International Journal of Impotence Research (2013) 25, 155–159

www.nature.com/ijir

ORIGINAL ARTICLE

Association between cigarette smoking and erectile tumescence: the mediating role of heart rate variability

CB Harte[1,2] and CM Meston[3]

Cigarette smoking deleteriously affects erectile function, and conversely, quitting smoking improves erectile hemodynamics. Underlying mechanisms by which smoking (or reduction of smoking frequency) may affect erectile physiology are not well understood. This study examined the mediating role of heart rate variability (HRV; a marker of sympathovagal balance) among a sample of male chronic smokers from the United States. Sixty-two healthy men ($M_{age} = 38.27$ years; s.d. = 10.62) were assessed at baseline (while smoking regularly), at mid-treatment (while using a nicotine patch) and at follow-up, 4 weeks after patch discontinuation. Cigarette use, frequency-domain parameters of HRV (low frequency (LF), high frequency (HF), LF/HF ratio) and physiological sexual arousal responses (via penile plethysmography) were assessed at each visit. Results were consistent with mediation, in that greater reductions in cigarette use from baseline to follow-up were associated with longitudinal increases in LF, which in turn showed positive relationships with across-time changes in erectile tumescence. Neither HF nor LF/HF ratio mediated the relationship between smoking and erection. In conclusion, HRV mediated the inverse relationship between reductions in smoking and enhancements in erectile tumescence. Results underscore the possibility that cigarette use may deleteriously affect erectile function peripherally, in part, by disrupting cardiac autonomic function.

International Journal of Impotence Research (2013) **25,** 155–159; doi:10.1038/ijir.2012.43; published online 10 January 2013

Keywords: erectile function; heart rate variability; mediation; penile hemodynamics; smoking; smoking cessation

INTRODUCTION

Cigarette smoking is an independent risk factor for erectile dysfunction (ED), and results of large cross-sectional[1–3] and longitudinal[4] epidemiological studies show that smokers are ~1.5–2 times as likely as non-smokers to experience ED. Acute effects of smoking/nicotine intake on sexual health in men have also been demonstrated in several laboratory-based studies. Specifically, smoking has been shown to acutely attenuate sexual arousal responses in habitual smokers,[5] and ingestion of isolated nicotine (for example, nicotine gum) has been shown to acutely reduce physiological sexual arousal in non-smokers.[6,7] This relationship also holds in the reverse direction. That is, longitudinal studies have shown that quitting smoking promotes improvements in erectile function,[8] even as soon as 24 h post cessation.[9,10]

Mechanisms by which smoking (or reduction of smoking rate) may affect erectile physiology are not well understood. Smoking may exert its deleterious effects on sexual arousal in a number of ways: (i) centrally, by eliciting dose-dependent neurotransmitter and neuroendocrine effects;[11,12] (ii) peripherally, by acting as a sympathetic nervous system agonist;[13] (iii) or at the biochemical level by disrupting nitric oxide synthesis, responsible for endothelium-dependent smooth muscle relaxation.[14] Complex interactions among these pathways may also exist.[15]

Despite emerging literature describing the beneficial effects of smoking cessation on sexual health, no data exist regarding potential mediators of this salutatory effect. One potential mechanism by which smoking cessation may affect erectile function is via changes in heart rate variability (HRV). HRV is a measure of the balance between parasympathetic and sympathetic maneuvers, and reflects the degree of variability from mean heart rate across time. While in a resting state, the heart beats naturally in irregular intervals, due to parasympathetic dominance, which decelerates heart rate and increases HRV. Conversely, sympathetic nervous system activation accelerates heart rate and decreases HRV. HRV is therefore an indicator of cardiac health; elevations in HRV represent healthy cardiac function, whereas reductions in HRV leave the heart vulnerable to arrhythmia and sudden death.[16] It has been shown that smoking cessation improves a number of autonomic nervous system indices, including HRV.[17,18] Additionally, HRV has been implicated in erectile function. Specifically, individuals with erectile impairments have been shown to display abnormal cardiac autonomic regulation (that is, sympathetic hyperactivity).[19]

As a first step to begin to identify potential mechanisms underlying tobacco's effects on penile hemodynamics, this study examined the mediating role of HRV among a sample of male chronic smokers from the United States who were enrolled in a smoking cessation intervention. HRV was chosen as a potential mediator, given that this parameter is a marker of sympathovagal balance, which is a chief underlying mechanism of erectile response (that is, parasympathetic dominance is pro-erectile, whereas sympathetic dominance is anti-erectile).[20] It was hypothesized that changes in HRV (from baseline to post-cessation follow-up) would mediate the relationship between changes in smoking frequency and changes in erectile hemodynamics. More specifically stated, it was hypothesized that decreases in cigarette use over time would be associated with

[1]Research Service, VA Boston Healthcare System, Boston, MA, USA; [2]Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA and [3]Department of Psychology, University of Texas at Austin, Austin, TX, USA. Correspondence: Dr CB Harte, Research Service, VA Boston Healthcare System, 150 South Huntington Avenue (116-B4), Boston, MA 02130, USA.
E-mail: christopher.harte@va.gov
Received 23 July 2012; revised 11 October 2012; accepted 26 November 2012; published online 10 January 2013

increases in HRV, which in turn would be associated with temporal enhancements in erectile responses.

SUBJECTS AND METHODS

Participants

All data presented herein were taken from a non-randomized intervention study examining the association between smoking cessation and sexual health indices in men.[21] Participants were adult male smokers who were motivated and committed to quit. Men were recruited between 2008 and 2010 via community and online advertisements. Inclusionary criteria included: (i) being an adult between the ages of 23 and 60; (ii) smoking at least 15 cigarettes per day for a minimum of 5 consecutive years; (iii) no self-reported sexual dysfunction before smoking onset; (iv) being sexually active; and (v) reporting a heterosexual sexual identity. Exclusion criteria were as follows: (i) use of medications or report of medical conditions known to affect sexual or vascular functioning; (ii) medical conditions that could make nicotine administration unsafe (for example, history of myocardial infarction, stroke, heart arrhythmias, angina, uncontrolled hypotension or hypertension); (iii) history of severe drug or alcohol abuse during the past 12 months ($\geqslant$16 points on the Alcohol Use Disorders Identification Test (AUDIT)[22] and $\geqslant$6 on the Drug Abuse Screening Test (DAST-10)[23]); (iv) a body mass index of $<$18.5 or $>$35 kg m^{-2}; and (v) self-report of a sexually transmitted infection. A total of 65 men were enrolled in the parent study; however, for the current report, 3 individuals reporting cardiovascular disease (CVD) were removed, resulting in a final sample size of 62 participants.

Heart rate variability

Cardiac autonomic function was assessed using a three-channel electrocardiograph. Signals were collected at a rate of 80 samples per second, low-pass filtered (to 0.5 Hz), digitized (40 Hz), and recorded using a Model MP100WS data acquisition unit (BIOPAC Systems, Inc., Santa Barbara, CA, USA) and the software package AcqKnowledge III, Version 3.73 (BIOPAC Systems, Inc.). Inter-beat intervals were derived, and artifacts were then identified and removed manually. Fast Fourier Transform, which derived the spectral distribution, was conducted automatically using Kubios HRV Analysis Software (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland). This resulted in the calculation of low-frequency (LF) power (0.04–0.15 Hz), high-frequency (HF) power (0.15–40 Hz), and the ratio of these two indices (LF/HF), reflecting sympathovagal balance.[24]

Erectile tumescence

Erectile hemodynamics were assessed via penile plethysmography using a mercury-in-rubber strain gauge (Hokanson, Inc., Bellevue, WA, USA) to capture continuous changes in penile circumference. The signal was sampled at a rate of 80 samples per second, bandpass filtered (to 0.5 Hz), digitized (40 Hz), and recorded using a Model MP100WS data acquisition unit (BIOPAC Systems, Inc.) and the software package AcqKnowledge III, Version 3.73 (BIOPAC Systems, Inc.). The primary index of physiological sexual arousal was within-session percent change from the unaroused state (that is, penile flaccidity) to maximum arousal (largest circumferential measurement obtained) in response to erotic stimuli.

Procedure

A detailed description of procedures are described in the parent study.[21] In brief, eligible participants were scheduled for three separate laboratory visits: at baseline while smoking regularly, 4 weeks later while using a high-dose nicotine transdermal patch, and 4 weeks after completing the 8-week patch intervention (follow-up). Participants were allowed to enter the laboratory at their preferred nicotine levels; however, they were not allowed to smoke during the testing session. On average, participants reported consuming 7.19 cigarettes (s.d. = 4.79; range = 1–20) from awakening that day until presenting to the laboratory for the experimental session, and reported an average duration of 29.50 min (s.d. = 18.59; range = 5–90) since smoking their last cigarette. During each visit, self-report data were collected (socio-demographic information, medical history, substance use per the AUDIT and DAST, erectile function per the International Index of erectile Function (IIEF),[25] and smoking characteristics, including nicotine dependence assessed via the Fagerstrom Test for Nicotine Dependence[26]), as well as anthropometric (height and weight), cardiovascular (systolic and diastolic blood pressures), electrocardiographic (HRV) and physiological sexual arousal data. Electrocardiographic and sexual arousal data were collected simultaneously while participants viewed stimuli designed to facilitate sexual arousal responses. Specifically, participants were randomized to view one of three 11-min audiovisual sequences that consisted of an initial 3-min non-sexual segment (one of three documentary film presentations), immediately followed by an 8-min erotic film presentation. For all film sequences, the erotic film segments depicted a heterosexual couple engaging in consensual petting (1 min), oral sex (3 min) and vaginal intercourse (4 min). Pilot testing established that the erotic films induced equivalent genital and self-reported increases in sexual arousal. The film segments (neutral, erotic) within each film sequence were always presented in the same order, and the three film sequences were counterbalanced across participants. For the purposes of the current study, only electrocardiographic data from the initial 3-min baseline period were examined. At the completion of the laboratory visit, participants were given nicotine patches and they were asked to start the 8-week nicotine replacement therapy the following morning. The procedures of visits 2 and 3 were identical to the first session. The protocol was approved by the university Institutional Review Board.

Statistical analysis

Pack years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years smoked. Missing HRV, smoking frequency and sexual arousal values were imputed using full information maximum likelihood estimation,[27] which produces more accurate parameter estimates compared with per protocol analyses or last observation carried forward techniques.[28] Change scores were calculated separately for smoking frequency, HRV and erectile tumescence by subtracting values obtained at follow-up from values obtained at baseline. Tests of simple indirect effects were employed with an SPSS (SPSS Inc., Chicago, IL, USA) application developed by Preacher and Hayes.[29] This macro provides a test of the indirect effect (that is, changes in smoking frequency on changes in erectile tumescence though changes in HRV, with age, pack years and drinking severity as covariates; see Figure 1), using a bootstrapping procedure (n = 10 000 resamples), which generated a sampling distribution for *ab*. The macro also incorporates traditional tests of mediation using the Baron and Kenny approach.[30] The simple indirect effects approach is a more sensitive and powerful test of mediation[31] and is not dependent on the normality assumption underlying the Sobel[32] test and the causal steps approach to mediation proposed by Baron and Kenny.[30] To assess indirect effects, 95% confidence intervals were generated for the parameter estimates. These parameter estimates were considered statistically significant if the confidence intervals did not include zero. Squared semipartial correlations (sr^2) were reported for the both the direct and indirect effects, to illustrate the reduction in proportion of explained unique variance.

RESULTS

Participant characteristics

Please see Table 1 for sociodemographic and smoking characteristics. The total sample (N = 62) ranged in age from 23 to 58 years with a mean age of 38.27 years (s.d. = 10.62). Eight participants reported taking medications at the time of enrollment (mood

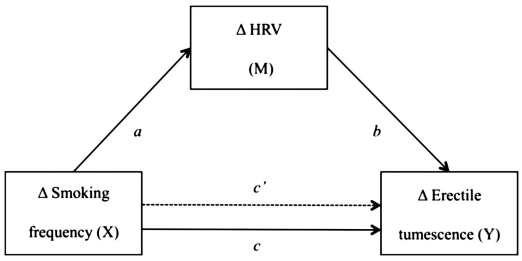

Figure 1. Changes in heart rate variability (HRV) mediating associations between changes in smoking frequency and changes in erectile tumescence. Change scores were derived for each variable by subtracting values obtained at follow-up from values obtained at baseline. The dashed line represents the direct effect controlling for HRV.

Table 1. Baseline characteristics of the participant sample

Characteristic	M	*s.d.*	n	%
Age (years)	38.27	10.62		
Education (years)[a]	14.78	2.21		
Ethnicity				
White			55	88.7
Black/African-American			2	3.2
Latino/a			2	3.2
Asian			2	3.2
Other			1	1.6
Marital status				
Single			32	51.6
Married/cohabiting			21	33.9
Divorced			9	14.5
Substance use measures				
Alcohol use[b]	5.08	3.41		
Drug use[c]	0.63	0.85		
Smoking measures				
Pack years	20.54	15.27		
Smoking frequency (cigarettes/day)	20.95	7.31		
Nicotine dependence level[d,e]	5.44	1.96		
IIEF–EF score[f]	26.61	5.09		
ED[g]			18	29.0
BMI (kg m^{-2})	25.79	4.35		
Cardiac function				
Resting HR (b.p.m.)	79.77	12.92		
Systolic BP (mm Hg)	129.35	16.36		
Diastolic BP (mm Hg)	84.89	13.27		

Abbreviations: BMI, body mass index; BP, blood pressure; b.p.m., beats per minute; ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function;[25] mm Hg, millimeters mercury; HR, heart rate; M, mean.
Note. $N = 62$. [a]Data missing for two participants. [b]Assessed with the Alcohol Use Disorders Identification Test.[22] Possible score ranges from 0 to 40, with higher scores reflecting increasing levels of problematic drinking. [c]Assessed with the Drug Abuse Screening Test, 10-item.[23] Possible score ranges from 0 to 10, with higher scores indicating greater substance abuse severity. [d]Data missing for one participant. [e]As per the Fagerström Test of Nicotine Dependence.[26] Possible score ranges from 0 to 10, with higher scores indicating greater dependency to nicotine. [f]IIEF–EF score is based on a scale from 1 to 30, with 1 indicating the most severe erectile difficulties and 30 indicating the least severe (or no difficulty). [g]According to the IIEF erectile functioning threshold score of 25.

stabilizer: $n = 3$, antidepressant: $n = 1$; anticonvulsants, $n = 1$; benzodiazepine: $n = 1$, serotonin modulator: $n = 1$, H_2 blocker: $n = 1$; antihistamine, $n = 2$). No participants reported a history of myocardial infarction or current CVD, and none were taking cardiac/cardiovascular medications. Regarding participant flow, 17 participants dropped out after the initial visit, and an additional 12 after the second visit, resulting in a total of 33 participants who completed the follow-up session. Additional details pertaining to participant flow using CONSORT guidelines can be found in the parent study.[8]

Associations between smoking, HRV and erectile tumescence characteristics

Zero-order correlations among study variables are presented in Table 2. Age was positively associated with pack years, $r = 0.78$, $P < 0.001$, and negatively correlated with drinking severity, $r = -0.36$, $P < 0.01$. Pack years was negatively correlated with erectile tumescence, $r = -0.25$, $P < 0.05$; both cigarette use and alcohol use were positively associated with one another, $r = 0.43$, $P < 0.001$. Changes in cigarette consumption were negatively associated with changes in erectile tumescence, $r = -0.25$, $P < 0.05$, changes in LF, $r = -0.35$, $P < 0.01$, and changes in HF, $r = -0.28$, $P < 0.05$. Furthermore, changes in LF were associated with changes in erectile tumescence, $r = 0.34$, $P < 0.01$. Finally, both LF and HF were highly correlated with one another, $r = 0.82$, $P < 0.001$.

Mediation analyses

After entering age, pack years and baseline drinking severity as covariates, changes in cigarette frequency inversely predicted changes in LF ($B = -12.37$, s.e. $= 4.60$, $P = 0.01$), and changes in LF positively predicted changes in erectile tumescence ($B = 0.001$, s.e. $= 0.001$, $P = 0.02$) (Table 3). Furthermore, the indirect effect of changes in cigarette consumption through changes in LF was significant, as indicated by 95% confidence intervals (CIs) not containing a value of zero (CI $= -0.067, -0.001$). When the effect of changes in cigarette use on erectile tumescence was controlled, the direct effect was reduced (although still statistically significant) ($B = -0.09$, s.e. $= 0.02$, $P = 0.001$, $sr^2 = 0.14$ to $B = -0.07$, s.e. $= 0.02$, $P = 0.01$, $sr^2 = 0.05$), which was suggestive of partial mediation.[30] Both HF power and the LF/HF ratio did not mediate the relationship between changes in cigarette use and erectile tumescence.

To strengthen the interpretation of the above mediation analyses, we conducted an additional analysis reversing the mediator and dependent variable.[33,34] Results were not consistent with mediation in this direction. Specifically, the indirect effect of changes in cigarette use through changes in erectile tumescence was non-significant, as indicated by 95% CIs containing a value of zero (CI $= -14.04, 0.43$).

DISCUSSION

The current study examined the mediating role of HRV on the association between changes in cigarette use and changes in erectile tumescence among a sample of male chronic smokers without CVD from the United States who were enrolled in a smoking cessation intervention. Results were consistent with a causal mediation chain, indicating that changes in LF power (a frequency-domain parameter of HRV) mediated the inverse relationship between changes in cigarette frequency and changes in erectile tumescence. Alternatively stated, greater reductions in cigarette use (from baseline to follow-up) were associated with increased HRV over time, which in turn showed positive relationships with longitudinal changes in physiological sexual arousal responses. Both the formal test of this indirect effect[29] and the traditional causal steps approach[30] were significant.

Taken together, results suggest that reductions in cigarette smoking were associated with decreases in sympathetic tone and enhanced autonomic cardiac function. This finding is in line with the results of prior studies showing increases in frequency-domain measures of HRV as a result of smoking cessation.[17,18,35,36] Additionally, results point toward the potential underlying role of cardiac autonomic function in the physiological sexual arousal process. That enhancement in HRV promoted improvements in erectile tumescence adds to the scarce, yet emerging, body of literature delineating the possible relationship between HRV and erectile function.[19] Although this study highlights the potential mediating role of the peripheral nervous system on the relationship between smoking and erectile response, it by no means rules out the possibility that other mediating pathways are concomitantly implicated (for example, neurotransmitter and neuroendocrine effects under central nervous system control,[11,12] and/or activity at the biochemical level[14]).

Strengths of the current study include: (i) longitudinal (across a 12-week time frame) examination of the interplay between

Table 2. Zero-order correlations among study variables

Variable		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	M	*s.d.*
1	Age (years)	—	0.78***	−0.36**	0.01	−0.05	0.17	−0.22	−0.07	38.27	10.62
2	Pack years		—	−0.17	0.15	−0.04	0.11	−0.17	−0.25*	20.54	15.27
3	Baseline drinking severity[a]			—	0.43***	−0.11	−0.23	0.26*	0.17	5.08	3.41
4	Δ Cigarette use frequency (cigs/day)				—	−0.35**	−0.28*	0.17	−0.25*	−8.06	33.16
5	Δ LF power ($msec^2$)					—	0.82***	−0.03	0.34**	−76.00	1085.49
6	Δ HF power ($msec^2$)						—	−0.32**	0.17	−127.31	565.58
7	Δ LF/HF ratio ($msec^2$)							—	0.08	−0.05	2.48
8	Δ Erectile tumescence (mm)								—	−4.83	6.79

Abbreviations: HF, high-frequency power; LF, low-frequency power; LF/HF, low frequency-to-high frequency ratio; M, mean.
Note. $N = 62$. Change (Δ) represents a variable's value at follow-up subtracted from the value obtained at baseline. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. [a]Assessed with the Alcohol Use Disorders Identification Test.[22]

Table 3. Mediation analyses

	M	s.e.	*LL, 95% CI*	*UL, 95% CI*
Indirect effects				
Bootstrap results	−0.019	0.015	−0.067	−0.001
	B	*s.e.*	t	sr^2
Causal steps approach[30]				
Step 1: Path c	−0.09	0.02	−3.67***	0.14
Step 2: Path a	−12.37	4.60	−2.69**	0.11
Step 3: Path b	0.001	0.001	2.32*	0.12
Step 4: Path c′	−0.07	0.02	−2.81**	0.05
	B	*s.e.*	t	
Partial effects of covariate on erectile function				
Age	−0.37	0.11	−3.39***	
Pack years	0.36	0.07	4.85***	
Baseline drinking severity	0.53	0.24	2.19*	

Abbreviations: *B*, unstandardized regression coefficient; CI, confidence interval; LL, lower limit; M, mean; UL, upper limit.
Note. Bootstrap sample size = 10 000. Model summary for dependent variable model: $R^2 = 0.43$, Adj $R^2 = 0.38$, $F(5,56) = 8.56$, $P < 0.001$. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

smoking, HRV and erectile hemodynamics; (ii) examination of a variety of frequency-domain HRV parameters; (iii) exclusion of individuals with a history of myocardial infarction, CVD and cardiovascular medication use, all of which are conditions that have been associated with cardiac autonomic imbalance;[37,38] and (iv) use of rigorous statistical methods employing both traditional and state-of-the-art approaches to mediation. Despite this investigation's novel findings, several study limitations warrant mention. First, smoking was assessed via self-report rather than via biochemical verification, and therefore, the validity of this dependent measure cannot be determined with absolute certainty. However, participants provided saliva samples at all experimental visits and they were spuriously told that these would be assayed for nicotine content. This 'bogus pipeline' technique has been shown to produce accurate and reliable estimates of smoking.[39] The second limitation was with regard to the generalizability of the participant sample; African-American individuals were under-sampled compared with the general population of the United States.[40] Furthermore, although a notable proportion of men reported ED (29%), the mean age—and consequently the mean smoking duration—of the current sample was lower compared with other studies examining relationships between smoking, sexual function and cardiac function. As such, it is unclear if results herein can be extrapolated to typical male patients presenting with ED who are characteristically older, have lower IIEF scores, and have longer smoking histories.

In conclusion, this is the first study to examine the mediating role of HRV on the relation between cigarette use and erectile tumescence among male chronic smokers without a history of myocardial infarction or CVD. Results indicated that greater reductions in cigarette use from baseline to follow-up were associated with increases in HRV, which in turn showed positive relationships with across-time changes in erectile tumescence. Given the salutatory effects of reducing smoking frequency on penile hemodynamics, results underscore the possibility that cigarette use may deleteriously affect erectile function peripherally, in part, by disrupting cardiac autonomic function. Further research examining other underlying biological mechanisms is necessary to establish a causal link between these variables.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This project was supported by Award Number F31DA026276 from the National Institute on Drug Abuse (NIDA) to Christopher Harte. The contents of this work are solely the responsibility of the author and do not necessarily represent the official views of the NIDA or the National Institutes of Health. Portions of this work were also made possible by Grant Number 1 RO1 HD051676-01 A1 to Cindy M Meston from the National Institute of Child Health and Human Development (NICHD). The contents

are solely the responsibility of the authors and do not necessarily represent the official views of the NICHD. This project was also supported by the following fellowships/awards to the first author: The Sexual Medicine Society of North America Student Research Grant; two Graduate Dean's Prestigious Fellowship Supplements, and a College of Liberal Arts Graduate Research Fellowship, all from the University of Texas at Austin; the American Psychological Association Dissertation Research Award; and The Kinsey Institute Student Research Grant. We thank Tyler Watts, Hillary Perlman, Olivia Bentkowski, Alicia Whitaker, Gail Dalton and Katy Siciliano for help with participant recruitment, screening and data management.

REFERENCES

1 He J, Reynolds K, Chen J, Chen CS, Wu X, Duan X *et al.* Cigarette smoking and erectile dysfunction among Chinese men without clinical vascular disease. *Am J Epidemiol* 2007; **166**: 803–809.
2 Tengs TO, Osgood ND. The link between smoking and impotence: Two decades of evidence. *Prev Med* 2001; **32**: 447–452.
3 Dorey G. Is smoking a cause of erectile dysfunction? A literature review. *Br J Nurs* 2001; **10**: 455–465.
4 Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB *et al.* Erectile dysfunction and coronary risk factors: Prospective results from the Massachusetts male aging study. *Prev Med* 2000; **30**: 328–338.
5 Gilbert DG, Hagen RL, D'Agostino JA. The effects of cigarette smoking on human sexual potency. *Addic Behav* 1986; **11**: 431–434.
6 Harte CB, Meston CM. Acute effects of nicotine on physiological and subjective sexual arousal in nonsmoking men: a randomized, double-blind, placebo-controlled trial. *J Sex Med* 2008; **5**: 110–121.
7 Harte CB, Meston CM. The inhibitory effects of nicotine on physiological sexual arousal in nonsmoking women: Results from a randomized, double-blind, placebo-controlled, cross-over trial. *J Sex Med* 2008; **5**: 1184–1197.
8 Harte CB, Meston CM. Association between smoking cessation and sexual health in men. *BJU Int* 2011; **109**: 888–896.
9 Sighinolfi MC, Mofferdin A, De Stefani S, Micali S, Cicero AF, Bianchi G. Immediate improvement in penile hemodynamics after cessation of smoking: previous results. *Urology* 2007; **69**: 163–165.
10 Guay AT, Perez JB, Heatley GJ. Cessation of smoking rapidly decreases erectile dysfunction. *Endocr Pract* 1998; **4**: 23–26.
11 Kapoor D, Jones TH. Smoking and hormones in health and endocrine disorders. *Eur J Endocrinol* 2005; **152**: 491–499.
12 Pomerleau OF. Nicotine and the central nervous system: biobehavioral effects of cigarette smoking. *Am J Med* 1992; **93**: 2S–7S.
13 Hering D, Kucharska W, Kara T, Somers VK, Narkiewicz K. Smoking is associated with chronic sympathetic activation in hypertension. *Blood Press* **19**: 152–155.
14 McVary KT, Carrier S, Wessells H. Subcommittee on Smoking and Erectile Dysfunction Socioeconomic Committee Sexual Medicine Society of North America. Smoking and erectile dysfunction: Evidence based analysis. *J Urol* 2001; **166**: 1624–1632.
15 Sartori C, Lepori M, Scherrer U. Interaction between nitric oxide and the cholinergic and sympathetic nervous system in cardiovascular control in humans. *Pharmacol Ther* 2005; **106**: 209–220.
16 La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O *et al.* Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003; **107**: 565–570.
17 Harte CB, Meston CM. Effects of smoking cessation on heart rate variability among long-term male smokers. *Manuscript under review* 2012.
18 Stein PK, Rottman JN, Kleiger RE. Effect of 21 mg transdermal nicotine patches and smoking cessation on heart rate variability. *Am J Cardiol* 1996; **77**: 701–705.
19 Chen CJ, Kuo TBJ, Tseng YJ, Yang CCH. Combined cardiac sympathetic excitation and vagal impairment in patients with non-organic erectile dysfunction. *Clin Neurophysiol* 2009; **120**: 348–352.
20 Giuliano F, Rampin O. Neural control of erection. *Physiol Behav* 2004; **83**: 189–201.
21 Harte CB, Meston CM. Association between smoking cessation and sexual health in men. *BJU Int* 2012; **109**: 888–896.
22 Saunders J, Aasland O, Babor T, de la Fuente J, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction* 1993; **88**: 791–804.
23 Skinner HA. The Drug Abuse Screening Test. *Addict Behav* 1982; **7**: 363–371.
24 Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P *et al.* Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; **59**: 178–193.
25 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–830.
26 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Br J Addict* 1991; **86**: 1119–1127.
27 Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 2nd edn. Wiley-Interscience: Hoboken, NJ, 2002.
28 Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002; **7**: 147–177.
29 Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods* 2008; **40**: 879–891.
30 Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**: 1173–1182.
31 Hayes AF. Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Commun Monogr* 2009; **76**: 408–420.
32 Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociol Methodol* 1982; **13**: 290–312.
33 Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Method Instrum Comput* 2004; **36**: 717–731.
34 Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychol Methods* 2002; **7**: 422–445.
35 Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. *Hypertension* 1999; **33**: 586–590.
36 Yotsukura M, Koide Y, Fujii K, Tomono Y, Katayama A, Ando H *et al.* Heart rate variability during the first month of smoking cessation. *Am Heart J* 1998; **135**: 1004–1009.
37 Salo TM, Kantola I, Voipio-Pulkki LM, Pelttari L, Viikari JSA. The effect of four different antihypertensive medications on cardiovascular regulation in hypertensive sleep apneic patients—Assessment by spectral analysis of heart rate and blood pressure variability. *Eur J Clin Pharmacol* 1999; **55**: 191–198.
38 Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol* 2010; **141**: 122–131.
39 Murray D, O'Connell C, Schmid L, Perry C. The validity of smoking self-reports by adolescents: a reexamination of the bogus pipeline procedure. *Addict Behav* 1987; **12**: 7–15.
40 US Bureau of the Census. *Native resident population estimates of the United States by sex, race, and Hispanic origin: April 1, 1990 to July 1, 1999.* Washington, DC, Retrieved 5 February 2010 from http://www.census.gov/population/estimates/nation/nativity/nbtab003.txt, 2000.