild and moderate forms of DE (MMDE) recognized different risk factors than the most
36 severe ones (anejaculation/severe DE; ASDE). ASDE was essentially coupled to the presence of
37 neurological diseases or to the use of serotonergic drugs. Serotonergic drugs also significantly
38 increase (by at least ten-fold) the risk for MMDE, which, however was also coupled to other
39 relational (impaired partner's climax, patient's hypoactive sexual desire, HSD) or intra-psychic
40 (stress at work) factors. At multiple regression analysis, some organic pathological conditions (such
41 as psychiatric disorders and hypogonadism) were also associated to MMDE. In particular,
42 hypogonadism retained significance for DE even after adjustment for HSD (Adj. OR= 2.08[1.11-
43 3.89]; $p < 0.05$), suggesting other effects of testosterone deficiency on the ejaculatory reflex, besides
44 reduced libido. In conclusion, the present study demonstrates that multiple psychobiological
45 determinants are associated to DE, a still obscure condition that substantially impairs psychosexual
46 equilibrium of the couple.

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48 Key words: delayed ejaculation, SIEDY, structured interview, testosterone, male sexual
49 dysfunctions.

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52 **INTRODUCTION**

53 The ejaculatory reflex comprises a set of neuromuscular events coordinated by serotonergic
54 (inhibitory) and dopaminergic (facilitatory) neurons in hypothalamic nuclei; peripherally, it consists
55 of two separate phases: emission and expulsion (or true ejaculation) (see in Ralph and Wylie, 2005
56 and Jannini and Lenzi, 2005 for reviews). The first one involves the entire male genital tract
57 (MGT), is essentially under sympathetic control and allows seminal fluid to reach posterior urethra
58 and closure of the bladder neck. Other purinergic (ATP; Mulryan et al, 2000), peptidergic
59 (oxytocin, endothelin-1; Filippi et al, 2002; Filippi et al, 2005) or gaseous (nitric oxide, carbon
60 monoxide; Burnett et al, 1998; Mancina et al, 2005) neuromediators participate to the semen
61 emission process. Emission is not accompanied by any intense sensation: it is just a warning of the
62 growing approach to climax. The second phase, expulsion, comprises the passage of the ejaculate
63 through the urethra and its outer propulsion. The expulsion phase is under parasympathetic and
64 somatic control and requires the contraction of the perineal muscles. It is responsible for the final,
65 vigorous semen propelling activity and the pleasant sensation, which the orgasm reaction can bring.

66 In andrology practice, concern about ejaculation - and in particular about an inappropriately rapid or
67 premature ejaculation (PE) - is quite common. Retarded, inhibited or delayed ejaculation (DE) is
68 another ejaculatory dysfunction, although less frequently referred than PE. Therefore, until now,
69 only few systematic studies targeted biological and psychological correlates of DE (Rowland et al,
70 2004; Rowland et al, 2005). Even the definition of DE is not completely clarified. The Diagnostic
71 and Statistical Manual of Mental Disorders (DMS IV; 2000) included DE (and anorgasmia) into the
72 male orgasmic disorders, with the following definition: “after a normal phase of sexual excitement,
73 the man's orgasm is persistently or repeatedly delayed or absent” Delayed ejaculation refers

74 essentially to an over-control of the ejaculatory reflex, despite a normal genital arousal. Hence,
75 affected men have normal erections but are often unable to ejaculate during intercourse or, in some
76 cases, during manual stimulation. Kaplan (1974) identified different degrees of DE. In the milder
77 form, men are able to ejaculate, but only with great effort and after prolonged intercourse. In an
78 intermediate form men did not reach orgasm during sexual intercourse but only with vigorous
79 manual stimulation, although in the presence of the partner. In the most severe forms, orgasm can
80 be obtained only with autoerotism, in the absence of the partner, or it cannot be obtained at all
81 (anejaculation). DE should not be confused with the more common condition known as retrograde
82 (or dry) ejaculation (RE). In the latter case, ejaculatory bolus goes back into the bladder, instead of
83 out the urethra, owing to incompetence of the bladder neck. Remarkably, in RE, although there is
84 not appearance of an anterograde ejaculate, orgasm is still present. Both DE and RE impairs couple
85 fertility, because of no semen deposition in vagina. However, only DE severely affects couple
86 sexual enjoyment, because male orgasm is not timely reached or is not reached at all.

87 The aim of the present study is to investigate on the psychobiological factors associated with DE in
88 a large sample of patients referring to an Andrology Clinic for sexual dysfunction.

89 **PATIENTS AND METHODS**

90 A consecutive series of 1632 patients attending for the first time to the Outpatient Clinic for sexual
91 dysfunction of the Andrology Unit of the University of Florence at Careggi Hospital. Patients with
92 mental retardation, or not fluent in Italian, were excluded. In particular the exclusion of foreign
93 people was due to the fact that the national version of SIEDY has not completely validated for
94 foreign subjects. Patients with a history of radical prostatectomy, retroperitoneal surgery or other
95 causes of RE were also excluded from the analysis, because RE might overlap with DE and mask its
96 true psychobiological determinants.

97 The patients enrolled underwent the usual diagnostic protocol applied to newly-referred subjects at
98 the Andrology Outpatient clinic. All the data provided were collected as part of the routine clinical

99 procedure. Patients were interviewed prior to the beginning of any treatment, and before any
100 specific diagnostic procedures, using the SIEDY Structured Interview (Petrone et al, 2003). This is
101 a 13-item interview composed of three scales, which identify and quantify components concurring
102 to sexual dysfunctions. Scale 1 deals with organic disorders, Scale 2 with disturbances in
103 relationship with partner, and Scale 3 with psychological traits. Delayed ejaculation was defined as
104 “slowness to ejaculate” (as reported by the patient by using a stop watch method) according to
105 previously described criteria (Kaplan, 1974, Apfelbaum, 2005). In particular, severity of DE was
106 categorized on a 3-point scale using a standard question “In the last three months is it difficult to
107 ejaculate during sexual intercourse?” and rating: 0 (no DE); 1 (mild/moderate DE or MMDE) and 2
108 (anejaculation/severe DE or ASDE). MMDE was diagnosed if ejaculation and climax were still
109 possible, but only with great effort and after prolonged intercourse (mild DE) or possible only with
110 autoerotism, although in the presence of the partner, but not during coitus (moderate DE). ASDE
111 was diagnosed if orgasm and ejaculation could not be obtained at all (anejaculation) or could be
112 obtained but only with autoerotism conducted in the absence of the partner (severe DE). Stress at
113 work was assessed with question #3 of SIEDY (“Do you ever think of your job out of the working
114 hours?”), patient’s partner’s libido with question #8 (“Does your partner have more or less desire to
115 make love than in the past?”), partner’s climax with question #9 (“Does your partner reach
116 climax?”) and patient’s hypoactive sexual desire with question #14 (“Did you have more or less
117 desire to make love in the last three months?”) of SIEDY and rating 0=no, 1= mild, 2=moderate and
118 3=severe problem. The presence of neurological diseases was assessed with question #4B of
119 SIEDY.

120 Patients were asked to specify any current pharmacological treatment in the last three months.
121 Among serotonergic drugs were included: citalopram, paroxetine, sertraline, fluoxetine,
122 fluvoxamine, escitalopram, venlafaxine, chlorimipramine. Among anti-dopaminergic drugs were
123 included: domperidone, fluphenazine, perphenazine, promazine, risperidone, haloperidol, L-
124 sulphiride, metoclopramide, clopixol, cisapride, clebopride.

125 All patients underwent a complete general and andrological physical examination, with
126 measurement of blood pressure (mean of three measurements 5 minutes apart, in sitting position,
127 with a standard sphygmomanometer), height, weight, and testis volume (Prader orchidometer),
128 penis evaluation and digital rectal examination. . Blood samples were drawn in the morning, after
129 overnight fast, for determination of blood glucose (by glucose oxidase method; Aerosef Abbott,
130 Rome, Italy), total cholesterol, HDL cholesterol and triglyceride (by automated enzymatic
131 colorimetric method; Aerosef Abbott, Rome, Italy), glycated hemoglobin (HbA1c; high pressure
132 liquid chromatography method, with upper limit of the normal range of 5.9%; Menarini
133 Diagnostics, Florence, Italy), total testosterone, prolactin, FSH, LH, TSH, and PSA (by
134 elettrochemiluminescent method, Modular Roche, Milan, Italy). Hypogonadism was defined when
135 circulating total testosterone (T) was below 10.4 nmol/l (300 ng/dL; lower limit of our laboratory
136 normal range) and hyperprolactinemia when prolactin was higher than 288 mU/l (14ng/dl; upper
137 limit of our laboratory normal range).

138 Data were expressed as mean \pm SD when normally distributed, and as median [quartiles] for
139 parameters with non-normal distribution, unless otherwise specified. Differences between more
140 than two groups were assessed with one-way ANOVA or Kruskal-Wallis test, whenever
141 appropriate. Relative risk and 95% confidence interval for DE were derived from crosstab analysis.
142 Chi-square test was used for comparison of categorical parameters. Stepwise multiple logistic
143 regressions were applied for multivariate analysis, whenever appropriate.

144 All statistical analysis was performed on SPSS for Windows 12.1.

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148 **RESULTS**

149 Among the 1632 patients studied, 82 (5.0%) reported DE; of those, 62 reported MMDE and 20
150 ASDE. Patients with any type of DE did not show any significant difference in socio-demographic
151 characteristics, including age, when compared to the rest of the sample (Table 1).

152 Patients with any type of DE have a higher score of erectile function (as assessed by question #1A
153 of SIEDY Appendix A), than the rest of the sample (1.29 ± 0.16 vs. 0.97 ± 0.03 ; $p < 0.05$).

154 Figure 1 reports relative risk (RR) for MMDE (1A) and ASDE (1B) associated with different
155 psychological, relational and physiological parameters. The presence of stress at work (as explored
156 by question #3 of SIEDY) and serious psychiatric diseases at anamnesis, such as major depression,
157 delusional disorders or schizophrenia, were significantly related to MMDE but not to ASDE. At
158 logistic regression analysis, considering stress at work and psychiatric diseases as putative predictor
159 of MMDE, both factors resulted independent contributors to MMDE (Adj. OR.= $2.11[1.16-3.84]$;
160 $p < 0.05$ and $4.52[2.02-9.27]$ $p < 0.0001$, respectively).

161 The use of serotonergic drugs significantly contributed to both ASDE and MMDE. The latter
162 association retained significance even after adjustment for psychiatric diseases (Adj. OR =
163 $10.66[4.70-24.18]$; $p < 0.0001$). The use of anti-dopaminergic medicaments was associated with
164 MMDE only, but such a relationship was lost at logistic regression analysis, after adjustment for
165 psychiatric diseases (data not shown).

166 Considering other organic factors, the presence of neurological diseases (as explored by question
167 #4B of SIEDY) significantly contributed only to ASDE, but not to MMDE. In particular among 20
168 patients with ASDE, 9 reported a neurological disease (4 multiple sclerosis, 3 traumatic spinal cord
169 injury, 1 diabetic neuropathy, 1 idiopathic tremor). At logistic regression analysis, considering
170 neurological diseases and use of serotonergic drugs as putative factors of ASDE, both parameters
171 were significantly related to ASDE (Adj. OR= $4.69[1.27-17.40]$; $p < 0.05$ and $1.98[1.45-2.70]$,
172 $p < 0.0001$ respectively).

173 Among hormonal parameters, the presence of hyperprolactinemia ($PRL > 288$ mU/L) contributed to
174 both MMDE and ASDE, however, these associations were lost after adjustment for confounding
175 factors, as the use of anti-dopaminergic or serotonergic drugs (data not shown). A reduced
176 testosterone plasma level ($T < 10.4$ nmol/L) was significantly associated with MMDE, but not with
177 ASDE. Furthermore, testis volume was lower ($p < 0.001$) in MMDE (17.9 ± 0.6 ml) - but not in

178 ASDE (19 ± 1.4 ml) - patients than in the rest of the sample (20 ± 0.1 ml). No other biochemical and
179 hormonal parameters significantly contributed to DE (data not shown).

180 Finally, considering psycho-relational factors, patient's hypoactive sexual desire (HSD, question
181 #14 of SIEDY), impaired partner's climax (question #9 of SIEDY) and decreased partner's libido
182 (question #8 of SIEDY) all significantly contributed to MMDE, but not to ASDE. At logistic
183 regression analysis, considering HSD, loss of partner's climax and loss of partner's libido as
184 putative factors of MMDE, only HSD and impaired partner climax's retained significance (Adj.
185 OR= $2.93[1.62-5.31]$ and $2.49[1.26-4.91]$, respectively; both $p<0.01$). Furthermore, at multiple
186 regression analysis both HSD and hypogonadism resulted independent determinants of MMDE
187 (Adj. OR= $3.00[1.67-5.39]$ and $2.08[1.11-3.89]$, both $p<0.05$).

188 Patients with MMDE showed higher SIEDY scale 2 and 3 scores when compared with the rest of
189 the sample (2.8 ± 0.5 vs. 1.9 ± 0.1 for scale 2 and, 5.9 ± 0.3 vs. 5.2 ± 0.1 for scale 3, both $p<0.05$) while
190 no difference was observed in scale 1 score (4.2 ± 0.4 vs. 3.7 ± 0.1 $p=NS$). On the other hand, patients
191 with ASDE did not show any significant difference in SIEDY scores in comparison with the rest of
192 the sample (data not shown).

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195 **DISCUSSION**

196 Although a neurobiological approach to DE is greatly warranted (Waldinger et al, 2005a), yet the
197 most common cause of DE is still considered psychological, essentially due to an over control of
198 sexual enjoyment, often coupled to fear of failure, because unresolved conflicts with conscious and
199 unconscious worries (religious, marital, or intrapsychic) might impair ejaculation. Recent studies
200 indicate that psychogenic DE is essentially characterized by an uncoupling in sexual arousal
201 between a decreased subjective and a preserved genital reaction (Rowland et al, 2004; Rowland et
202 al, 2005). The present study partially confirms these assumptions. In fact, several relational and

203 intra-psychic factors resulted associated with DE, at least in its milder form (MMDE). In fact,
204 patient's hypoactive sexual desire and impaired partner's climax significantly and independently
205 contributed to MMDE, even after adjusting for confounding factors, such as hypogonadism. This is
206 interesting, because an adequate partner's climax reaction during intercourse is reinforcing the
207 patient's sexual competence and therefore patient's sexual desire (Corona et al, 2004, Corona et al,
208 2005), transforming a merely vasocongestive event (the penile erection *per se*) in a complete sexual
209 act. Hence, both the reduced patient's sexual drive and the lack of partner's orgasmic reaction might
210 contribute to the hypoexcitability of MMDE subjects and to the previously described uncoupling
211 between genital and subjective arousal (Rowland et al, 2005). In addition, we found that life
212 stressors, as stress at work, also significantly contribute to MMDE, most probably by distracting the
213 subject from pleasant emotions derived from attractiveness of the intercourse and by freezing sexual
214 fantasies. Overall, the higher scores in SIEDY's Scale 2 and 3 (exploring the relational and
215 intrapsychic domains, respectively) obtained in patients with MMDE further corroborate these
216 notions. It should also be considered that DE is defined on the basis of the subjective perception of
217 inadequately long duration of the sexual act, which, in its milder forms, can be influenced by
218 relational factors. In fact, the perceived partner's reaction to sexual intercourse (e.g. partner's
219 anorgasmia, or reduced sexual satisfaction), could affect the determination of a "proper" duration of
220 the sexual act.

221 In this study we found that, in addition to distorted cognitive and behavioral aspects of sexual life,
222 also some organic factors are associated with MMDE. Among these, an important role is played by
223 the presence of psychiatric disturbances and by the use of selective serotonin uptake inhibitors
224 (SSRIs) and other serotonergic drugs. SSRIs are antidepressant drugs, often with anxiolytic
225 properties, used to treat several psychiatric disorders. Interestingly, both conditions, i.e. the
226 presence of a psychiatric diseases and the use one of their more common treatment, serotonergic
227 drugs, are independently and significantly associated with MMDE, although to a different extent. A

228 ten-fold increase in risk of MMDE is indeed associated with serotonergic drug treatment. It is
229 well known that SSRIs and some tricyclic antidepressants, by increasing central serotonergic
230 transmission, quite often induce a variable delay in the ejaculatory reflex (Ralph et al, 2005;
231 Montgomery et al, 2005), therefore representing the most often employed therapy for PE
232 (Waldinger et al, 2004; Waldinger et al, 2005b). Being PE and depression very common -
233 depression will soon become the second most disabling condition worldwide (Murray and Lopez,
234 1997) - the use of serotonergic drugs will probably increase in the future. Hence, the frequency of
235 DE will probably also increase, although general practitioners do not frequently recognize its link
236 with serotonergic drugs (Pareman et al, 2003). In the present study, we demonstrated that use of
237 serotonergic drugs is not only associated with the mildest forms of DE, but also with the most
238 severe ones, such as anejaculation. In addition, in a previous study we reported that serotonergic
239 drug treatment was also associated with a reduced sexual desire (Corona et al, 2005), which, in turn,
240 as reported now, can contribute to DE. In conclusion, this study confirms previous evidences (see
241 in Montgomery et al, 2005 and Rosen et al, 1999 for reviews) that serotonergic drugs can induce
242 various degrees of impaired ejaculation and sexual desire that should be promptly recognized, to
243 reassure the patient on the real nature of his sexual dysfunction and to tailor pharmacological
244 treatment to the individual patient's needs. The present study confirms that DE might also be caused
245 by several neurological diseases that, by disrupting the sympathetic and/or somatic innervations to
246 the MGT, impair the peripheral ejaculatory reflex. Therefore, both emission and expulsion might be
247 affected. However, if only sympathetic nerves are damaged, as in retroperitoneal lymph node
248 dissection during extirpative surgery, the climax reaction can be preserved, despite a lack of
249 anterograde ejaculate (Vale, 1999). In this latter condition, DE is more similar to, and difficult to
250 distinguish from, RE. For this reason, patients who underwent extirpative pelvic surgery were
251 excluded from the analysis. It is noteworthy that, in our sample, neurological diseases are associated
252 with severe, rather than with moderate, DE.

253 An original finding of the present study is the significant association between MMDE and reduced
254 androgenicity (reduced testosterone plasma levels and testis volume). In particular, hypogonadism
255 doubles the relative risk for DE, even after adjustment for possible confounding factors, as reduced
256 libido. The association between hypogonadism and DE, although anecdotically reported (Waldinger
257 et al, 2005a), has never been demonstrated. How hypogonadism might influence the ejaculatory
258 reflex, besides decreasing sexual desire, is rather difficult to explain. At a peripheral level, motility
259 of the MGT is under negative influence of nitrergic transmission. In fact, mice lacking the gene for
260 endothelial nitric oxide synthase (eNOS) show ejaculatory abnormalities characterized by an
261 increased propensity to ejaculate on a reduced stimulus (Kriegsfeld et al, 1999). In addition, in
262 several clinical studies, prolonging NO activity, by blocking phosphodiesterase 5 (PDE5), resulted
263 in a variable increase in ejaculatory latency (Abdel-Hamid et al, 2001; Salonia et al, 2002; Chen et
264 al, 2003; Ekmekcioglu et al, 2005; McMahon et al, 2005). We originally demonstrated that PDE5 is
265 expressed in several portions of the human MGT (Morelli et al, 2004), and is androgen-dependent
266 (Mancina et al, 2005). In particular, in an experimental model of hypogonadotropic hypogonadism,
267 we found that in vas deferens NO degradation was reduced and PDE5 less expressed and active
268 (Mancina et al, 2005). Hence, it is possible that hypogonadism-associated DE is coupled to an
269 increased inhibitory nitrergic tone on smooth muscle cells of MGT.

270 It is interesting to note that hypogonadism and other concurrent conditions which were allocated
271 with MMDE, did not show any allocation with ASDE, except SSRI. It can be specified that
272 neurological disorders which are often present in patients with ASDE, have such a great impact in
273 DE that the effect of others possible risk factors becomes irrelevant in more severe forms of delayed
274 ejaculation.

275 It should be considered that this study was performed on patients referring to an Andrologic Clinic
276 for sexual dysfunction. For this reason, the sample cannot be considered representative of general
277 male population, nor of subject referring to general practices for sexual problems. However, there is

278 no reason to believe that relationship between ejaculation and gonadal function observed in the
279 present study cannot be extended to a broader population.

280 In conclusion, several biological, intra-psychic, marital and pharmacological conditions might
281 negatively affect the ejaculatory process, partially or completely impairing it and therefore causing
282 varying degrees of derangement in sexual intimacy, even disrupting the psychosexual equilibrium
283 of the couple.

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391 **TABLES**

392 **Table 1**

	NO DE	MMDE	ASDE	p
Age (years)	51.5±13	50±12.5	48.7±13	NS
Marital status (%)				
Stable relationship	88.5	87.1	89.5	NS
No stable relationship	11.5	12.9	10.5	NS
Education (%)				
Not graduated	44.4	40	22.2	NS
Graduated (high school or University)	55.6	60	77.8	NS
Employment (%)				
Retired/ Unemployed	39.4	39.2	42.1	NS
Employed	59.6	60.8	57.9	NS

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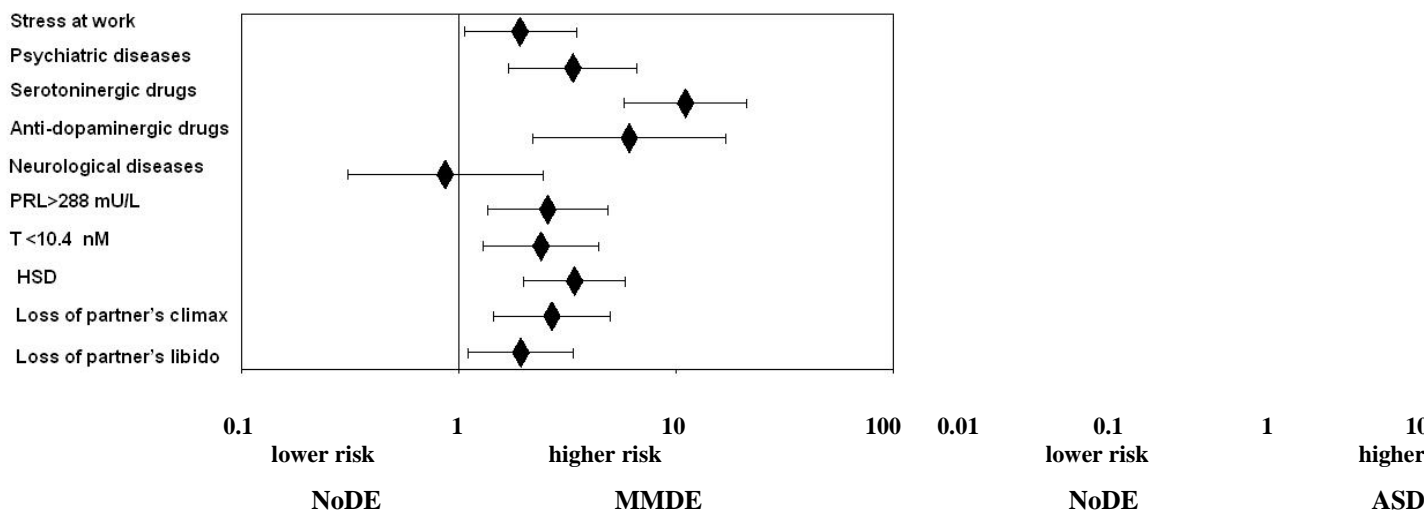
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409 **Table 1:** Socio-demographic characteristics of the sample. DE= delayed ejaculation; MMDE =
410 mild/moderate DE; ASDE= anejaculation/severe DE.

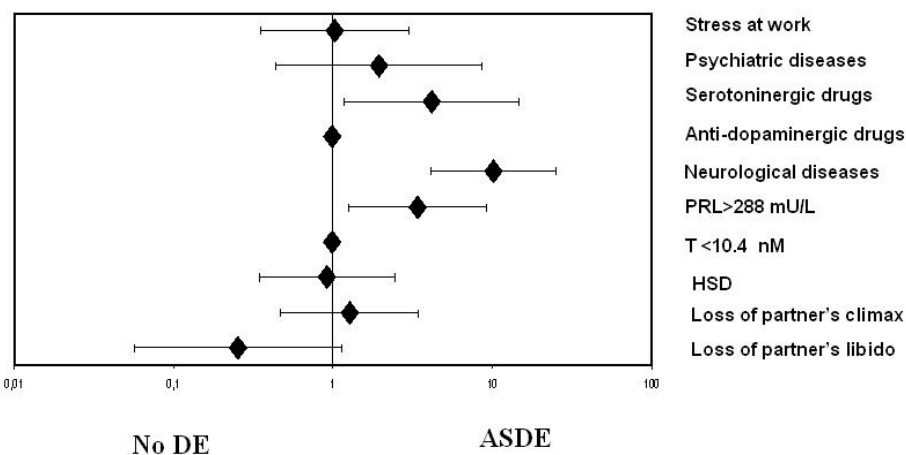
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434 **Figure 1.** Relative risk for mild-moderated delayed ejaculation (MMDE; A) and anejaculation-

435 severe delayed ejaculation (ASDE, B) associated with different psychological, relational and

436 physiological parameters

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