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Telma Cristiana Resse Nunes dos Santos
Erectile Dysfunction in Obstructive Sleep Apnea Syndrome –
Prevalence and Determinants

Abril, 2011

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Mestrado Integrado em Medicina

Área: Pneumologia

**Trabalho efectuado sob a Orientação de:
Prof. Dr^a Marta Susana Monteiro Drummond Freitas**

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

Nome: Telma Cristiana Resse Nunes dos Santos

Endereço electrónico: med05101@med.up.pt **Telefone ou Telemóvel:** 910774298

Número do Bilhete de Identidade: 13225299

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Assinatura: Telma Cristiana Resse Nunes dos Santos

CARTA DE APRESENTAÇÃO

Exmo Sr. Editor da Revista da Portuguesa de Pneumologia,

Gostaríamos de lhe enviar o artigo de investigação “Erectile dysfunction in Obstructive Sleep Apnea Syndrome – prevalence and determinants” que tem por objectivo aferir a prevalência e os determinantes da Disfunção eréctil numa população de doentes seguidos no Laboratório do Sono do Serviço de Pneumologia do Hospital de S. João.

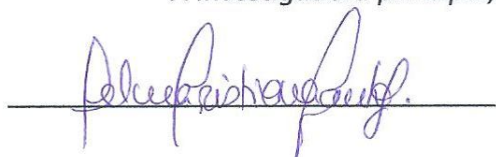
Efectivamente, uma vez que a Disfunção Eréctil constitui uma das potenciais complicações inerentes ao Síndrome de Apneia Obstrutiva do Sono parece-nos importante aferir a sua prevalência e o impacto de outras comorbilidades. Assim, este trabalho de investigação parece-nos ser uma mais-valia para a comunidade científica.

AUTORIA:

Telma Cristiana Santos concebeu o projecto, construiu a base de dados, efectuou o tratamento estatístico e a interpretação dos resultados e escreveu o artigo.

Prof^a Dr^a Marta Drummond contribuiu para a concepção do projecto e para a interpretação dos resultados, bem como para a revisão do manuscrito.

A investigadora principal,



A handwritten signature in blue ink, appearing to read 'Telma Cristiana Santos', is written over a horizontal line.

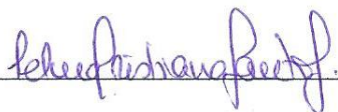
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Eu, Telma Cristiana Resse Nunes Santos, abaixo assinado, nº mecanográfico 050801101 estudante do 6º ano do Mestrado Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração deste projecto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (acto pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

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Assinatura: _____



ERECTILE DYSFUNCTION IN OBSTRUCTIVE SLEEP APNEA SYNDROME

– PREVALENCE AND DETERMINANTS

Telma Cristiana Resse Nunes dos Santos

(med05101@med.up.pt)

Prof. Dr^a Marta Susana Drummond Freitas

(marta.drummond@gmail.com)

Laboratório do sono - Serviço de Pneumologia Hospital de S. João

Alameda Professor Hernâni Monteiro

4200-Porto

Correspondence to: med05101@med.up.pt

ABSTRACT

Introduction: OSAS (Obstructive Sleep apnea syndrome) is defined by recurrent episodes of upper airway obstruction during sleep, causing multiple clinical consequences. Literature review suggests that OSAS induces a spectrum of abnormalities in neural, hormonal and vascular regulation that contribute to the development of ED (erectile dysfunction).

The aims of this study were to estimate the prevalence of ED in OSAS patients and evaluate its determinants.

Methods: 62 patients from Sleep Laboratory of Hospital S. João with newly diagnosed OSAS were included in the study and answered the IIEF-5 (international index erectile function 5 item version) questionnaire.

Results: The prevalence of ED in OSAS patients was 64,41%. Age and Diabetes constituted themselves as independent risk factors for more severe degrees of ED: OR=1,226 (95%CI:1,062 – 1,415) and OR=31,205 (95%CI:1,222 – 796,557), respectively. Compared with nonsmokers, ex-smokers group revealed a positive association with ED: OR=4,32 (95%CI:1,09 – 17,11). Hypertension and ACEI (angiotensin converting enzyme inhibitors) or ARB (angiotensin II receptor blockers) therapy were also correlated to ED symptoms: OR=3,25 (95%CI:1,09-9,65) and 7,39 (95%CI:1,52-35,99), respectively.

No association was found between BMI ($p=0,254$), alcoholic habits ($p=0,357$), acute myocardial infarction ($p=0,315$), dyslipidemia ($p=0,239$) and metabolic syndrome ($p=0,215$) and ED.

Conclusions: The prevalence of ED in OSAS patients was 64,41%. ED determinants in our sample were age and diabetes. Past smoking habits, hypertension, ACEI/ARB therapy also revealed a statistically significant association.

Key- words:

Sleep Apnea, Obstructive

Erectile Dysfunction

Aging

Diabetes mellitus

Hypertension

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent inability to obtain and/or maintain penile erection sufficient to permit satisfactory sexual intercourse, which has a negative impact on self esteem, quality of life, and interpersonal relationships of affected patients [1,2]. Its prevalence is estimated in 48% among Portuguese man aged 40 to 69 years old [3].

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive collapse of the upper airway due to the pharyngeal dilator muscles laxity [4], during sleep. Clinically, OSAS is defined by the presence of at least 5 obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep in association with daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking [5]. The presence of 15 or more obstructive respiratory events in the absence of sleep related symptoms is also sufficient for the diagnosis [5]. OSAS affects an estimated 4% of men between the ages of 30 and 60 years [6], but it is believed that the proportion of clinically diagnosed OSAS is underestimated [7-9]. This is one of the most important medical conditions identified in the last 50 years [10], which is related to the elevated morbidity and mortality due to clinical complications as hypertension [11], congestive heart failure [12], acute myocardial infarction [13], stroke [14], diabetes [15], cognitive dysfunction [16] and depression [17].

In every REM sleep stage most men experience sleep related erections (SRE) [18], which are believed to be part of an intrinsic mechanism aimed to protect the morphological integrity of *corpora cavernosa* [19]. In OSAS, intermittent hypoxic events and sleep fragmentation restrain SRE, causing deleterious effects on erectile physiology [20-23].

Sleep dysfunction may also interfere on hypothalamic-pituitary axis as the usual REM-sleep testosterone increment is abolished in OSAS patients [24, 25]. Testosterone and luteinizing hormone (LH) nocturnal levels are decreased compared to normal controls [26], which are reversed by Continuous Positive Airway Pressure (CPAP) treatment [27].

Neural integrity may also be affected by the continuous sympathetic nervous system hyperactivity intrinsic to OSAS [28], opposing the physiological erectile mechanism [29]. A peripheral nerve dysfunction, whose presence and severity is related to the level of hypoxia, has also been described by bulbocavernous reflex latency tests [30-31].

Repetitive hypoxic events induce oxidative stress, which is responsible for the decreased nitric oxide (NO) levels [32]. Endothelial dysfunction is also suggested by the increased endothelin levels [33]. This discrepancy between vasodilator and vasoconstrictor mediators impairs penile tumescence [34] contributing to erectile dysfunction in OSAS patients. CPAP treatment decreases the oxidative stress [35] and endothelin levels [36].

Furthermore, a psychological component may be involved due to, for instance, depression [37] or fatigue excess [21].

ED could also be a direct consequence of hypertension and diabetes, common co-morbidities in OSAS patients [22].

Some inconsistencies have been found concerning prevalence data [19]. Thus, the main purpose of this study was to estimate the prevalence of ED in a population of OSAS patients sent to Hospital S. João for diagnosis and follow-up. Additionally, clinical and demographic issues were gathered to obtain the ED determinants in our population.

METHODS

Study population

Between 28 September and 31 December 2010, all men admitted in sleep laboratory of Hospital de S. João Pulmonology Service for a first medical appointment because of a suspected OSAS, were invited to participate in the study. Every patient received an Informed Consent, IIEF-5 questionnaire and written form with information about the study, which they should deliver fulfilled thereafter.

Information about BMI, previous medical history (diabetes, hypertension, stroke, acute myocardial infarction) and usual pharmacological therapy was obtained from medical files.

We excluded patients without OSAS diagnostic confirmation and patients with ED already diagnosed.

This study was approved by Ethics Commission from Hospital de S. João.

IIEF -5 (International Index Erectile dysfunction - 5 item version)

IIEF-5 is a simple and useful questionnaire to screen patients with ED [38]. Designed as a simplified version of IIEF, it is composed by 5 questions regarding erectile function and satisfaction [39] (**annex 1**). Intervals 22 to 25, 17 to 21, 12 to 16, 8 to 11 and 5 to 7 points represent, respectively, ED absent, mild ED, mild to moderate ED, moderate ED and severe ED categories [39]. It was validated to be used in Portuguese language [40].

Polygraphic cardiorespiratory sleep study (PCSS)

Polysomnography is routinely indicated for the diagnosis of sleep related breathing disorders [5, 41-45], but its use is limited by economical costs and waiting lists [46].

PCSS is an alternative to the Polysomnography in the presence of an elevated pre-test probability [5]. A portable monitor with channels (at least 4) [47] is used, recording oro-nasal airflow, oxygen saturation, cardiac frequency, upper limb, abdominal and thoracic movements, body position and loud snoring [48].

All participants underwent PCSS with ApneaLink[®], AlphaScreen Pro[®], EMBLETTA[®] or Stardust[®] devices. We used variables as Apnea-hypopnea index (AHI), desaturation index (DI), minimum and medium oxygen saturation to assess OSAS severity.

Mild, moderate and severe OSAS are defined, respectively, by an AHI 5-15; AHI >15 e <30 e AHI \geq 30, according to established criteria [5].

Statistical analysis

SPSS[®] (Statistical Package for Social Sciences), 18.0 version, was the software used to analyze statistical data.

A frequency analysis was made to describe the population. Then Chi-Square test was used to determine the association between categorical variables and Kruskal wallis test to define any association between continuous and categorical variables. Multivariate logistic regression was used to evaluate the effect of each variable adjusted to other possible confounding factors.

It was considered statistically significant every association with $p < 0,05$.

RESULTS

The general characteristics of the population are described in **table 1**. The mean age was 52 years. In 62 patients, 28 (45,1%) were obese, 23 (37,1%) had dyslipidemia, 11 (17,7%) metabolic syndrome (MS), 36 (58,1%) arterial hypertension, 10 (16,1%) diabetes and 4 (6,5%) cardiac failure. Previous acute myocardial infarction, stroke and pelvic surgery were identified in 2 (3,2%), 6 (9,7%) and 2 (3,2%) participants, respectively. It was diagnosed mild OSAS in 30 (48,4%), moderate OSAS in 14 (22,6%) and severe OSAS in 17 (27,4%) individuals. The ED prevalence was 64,41%, being mild in 24 (38,7%), mild to moderate in 11 (17,7%), moderate in 2 (3,2%) and severe in 3 (4,8%) participants.

Univariate analysis results are expressed in **table 2**. Aging was significant and directly related to the presence of ED: OR (CI 95%) of 3,90 (1,00 – 15,28); 5,50 (1,16 – 26,14); and 6,00 (1,00 – 35,91) in age groups 46-55, 56-65 and >65 years, respectively. Past smoking habits also showed association with ED (OR 4,32 (1,09 – 17,11)). Hypertension and ACEI (Angiotensin Converting Enzyme Inhibitors) or ARB (Angiotensin II Receptor Blockers) therapy revealed a statistically significant association with ED (OR 3,25 (1,09-9,65) and 7,39 (1,52-35,99)).

No association was found between dyslipidemia ($p=0,239$), metabolic syndrome ($p=0,215$), chronic therapy with beta blockers ($p=0,217$), calcium antagonists ($p=0,827$) and serotonin-selective reuptake inhibitors ($p=0,250$).

All patients with diabetes, stroke, cardiac failure and previous pelvic surgery referred ED on questionnaire, so it was not possible to calculate odds ratio (OR) for these variables.

PCSS parameter analysis is described in **table 3**. Although not statistically significant, a trend of association was verified between ED and OSAS severity, measured by DI,

minimum and medium oxygen saturation and AHI ($p=0,494$, $p=0,657$, $p=0,498$ e $p=0,403$, respectively).

Multivariate analysis is expressed on **table 4**. Age and diabetes were independent risk factors for more severe degrees of ED: OR (CI 95%) of 1,226 (1,062 – 1,415) and 31,205 (1,222 – 796,557), respectively. BMI ($p=932$), smoking habits ($p=853$), alcohol consumption ($p=0,683$), hypertension ($p=0,077$) and OSAS ($p=0,661$) did not provide evidence to be independent risk factors for ED.

DISCUSSION

In 1981, Schmidt and Wise were the first to describe a relationship between ED and sleep disorders [49]. Thereafter, several studies confirmed the elevated prevalence of ED in OSAS patients [52-55]: Guilleminault et al reported ejaculatory dysfunction and decreased libido in 48% men with OSAS [50]; Hirshkowitz et al. verified that 91,3% patients with ED symptoms had also OSAS [51]; Seftel et al. concluded that 40% OSAS patients had ED [52]. However, this association is denied by Schiavi RC et al. [53]. In the present study, it was found a 64,41% ED prevalence, supporting most publications.

Margel D et al. concluded that ED is associated with severe OSAS [54]. Therefore, despite the absence of statistical significance it was verified that patients who reported severe ED obtained the worst results in PCSS study (**Table 3**).

Age, in the present study, proved to be an independent risk factor for ED, similar to what is suggested by the literature [55]. It was also confirmed that ED risk increases with aging. It is established that age has more impact on erectile function than OSAS severity [56], as we could also find.

Furthermore, the present data confirmed that Diabetes is an independent risk factor for ED. It was verified that diabetic patients have a risk 31 times superior to more severe degrees of ED, which is supported by the effect of endothelial dysfunction on erectile tissue structure [57].

Arterial hypertension was associated with ED in the univariate analysis. However, an association with more severe ED degrees was not confirmed within multivariate analysis. This difference is probably due to a confounding effect of diabetes, suggested by the fact that 9 out of 10 diabetic patients also described hypertension.

An association between MS and ED was not found. Nevertheless, it is possible that the used classification have underestimated the real proportion of affected patients since it was based on the patient report and did not include triglycerides or cholesterol plasmatic measurements [58]. Similarly, this study did not prove an association between BMI and ED, with patients in BMI interval 25-29 reporting more symptoms than those included in superior BMI categories. This is probably related to the fact that the BMI interval 25-29 included older patients (43% patients between 56 and 65 years and 50% of patients older than 65 years), compared to the other categories (data not shown in tables). It is possible to conclude that, in our sample, aging is an important confounding when analyzing BMI data.

As a marker of systemic endothelial dysfunction, dyslipidemia may be more prevalent in ED patients [59]. Fibrats and Statins, lipid-lowering drugs, can also provoke ED as a side effect [60]. These consequences were not observed in our sample maybe due to a recall bias.

Concerning smoking habits, only ex-smokers showed a statistically significant association with ED, eventually due to the fact that this group reported heavier smoke loads (34 pack-years), compared to current smokers (25 pack-years). In a recent cross-sectional study [61] smoking careers of more than 23 years or 20 cigarettes per day were significantly associated with ED.

Regarding chronic medication, an association was found between ACEI/ARA and ED. Actually, anti-hypertensive therapy is associated with adverse sexual effects, most commonly involving diuretics and beta-blockers [62]. ACEI/ARA were the most frequently used drugs and its association with ED may be due to hypertension itself. Beta-blockers were used only by 4 patients, explaining the absence of a statistical significant association with ED.

This study has some advantages. Patients with co-morbidities were not excluded, allowing measuring their impact on erectile function. The effect of chronic medication was also evaluated.

Though, this investigation has some limitations. The sample size is smaller compared to other studies due to a high refusal rate in patients' participation, possibly related to the embarrassment in describing such private subject. In contrast with other studies [55], the protocol did not include testosterone measurements so the ED was exclusively assessed by a questionnaire.

For future work it is suggested that larger scale studies be conducted and performed and also multidisciplinary approach is crucial to OSAS patients as this is a syndrome with such wide manifestations and consequences.

CONCLUSIONS

The ED prevalence was 64,41%.

ED determinants were age and diabetes, which constituted themselves as independent risk factors for more severe degrees of ED. Past smoking habits, hypertension and ACEI/ARB therapy also revealed a statistically significant association with ED.

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TABLES

Table 1: Population general description (n= 62)

	<i>Variables</i>	<i>Frequencies</i>
	Mean (years)	52,16
Age	≤ 45	20 (32,3 %)
	46-55	18 (29 %)
	56-65	14 (22 %)
	>65	10 (16 %)
	Mean	29,69
BMI	20-24,9	11 (17,7 %)
	25-29,9	23 (37,1 %)
	30-34,9	19 (30,6 %)
	>35	9 (14,5 %)
Smoking habits	Current	18 (29%)
	<i>Smoke load (mean)</i>	<i>25,16</i>
	Past	23 (37,1%)
	<i>Smoke load (mean)</i>	<i>34,12</i>
	Nonsmokers	21 (33,9%)
Alcohol consumption	Absent	29 (46,8%)
	≤ 60 g/day	23 (37,1%)
	>60g/day	10 (16,1%)

Table 1: Population general description (*cont.*)

	<i>Variables</i>	<i>Frequencies</i>
Comorbidities	Dyslipidemia	23 (37,1%)
	Hypertension	36 (58,1%)
	Diabetes	10 (16,1%)
	Metabolic syndrome	11 (17,7%)
	Cardiac failure	4 (6,5%)
Medical history	Stroke	2 (3,2%)
	Myocardial infarction	6 (9,7%)
	Pelvic surgery	2 (3,2%)
OSAS severity	Mild	30 (48,4%)
	Moderate	14 (22,6%)
	Severe	17 (27,4%)
Erectile dysfunction	Absent	22 (35,5%)
	Mild	24 (38,7%)
	Mild to moderate	11 (17,7%)
	Moderate	2 (3,2%)
	Severe	3 (4,8%)

BMI (body mass index); OSAS (obstructive sleep apnea syndrome); ED (Erectile dysfunction) classification: absent (IIEF-5 22-25); mild (IIEF-5 17-21); mild to moderate (IIEF-5 12-16); moderate (IIEF-5 8-11); DE severe (IIEF-5 5-7).

Table 2: ED prevalence and association with clinical and demographic variables

	<i>Variable</i>	<i>ED (%)</i>	<i>OR (CI 95%)</i>	<i>p</i>
Age	≤ 45	40,0	1	0,011
	46-55	72,5	3,90 (1,00 – 15,28)	
	56-65	78,6	5,50 (1,16 – 26,14)	
	>65	80	6,00 (1,00 – 35,91)	
BMI	20-24,9	63,6	1	0,254
	25-29,9	78,3	2,06 (0,42 - 9,97)	
	30-34,9	52,6	0,64 (0,14 – 2,91)	
	>35	55,6	0,71 (0,12 – 4,32)	
OSAS severity	Mild	66,7	1	0,723
	Moderate	50,0	0,50 (0,14 – 1,82)	
	Severe	76,5	1,63 (0,42 – 6,29)	
Metabolic syndrome	Absent	60,4	2,4 (0,59 – 9,76)	0,215
	Present	78,6		
Hypertension	Absent	48,0	3,25 (1,09-9,65)	0,032
	Present	75,0		

Table 2: ED prevalence and association with clinical and demographic variables (*cont.*)

	<i>Variable</i>	<i>ED* (%)</i>	<i>OR (CI 95%#)</i>	<i>p</i>
Dyslipidemia	Absent	59,0	1,97 (0,64-6,09)	0,239
	Present	73,9		
Myocardial infarction	Absent	62,5	3,00 (0,32-27,46)	0,215
	Present	83,3		
Alcohol consumption	Absent	69,0	1	0,357
	≤ 60 g/day	65,2	0,84 (0,26 – 2,70)	
	>60g/day	50,0	0,45 (0,10 – 1,95)	
Smoking habits	Nonsmokers	52,4	1	0,719
	Past	82,6	4,32 (1,09 – 17,11)	
	Current	55,6	1,14 (0,32 – 4,02)	
Myocardial infarction	Absent	62,5	3,00 (0,32-27,46)	0,215
	Present	83,3		
ACEI/ARA therapy	Absent	53,5	7,39 (1,52-35,99)	0,007
	Present	89,5		

*Erectile dysfunction (ED): IIEF ≤ 21; # 95% confidence interval

Table 3: PCSS study parameter analysis according to ED severity

<i>ED</i>		<i>DI</i>	<i>Min</i> _{O₂Sat}	<i>Med</i> _{O₂Sat}	<i>AHI</i>
Absent	<i>Median</i>	13,3	81,0	94,6	16,3
	<i>Min-Max</i>	1,8 – 85,0	63,0 – 94,0	91,0 – 96,7	8,2 – 48,8
Mild	<i>Median</i>	7,75	83,0	95,0	13,6
	<i>Min-Max</i>	0,6 – 70,0	24,0 – 91,0	88,0 – 98,0	5,3 – 76,0
Mild to moderate	<i>Median</i>	13,20	82,0	94,0	30,0
	<i>Min-Max</i>	1,4 – 67,2	22,0 – 92,0	77,0 – 97,0	6,3 – 91,0
Severe	<i>Median</i>	24,0	76,0	89,0	24,9
	<i>Min-Max</i>	9,0 – 81,3	50,0 – 84,0	84,4 – 96,4	9,9 – 83,2
p		0,494	0,657	0,498	0,403

It was not possible to analyze the category “moderate DE” because it was composed only by one subject

ED (Erectile dysfunction) classification: absent (IIEF-5 22-25); mild (IIEF-5 17-21); mild to moderate (IIEF-5 12-16); moderate (IIEF-5 8-11); DE severe (IIEF-5 5-7).

DI (desaturation index); *Min*_{O₂Sat} (minimum O₂ saturation); *Med*_{O₂Sat} (medium O₂ saturation); AHI (apnea-hypopnea index); Min-Max (minimum-maximum)

Table 4: Multivariate logistic regression[#] on the association between some clinical variables and ED

<i>Variable</i>	<i>p</i>	<i>OR</i>	<i>CI 95%*</i>
Age	0,005	1,226	1,062 – 1,415
BMI	0,932	0,989	0,759 – 1,287
Smoking habits (past and current)	0,853	1,136	0,293 – 4,407
Alcohol consumption	0,683	0,994	0,964 – 1,024
Diabetes	0,037	31,205	1,222 – 796,557
Hypertension	0,077	10,453	0,776 – 140,760
OSAS	0,661	1,580	0,204 – 12,233

[#] Dependent variable was categorized as “absent and mild ED”

and “mild to moderate to severe ED”

* 95% confidence interval

OSAS (Obstructive sleep apnea syndrome)

ANNEXES

Annex 1 – IIEF-5 Questionnaire

How do you rate your confidence that you could get and keep an erection

- 1) Very low
- 2) Low
- 3) Moderate
- 4) High
- 5) Very high

When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

- 1) Never/almost never
- 2) Rarely (much less than half the time)
- 3) Occasionally (about half the time)
- 4) Most of time (much more than half the time)
- 5) Almost always/always

During sexual intercourse how often were you able to maintain an erection after penetration?

- 1) Never/almost never
- 2) Rarely (much less than half the time)
- 3) Occasionally (about half the time)
- 4) Most of time (much more than half the time)

- 5) Almost always/always

During sexual intercourse, how difficult has it been to maintain your erection until completion of intercourse?

- 1) Extremely difficult
- 2) Very difficult
- 3) Difficult
- 4) Slightly difficult
- 5) Not difficult

When you attempted sexual intercourse, how often was it satisfactory to you?

- 1) Never/almost never
- 2) Rarely (much less than half the time)
- 3) Occasionally (about half the time)
- 4) Most of time (much more than half the time)
- 5) Almost always/always