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1149 men

ORIGINAL ARTICLE

Burdens and awareness of adverse self-reported lifestyle factors in men with sub-fertility: A cross-sectional study in

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Abstract

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Background: There are no current pharmacological therapies to improve sperm quality in men with sub-fertility. Reducing the exposure to lifestyle risk factor (LSF) is currently the only intervention for improving sperm quality in men with sub-fertility. No previous study has investigated what proportion of men with sub-fertility are exposed to adverse lifestyle factors. Furthermore, it is not known to what extent men with sub-fertility are aware of lifestyle factors potentially adversely impacting their fertility.

Methods: A cross-sectional anonymous questionnaire-based study on self-reported exposure and awareness of LSF was conducted in 1149 male partners of couples investigated for sub-fertility in a tertiary andrology centre in London, UK.

Results: Seventy per cent of men investigated for sub-fertility had ≥ 1 LSF, and twentynine per cent had ≥ 2 LSF. Excessive alcohol consumption was the most common LSF (40% respondents). Seventeen per cent of respondents used recreational drugs (RD) regularly, but only 32% of RD users believed RD impair male fertility. Twenty-five per cent of respondents were smokers, which is higher than the UK average (20%). Twenty-seven per cent of respondents had a waist circumference (WC) >36 inches (91 cm), and 4% had WC >40 inches (102 cm). Seventy-nine per cent of respondents wanted further lifestyle education to improve their fertility.

Conclusions: Our data suggest that men with sub-fertility are as follows: (a) exposed to one or more LSF; (b) have incomplete education about how LSF may cause male sub-fertility; (c) want more education about reducing LSF. Further studies are needed to investigate the potential of enhanced education of men about LSF to treat couples with sub-fertility.

KEYWORDS

education, fertility, lifestyle, male reproductive health, male sub-fertility, semen, sperm

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1 | INTRODUCTION

Male sub-fertility is defined as the inability to conceive following 1 year of regular unprotected intercourse, due to poor sperm quality in the male partner.¹ Male sub-fertility is one of the major indications for assisted reproductive techniques (ART) in the UK.² Despite this, there are currently no approved pharmacological therapies to directly stimulate spermatogenesis³; anti-oestrogens and aromatase inhibitors have limited effectiveness for the treatment of oligospermia⁴⁻⁶ and their usage is not supported by current guidelines.^{7,8} Consequently, couples with male factor sub-fertility unable to conceive naturally, require to undergo ART⁹ such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). ART is highly effective, but confers potential health risks, and is unaffordable for many patients¹⁰ and healthcare systems worldwide. It is therefore critical that couples with male sub-fertility are given effective advice to optimise their own fertility using non-pharmacological approaches.

Lifestyle factors play an important role in male fertility. Large cross-sectional studies demonstrate that adverse health behaviours such as excessive alcohol intake,^{11,12} smoking,^{13,14} recreational drugs^{15,16} and obesity¹⁷ are associated with reduced fertility in men.^{7,18} Furthermore, recent evidence suggests that amelioration of adverse lifestyle factors may improve markers of male fertility¹⁹⁻²¹ and quality of life.²² Despite observed improvements in semen parameters, the effects on pregnancy and live birth outcomes are scarce.^{23,24} Therefore, in the absence of approved pharmacological therapies for male sub-fertility, it is essential that men with sub-fertility are aware of adverse lifestyle factor' is used to refer to adverse health behaviours to appreciate the complexities of health behaviours as not solely a result of individual choices.

Recently published European Society for Human Reproduction & Embryology (ESHRE) consensus guidelines recommended that clinicians should elicit a history of adverse lifestyle factors in all couples with male sub-fertility.²⁵ Previous studies have reported the prevalence of specific adverse lifestyle factors such as smoking^{13,14} in men with sub-fertility. However, no previous study has investigated to what extent men with male sub-fertility have as follows: (a) awareness of lifestyle factors implicated in causing male sub-fertility. Such data have important healthcare implications for the overall effectiveness of treatment given to couples with male sub-fertility.

We conducted a large cross-sectional single-centre study investigating the clinical burden of self-reported lifestyle factors in men undergoing diagnostic semen analysis for investigation of sub-fertility. Additionally, we explored the level of pre-existing knowledge of adverse lifestyle factors associated with sub-fertility amongst these men, and their views on further education on adverse lifestyle factors implicated in causing male sub-fertility.

2 | MATERIALS AND METHODS

2.1 | Regulatory approval and subjects

A service evaluation was conducted by the Department of Andrology at Hammersmith Hospital, London, UK between March 2015 and March 2016 following necessary approvals from the Division of Blood Sciences, Imperial College National Healthcare Service Trust, London, UK. A total of 1149 men attending the Andrology department at Hammersmith Hospital for diagnostic semen analysis for investigation of sub-fertility were invited to complete an anonymous questionnaire. Institutional ethics committee approval was not required for this divisional service evaluation.

2.2 | Protocol

Patients were invited to complete an anonymous questionnaire in private and return it to the reception desk at Andrology department of Hammersmith Hospital (Appendix S1) whilst they were in the waiting room of the Andrology department for diagnostic semen analysis. In brief, the questionnaire asked the men about their selfreported lifestyle factors such as waist circumference and assessed their level of knowledge on the impact of their lifestyle choices on fertility. Six lifestyle factors associated with sub-fertility were investigated: smoking, obesity, exercise, alcohol consumption, caffeine consumption and recreational drug usage. It is generally accepted that couples with sub-fertility should be counselled about lifestyle factors that may adversely impact on fertility. We therefore investigated the extent to which respondents had been counselled about lifestyle factors.

Respondents were asked to state whether they thought each lifestyle factor improved, reduced or did not affect fertility; respondents were permitted to state if they did not know the answer to any question. Answers were then scored out of a maximum of six. A higher score would reflect greater awareness and knowledge of lifestyle factors on sub-fertility. Respondents were excluded if they answered less than 80% of the survey questions.

All patients underwent diagnostic semen analysis for investigation of sub-fertility within 3-5 days of abstinence. The semen analysis was carried out by trained laboratory technicians based at the Andrology lab of Hammersmith Hospital within 1 hour of production. Semen parameters such as sperm concentration, total motility, morphology, semen volume and pH were reported according to the WHO 2010 manual semen parameters reference values.²⁶

2.3 | Statistical methods

ANOVA one-way analysis, linear regression, univariate logistic regression and multivariable logistic regression were used for analysis, using GRAPHPAD PRISM (v.7) and STATA (v.14). Continuous variables such as sperm count and total motile sperm were analysed using unadjusted linear regression for the following variables: age (years), education (school, university or higher), ethnicity (Caucasian, Black, South Asian, East Asian, Middle-Eastern, Other), self-reported waist circumference (26-30 inches, 32-34 inches, 36-38 inches, 40-42 inches, 44-46 inches), exercise (never, <monthly, monthly, weekly, daily), smoking (never, <monthly, monthly, weekly, daily), cannabis use (never, <monthly, monthly, weekly, daily), class A drug use (never, <monthly, monthly, weekly, daily). Variables significantly associated with continuous outcome variables were included in a multivariate linear regression model. *P* <.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Study population characteristics

A total of 1149 sub-fertile men were recruited to the study. Forty-one (3.5%) men were excluded for incomplete questionnaire responses (ie less than 80% of survey questions answered) (Appendix S2). The mean (\pm SD) age of the remaining 1108 men was 38 \pm 6.0 years (range 19-63). Forty-six per cent of the respondents were from ethnic minority groups and 62% spoke a language other than English at home. Over 65% of respondents attained a higher education degree qualification or above. Further details about the study population are summarised in Table 1. All respondents had been referred from primary or secondary care for investigation of sub-fertility. Most respondents under investigation for sub-fertility had previously consulted

TABLE 1	Population characteristics of men under investigation
for sub-fert	ility

Characteristic	Number of respondents (N = 1108)	Percentage of total respondents (%)
Ethnicity		
Caucasian	569	51.4
South Asian	204	18.4
Middle-Eastern	156	14.1
Afro-Caribbean	95	8.6
Southeast Asian	30	2.7
Mixed	31	2.8
Not disclosed	23	2.1
Highest level of education		
No formal education	32	2.9
Lower secondary	124	11.2
Upper secondary	183	16.5
Undergraduate	427	38.5
Postgraduate	332	30.0
Not disclosed	10	0.9

their family doctor (general practitioner; GP) regarding their fertility (83%). In addition to their GP, 12% of men had consulted one or more hospital specialists, of which, the most common was the gynaecologist treating their female partner (81%).

3.2 | Prevalence of lifestyle factors associated with male sub-fertility

We analysed the reported prevalence of adverse lifestyle factors in men under investigation for sub-fertility (Table 2). Approximately 70% of respondents had at least one adverse lifestyle risk factor and 29% had two or more factors. Excess alcohol consumption was the most common lifestyle risk factor for sub-fertility; forty per cent of respondents consumed ≥8 alcohol units on one occasion at least monthly, which is a validated measure of alcohol-related health problems.²⁷

Waist circumference is a validated measure of central adiposity.^{28,29} Excessive waist circumference is associated with obesity,³⁰ type 2 diabetes and poor sperm parameters.^{31,32} More than 1 in 4 (27%) men with sub-fertility had a self-reported waist circumference >36 inches (91 cm), and 4% of men had a waist circumference >40 inches (102 cm).

Smoking is associated with reduced sperm quality in men⁷; 25.9% of sub-fertile men were smokers in our cohort, which is marginally higher than the reported national average of 20% in the UK.³³ Ten per cent of sub-fertile men admitted to cannabis use, which is higher than the prevalence of cannabis use in 16- to 59-year olds (6.6%) reported in the UK.³⁴ 7% of respondents used Class A recreational drugs such as heroin, cocaine or ecstasy. Only less than 1% of respondents declined to provide information on recreational drug use.

3.3 | Awareness about adverse lifestyle factors

The number and proportion of men who identified smoking, obesity, exercise, alcohol, caffeine and recreational drugs as improving, reducing or having no effect on their fertility are presented in Table 3. Awareness of lifestyle trends was significantly associated with a higher level of education of the respondents and did not significantly vary between ethnic groups.

Clinical guidelines identify smoking as a cause of impaired sperm quality.⁷ Awareness of the harmful effects of smoking on male fertility was almost identical in smokers (81%) when compared with non-smokers (80%).

Recreational drugs profoundly impair male fertility¹⁶; however, 32% of recreational drug users were unaware that recreational drugs may impair male fertility.

A recent systematic review concluded that caffeine consumption may adversely affect sperm quality and function³⁵; however, 55% of sub-fertile men did not know that caffeine could impair male fertility (Table 3).

TABLE 2 Exposure of men to lifestyle factors implicated in male sub-fertility

	None	Monthly	Weekly	Daily	No Response
Exercise	167 (14.5%)	120 (10.4%)	568 (49.4%)	278 (24.2%)	16 (1.4%)
Smoking	840 (73.1%)	115 (10.0%)	52 (4.5%)	131 (11.4%)	11 (1.0%)
Excess alcohol consumption ^a	444 (38.6%)	492 (41.9%)	202 (17.6%)	6 (0.5%)	15 (1.3%)
Cannabis use	1020 (88.8%)	74 (6.4%)	24 (2.1%)	18 (1.6%)	13 (1.1%)
Class A drugs eg cocaine	1051 (91.6%)	77 (6.7%)	7 (0.6%)	1 (0.1%)	12 (1.0%)
Waist circumference (inches)	<30	32-34	36-38	>40	No Response
	119 (10.4%)	654 (56.9%)	254 (22.1%)	51 (4.4%)	71 (6.2%)

Note: Self-reported exposure to lifestyle factors, in men under investigation for sub-fertility, using an anonymous questionnaire.

^aDefined according to the validated M-SASQ score,²⁴ as the usual frequency of consuming 8 or more alcohol units during a single occasion.

TABLE 3Beliefs of men about the effects of lifestyle factors ontheir fertility

Lifestyle factor	Correct response	Incorrect response	Don't know
Smoking	899 (81.1%)	28 (2.5%)	181 (16.3%)
Obesity	786 (80.0%)	49 (4.4%)	273 (24.6%)
Lack of regular exercise	859 (77.5%)	135 (12.2%)	244 (22.0%)
Alcohol	859 (77.5%)	40 (3.6%)	209 (18.9%)
Recreational drugs	765 (69.0%)	30 (2.7%)	313 (28.2%)
Caffeine	295 (26.6%)	200 (18.1%)	613 (55.3%)

Note: Men under investigation for sub-fertility were asked whether they thought that each of the six listed lifestyle factors increased, decreased or did not affect their own fertility. Lifestyle factors are ranked in descending order of correct responses. Correct responses were that smoking, obesity, alcohol, recreational drugs and caffeine reduce male fertility, and regular exercise improves male fertility.

3.4 | Views of male patients on the need for lifestyle education associated with sub-fertility

Seventy-nine per cent (n = 875) of surveyed men wanted further lifestyle education related to sub-fertility. The most requested modality for additional education was leaflets (55%), followed by multimedia resources (50%) such as videos (Table 4). Online resources such as webpages, emails, newsletters and early education in schools were also popular suggestions made by respondents.

3.5 | Associations of lifestyle characteristics with sperm parameters

Significant characteristics associated with sperm concentration using univariate regression included age, education and ethnicity (Table 5). Age was positively associated with sperm concentration (r = .50, 95% Cl 0.02-1.0; P = .04), but was negatively associated with total motility (adj. r = -.27, 95% Cl -0.52 to -0.02; P = .034) by univariate linear regression.

Men with undergraduate or postgraduate university education had higher mean levels of sperm concentration when compared with other men (mean \pm SD sperm concentration in mill/mL: 47.1 \pm 53.2, non-university; 54.2 \pm 50.5, undergraduate or postgraduate university, *P* = .038).

Men with undergraduate or postgraduate university education also had higher mean levels of sperm motility when compared with other men (mean sperm motility in %: 45.0 \pm 25.3, non-university; 50.2 \pm 23.6 undergraduate or postgraduate university, *P* = .002).

There was no significant association between waist circumference, frequency of exercise, current smoking, excess alcohol, cannabis use or class A drug use on any measured semen parameter (Table 5).

4 | DISCUSSION

A recent systematic review and meta-regression analysis reported that sperm counts have fallen by 50%-60% since the 1970s, in North America, Europe and Australasia.³⁶ Worsening exposure to adverse lifestyle factors may contribute to declining male fertility within the population. In the absence of any effective pharmacological interventions, delivery of lifestyle advice represents a critical aspect of treatment for couples with male sub-fertility. We report for the first time, the extent to which men with sub-fertility are exposed to several adverse lifestyle factors, and their awareness of the impact of these adverse lifestyle factors on their fertility. The majority of participants were aware that obesity, smoking and excessive alcohol intake could impair their fertility. However, obesity, problematic alcohol consumption and smoking were commonly observed in patients referred by their healthcare provider for investigation for sub-fertility.

A number of lifestyle factors have been implicated in the literature to decrease male fertility. Advancing male age has been associated with a decline in sperm quality, with the largest effect being on sperm motility.³⁷ Obesity is associated with poor sperm parameters.³⁸ A waist circumference > 102cm is inversely associated with both sperm concentration and total motile sperm count.³¹ Cigarette smoking is suggested to cause oxidative damage to sperm^{39,40.}

TABLE 4	Preferences for receiving lifestyle advice in men
investigated	for sub-fertility

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Modality	Number of respondents	Percentage of total (N = 1108) (%)
Written educational material	643	58.0
Video educational material	551	49.7
Appointment with family doctor	464	41.9
Appointment with hospital specialist	193	17.4
Group sessions	112	10.1
None of the above	53	4.8
Did not answer	15	1.4

Note: Respondents were asked which modalities would be most suitable for giving lifestyle advice to men with sub-fertility. The data reflect the number and percentage of men selecting each category. No limit was specified regarding the number of selections.

According to the conventional WHO 2010 criteria,²⁶ smoking is associated with lower sperm motility and increased sperm morphological defects.⁴¹ Furthermore, sperm concentration and fertility index (FI) are significantly lower in heavy smokers (over 20 cigarettes daily), compared with mild or non-smokers.⁴² Recreational drug use, such as opioids and cannabis abuse, is correlated with high DNA fragmentation in sperm⁴³ and reduced male fertility.⁴⁴ Alcohol abuse targets sperm morphology and sperm production, and is associated with increased incidence of teratozoospermia, asthenozoospermia and oligozoospermia.⁴⁵ Ethanol has been proposed to be a Leydig cell toxin,^{11,46} whilst high caffeine consumption could reduce antioxidant capacity of Sertoli cells causing oxidative damage.⁴⁷ In contrast, a health-conscious diet of fruits and vegetables is associated with lower sperm DNA fragmentation index.⁴⁸ However, the associations between education level and fertility have been mixed in previous research as there are multiple intervening variables such as age of marriage, desired family size and contraceptive knowledge.⁴⁹

Approximately 70% of men in our study under investigation for sub-fertility had at least one lifestyle risk factor for sub-fertility, 29% had two or more risk factors. This represents a significant proportion of men for whom lifestyle changes could be of potential benefit. Excess consumption of alcohol (40%) and obesity (27%) were the two most common risk factors. Furthermore, preliminary evidence has suggested that reversal of these two modifiable lifestyle factors: obesity^{21,24,50} and alcohol consumption⁵¹⁻⁵⁴ may improve fertility. Forty-three obese men losing 17.2%-25.4% of body weight after a 14-week residential programme had an increase in sperm count, semen volume and testosterone when compared with baseline.²¹ A preliminary study of randomised women (but not their male partners) to control or lifestyle intervention prior to IVF therapy suggested that voluntary weight loss amongst male partners was independently associated with increased live birth rate following IVF therapy.²⁴ Similarly, the consumption of alcohol had a negative influence on the fertilisation rate with ICSI.⁵⁵ Anecdotal evidence from mice models⁵⁶ and human case reports⁵¹⁻⁵³ suggest that the adverse effects of alcohol intake may be reversible upon discontinuation of alcohol consumption.

The benefits of lifestyle measures on general health and wellbeing are uncontroversial; however, the direct relationship between these adverse lifestyle factors and increase in paternity such as time to pregnancy and live birth rates are unknown. Well-designed prospective studies are required with outcome measures of fecundity and fertility. Furthermore, much of the current evidence comes from men presenting to infertility clinics and may not represent the effect of LSF on male fertility in the general population. Lastly, almost all the studies focus on the specific effects of one or at most two risk factors that were under evaluation. However, in reality, exposure to these risk factors does not occur individually but rather simultaneously.⁵⁷ Therefore, we may already be underestimating the consequences of each adverse lifestyle exposure.⁴⁵

Many countries have established strategies for health promotion amongst their populations. However, the effectiveness of public health campaigns in conveying the health message to sub-fertile men has not been investigated previously. Our study observed that there was reasonable awareness of the effect of lifestyle factors amongst sub-fertile men. Approximately 90% of respondents were aware of at least one lifestyle factor associated with sub-fertility. Studies have reported that patients with rudimentary levels of education were less likely to seek health information with lower health literacy and poor health outcomes.^{58,59} In support of this, our data reveal an apparent association between the level of education of men and the knowledge of fertility-related lifestyle factors. Higher level of education in our patients was significantly associated with higher sperm concentration and motility. This may be explained by increased health literacy, health consciousness and higher awareness of the negative impacts of adopting unhealthy lifestyles and undertaking more efforts to change their lifestyle behaviours. Therefore, strategies to improve health literacy in the population may help more men be aware of the health behaviours linked to fertility.

Variable level of awareness was observed in different lifestyle factors. Awareness of the harmful effects of smoking was the highest at 81%. About one quarter of the surveyed population was unaware that obesity could reduce fertility. Considering that 26% of the study population had a waist circumference greater than 34 inches, further health promotion could be aimed at these adverse factors that had lower levels of awareness such as obesity, caffeine intake and recreational drugs. Doctors play an important role in educating patients with sub-fertility about adverse lifestyle factors. All participants had received at least one prior medical consultation for sub-fertility, but only half felt that this information was sufficient. Furthermore, approximately 80% of respondents desired more lifestyle education for sub-fertility. Our data suggest that there is an important unmet health need for providing lifestyle education for men with sub-fertility. Furthermore, public education campaigns focused on health optimisation can be an effective strategy to improve fertility.

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	٩	value	9000.	.16		.011										.085	.22	.11	.31	.013											(Continues)
	Adjusted coefficient (95% CI)	Multivariate	A, Ed, WC, Al, Ca	-0.19 (-0.45-0.08)		Ι	4.6 (1.1-8.1)										5.4 (0.2-10.7)	0.6 (-5.3-6.5)	7.0 (-3.99-17.9)	-16.2 (-33.5-1.1)											- -
00000	٩	value	.034	.034		.002	.002		.21	.10	.35	.34	.11	.45		.003	.11	.79	.39	.02		.56	.33	.71	.16	.37		.40	.33	.7	
	Coefficient (95% CI)	Univariate		-0.27 (-0.520.02)		Ι	5.2 (1.9-8.5)		I	-4.9 (-10.6-0.9)	-1.8 (-5.6-2.0)	3.2 (-3.3-9.7)	-5.4 (-12.0-1.2)	-3.2 (-11.5-5.1)		I	4.32 (-0.91-9.54)	-0.78 (-6.61-5.04)	4.65 (-6.01-15.3)	-20.3 (-36.93.79)		Ι	4.1 (-4.0-12.2)	1.4 (-6.0-8.9)	4.5 (-1.7-10.7)	3.0 (-3.6-0.6)		I	-3.1 (-9.4-3.1)	1.7 (-7.0-10.5)	
	Total motility	(Mean ± SD)	n/a			45.0 ± 25.3	50.2 ± 23.6		49.2 ± 23.7	44.4 ± 25.3	47.4 ± 24.4	52.4 ± 23.7	43.8 ± 25.8	46.0 ± 26.9		45.8 ± 24.4	50.1 ± 24.2	45.0 ± 24.1	50.4 ± 25.5	25.4 ± 26.4		45.0 ± 25.3	49.1 ± 25.5	46.4 ± 25.5	49.5 ± 23.9	48.0 ± 24.3		49.3 ± 24.4	46.1 ± 23.8	51.0 ± 24.4	
		(%) N				297	653		485	79	229	09	59	35		97	565	212	25	6		68	71	102	475	238		701	63	31	
		P value	.0001	.015			.08			.13	.13	.022	.038	.27		.59	.91	69.	.49	.33											
	Adjusted coefficient (95% CI)	Multivariate	A, Ed, Eth, WC	0.64 (0.13-1.15)		I	6.2 (-0.74-13.0)		I	-9.0 (-20.6-2.5)	5.9 (-1.8-13.6)	16.1 (2.4-29.9)	-14.7(-28.60.80)	-9.5 (-26.4-7.4)		-14.0 (-64.3-36.3)	-3.0 (-52.5-46.6)	-10.0 (-59.9-39.8)	-18.5 (-70.9-33.9)	-28.7 (-85.8-28.7)											
2000	٩	value	.040	.040		.038	.038		.004	.41	.13	.022	.016	.373		.043	60.	.80	.89	.144		.544	.455	.320	.157	.092		.960	.960	909.	
	Coefficient (95% CI)	Univariate		0.5 (0.021.0)		I	7.1 (0.4-13.8)		I	-4.73 (-16.1-6.6)	5.93 (-1.7-13.6)	15.7 (2.28-29.2)	-16.0 (-29.13.0)	-7.46 (-23.9-9.0)		I	8.8 (-1.5-19.1)	1.48 (-9.9-12.9)	-1.4 (-20.8-18.0)	-21.6 (-50.6 -7.4)		I	6.3 (-9.9-22.6)	7.7 (-7.5-22.8)	9.0 (-3.5-21.5)	11.4 (-1.9-24.7)		I	0.3 (-12.5-13.2)	-4.5 (-21.5-12.5)	
	Sperm count	(Mean ± SD)		n/a		47.1 ± 53.2	54.2 ± 50.5		51.1 ± 51.0	46.4 ± 54.0	57.1 ± 54.1	66.9 ± 50.6	35.1 ± 38.0	43.7 ± 43.8	ches)	46.0 ± 43.8	54.9 ± 51.3	47.5 ± 52.1	44.6 ± 46.7	24.4 ± 28.5		43.5±46.6	49.8 ± 46.0	51.2 ± 50.6	52.5 ± 50.5	54.9 ± 57.3		52.7 ± 52.0	53.1 ± 50.4	48.2 ± 40.3	
		z		1074		333	724		544	91	250	62	66	40	rence (inc	108	610	244	34	13		75	81	111	533	260		785	67	37	
			Age (y)		Education	School	University	Ethnicity	Caucasian	Black	South Asian	East Asian	Middle- Eastern	Other	Waist Circumference (inches)	26-30	32-34	36-38	40-42	44-46	Exercise	Never	<monthly< td=""><td>Monthly</td><td>Weekly</td><td>Daily</td><td>Smoking</td><td>Never</td><td><monthly< td=""><td>Monthly</td><td></td></monthly<></td></monthly<>	Monthly	Weekly	Daily	Smoking	Never	<monthly< td=""><td>Monthly</td><td></td></monthly<>	Monthly	

TABLE 5 Univariate and multivariate regression analyses of associations between lifestyle factors and variation in sperm count and total sperm motility

		Sperm count	Coefficient (95% CI)	٩	Adjusted coefficient (95% CI)			Total motility	Coefficient (95% CI)	٩	Adjusted coefficient (95% CI)	0
	z	(Mean ± SD)	Univariate	value	Multivariate	P value	N (%)	(Mean ± SD)	Univariate	value	Multivariate	value
Weekly	50	51.4 ± 43.6	-1.3 (-16.1-13.4)	.858			47	46.0 ± 22.0	-3.3 (-10.5-3.9)	.37		
Daily	126	49.7 ± 54.8	-3.0 (-12.8-6.7)	.538			117	45.4 ± 25.0	-3.9 (-8.6-0.9)	.11		
Alcohol												
Never	415	49.7 ± 50.4	Ι	5.			368	46.7 ± 24.6	Ι	.023	Ι	
< Monthly	220	51.8 ± 53.4	2.1 (-6.4-10.5)	9.			196	50.1 ± 22.7	3.4 (-0.8-7.6)	.11	2.9 (-1.5-7.3)	.20
Monthly	229	57.3 ± 51.4	7.6 (-0.7-16.0)	1.8			213	52.4 ± 23.9	5.8 (1.7-9.8)	900.	5.0 (0.7-9.2)	.02
Weekly	193	52.0 ± 51.8	2.3 (-6.5-11.1)	5.			174	46.6 ± 24.9	-0.1 (-4.4-4.2)	.97	-0.3 (-4.8-4.3)	.91
Daily	9	49.9 ± 50.9	0.2 (-41.4-41.8)	.01			9	35.5 ± 31.4	-11.2 (-30.7-8.3)	.26	-6.5 (-26.1-13.2)	.52
Cannabis												
Never	953	52.3 ± 51.9	I	.94			852	48.8 ± 24.1	I	.24	1	
< Monthly	52	55.1 ± 48.6	2.8 (-11.6-17.2)	.71			50	50.4 ± 23.5	1.7 (-5.3-8.6)	.64	0.5 (-6.8-7.7)	06.
Monthly	18	52.4 ± 60.6	0.09 (-24.0-24.0)	66.			17	43.6 ± 29.3	-5.1 (-16.8-6.5)	.39	-2.6 (-14.2-9.0)	.66
Weekly	23	46.5 ± 34.4	-5.8 (-27.2-15.5)	.59			23	49.0 ± 26.3	0.22 (-9.8-10.3)	.97	-0.6 (-10.9-9.7)	.91
Daily	17	44.6 ± 51.7	-7.7 (-32.5-17.1)	.54			15	35.4 ± 23.5	-13.4 (-25.80.99)	.034	-11.4 (-24.3-1.45)	.08
Class A drugs												
Never	981	52.3 ± 51.8	I	.57			885	48.7 ± 24.3	I	.59		
< Monthly	56	48.7 ± 46.3	-3.6 (-17.5-10.3)	.61			50	47.0 ± 23.7	-1.7 (-8.6-5.2)	.63		
Monthly	20	50.0 ± 51.5	-2.3 (-25.1-20.5	.84			16	40.9 ± 24.4	-7.8 (-19.8-4.2)	.20		
Weekly	7	77.6 ± 45.8	25.4 (-13.0-63.7)	.20			7	56.0 ± 23.5	7.3 (-10.8-25.3)	.43		
Daily	7	2.0	-50.3 (-151.4-50.9)	.33			1	35.0	-13.7 (-61.4-33.9)	.57		
Abbreviations: /	A, age; Al,	alcohol; Ca, canni	abis; Ed, education; Etł	h, Ethnicit)	Abbreviations: A, age; Al, alcohol; Ca, cannabis; Ed, education; Eth, Ethnicity; WC, waist circumference.	ce.						

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TABLE 5 (Continued)

Contrary to other studies, our data did not show significant association between waist circumference, frequency of exercise, current smoking, excess alcohol, cannabis or class A drug use on any measured semen parameter. There are multiple potential reasons for this. Self-reporting of LSF such as waist circumference and alcohol/smoking habits may introduce bias and underestimate the true prevalence of the burden of these adverse health behaviours in our cohort of men being investigated for sub-fertility. Inclusion of self-reported height and weight may have improved our ability to assess obesity risk. Furthermore, confounders including the variability of a single semen sample and duration of abstinence prior to the semen collection may explain this. In addition, we did not collect clinical data about other risk factors associated with male sub-fertility and comorbidities (eg diabetes, history of mumps).

It is important to consider other limitations of this study. We did not measure the response rate of the questionnaires. The non-responders and the excluded incomplete questionnaire responders (Appendix S2) may have been more likely to have poor lifestyle factors, potentially underestimating the reported prevalence of adverse lifestyle factors in the men under investigation for sub-fertility. Due to a lack of a matched control group of men without sub-fertility and the cross-sectional nature of the study, a causative relationship between the lifestyle factors and sub-fertility cannot be assumed. The use of questionnaires is by definition subjective, but measures were implemented to eliminate as much bias as possible. For instance, whilst anthropometric measures of height and weight were not taken, we were careful to use self-reported waist circumference as an indicator of BMI.²⁸⁻³⁰ Not only is waist circumference shown to be directly associated with sperm parameters similar to BMI,³² self-reported BMI also tended to be inaccurate.^{60,61} Self-reported waist circumference as a measure of central adiposity, despite its noted limitations above, was preferred in our survey as the ease of men to remember their trouser waist size. To identify men with hazardous alcohol use, a single alcohol-screening question (M-SASQ) was used. M-SASQ is a validated method for determining problem drinkers⁶² and has high sensitivity and specificity when compared with the gold standard.⁶³ The results of this study are only limited to English speakers, which may have induced reporter bias in this multi-ethnic population. In addition, we recognise that levels of education about health issues may influence the likelihood of hospital attendance. Over 65% of our participants attained a higher education degree qualification or above; hence, our study may underestimate the burden of lifestyle factors. However, this study is strengthened by its inclusion of a large sample of patients. Furthermore, the inclusion of patients from several ethnic groups and geographical origins may increase the robustness of its findings.

In summary, we have investigated for the first time, the adverse lifestyle burden in men with sub-fertility attending our hospital for semen analysis. Excess alcohol consumption, excessive weight, smoking and insufficient exercise are all common lifestyle behaviours observed in men with sub-fertility. Our data also suggest that education influenced the awareness of adverse lifestyle factors in sub-fertile men. Furthermore, there appears to be an opportunity to provide sub-fertile men with enhanced learning resources and behavioural interventions as a potential novel strategy in optimising their fertility. Future, well-designed studies are required to determine the effectiveness of enhanced education and amelioration of adverse lifestyle factors on pregnancy or live birth outcomes.

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CONFLICTS OF INTEREST

The views expressed are those of the authors and not necessarily those of the above-mentioned funders, the NHS, the NIHR or the Department of Health. The authors have no conflicts of interest to disclose.

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REFERENCES

- Barratt CLR, Björndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities. *Hum Reprod Update*. 2017;23(6):660-680.
- Human Fertilisation and Embryology Authority. Fertility Treatment in 2013: Trends and Figures. Available from http://www.hfea.gov. uk/docs/HFEA_Fertility_Trends_and_Figures_2013.pdf. Accessed 23 March, 2019.
- 3. Winters BR, Walsh TJ. The epidemiology of male sub-fertility. Urol Clin North Am. 2014;41(1):195-204.
- Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male sub-fertility: a meta-analysis. *Andrology*. 2013;1(5):749-757.
- Willets AE, Corbo JM, Brown JN. Clomiphene for the treatment of male sub-fertility. *Reprod Sci.* 2013;20(7):739-744.
- Gudeloglu A, Brahmbhatt JV, Parekattil SJ. Medical management of male sub-fertility in the absence of a specific etiology. *Semin Reprod Med.* 2014;32(4):313-318.
- National Institute for Health and Care Excellence. Fertility Problems: Assessment and Treatment (NICE Guideline CG156). Available at https://www.nice.org.uk/guidance/cg156/chapter/ Recommendations. Accessed 23 March, 2019.
- Dohle GR, Colpi GM, Hargreave TB, et al. EAU guidelines on Male Sub-fertility. *Eur Urol.* 2005;48(5):703-711.
- Krausz C. Male sub-fertility: pathogenesis and clinical diagnosis. Best Pract Res Cli Endocrino Metab. 2011;25(2):271-285.

³²⁰ WILEY

- Kerr J, Brown C, Balen AH. The experiences of couples who have had sub-fertility treatment in the United Kingdom: results of a survey performed in 1997. *Hum Repro*. 1999;14(4):934-938.
- Van Thiel DH, Gavaler JS, Cobb CF, Santucci L, Graham TO. Ethanol, a Leydig cell toxin: evidence obtained in vivo and in vitro. *Pharmacol Biochem Behav.* 1983;18(Suppl 1):317-323.
- Anderson RA, Willis BR, Oswald C, Zaneveld LJ. Male reproductive tract sensitivity to ethanol: a critical overview. *Pharmacol Biochem Behav.* 1983;18(Suppl 1):305-310.
- Evans HJ, Fletcher J, Torrance M, Hargreave TB. Sperm abnormalities and cigarette smoking. *Lancet*. 1981;1(8221):627-629.
- Richthoff J, Elzanaty S, Rylander L, Hagmar L, Giwercman A. Association between tobacco exposure and reproductive parameters in adolescent males. *Int J Androl.* 2008;31(1):31-39.
- Close CE, Roberts PL, Berger RE. Cigarettes, alcohol and marijuana are related to pyospermia in sub-fertile men. J Urol. 1990;144(4):900-903.
- Bracken MB, Eskenazi B, Sachse K, Mc-Sharry JE, Hellenbrand K, Leo-Summers L. Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril*. 1990;53(2):315-322.
- 17. Kort HI, MasseyJB ECW, Mitchell-Leef D, Shapiro DB, Witt MA, Roudebush WE. Impact of body mass index values on sperm quantity and quality. *J Androl*. 2006;27(3):450-452.
- Braga DPDAF, Halpern G, Figueira RDCS, Setti AS, Iaconelli A Jr, Borges E Jr. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. *Fertil Steril.* 2012;97(1):53-59.
- 19. Oyeyipo IP, Raji Y, Bolarinwa AF. Nicotine alters male reproductive hormones in male albino rats: the role of cessation. *J Hum Reprod Sci.* 2013;6(1):40-44.
- Prentki-Santos E, López-Costa S, Chenlo P, et al. Impact of spontaneous smoking cessation on sperm quality: case report. Andrologia. 2011;43(6):431-435.
- 21. Håkonsen LB, Thulstrup AM, Aggerholm AS, et al. Does weight loss improve semen quality and reproductive hormones? results from a cohort of severely obese men. *Reprod Health*. 2011;8:24.
- Teskereci G, Oncel S. Effect of lifestyle on quality of life of couples receiving sub-fertility treatment. J Sex Marital Ther. 2013;39(6):476-492.
- Vanegas JC, Chavarro JE, Williams PL, et al. Discrete survival model analysis of a couple's smoking pattern and outcomes of assisted reproduction. *Fertil Res Pract.* 2017;3:5.
- Belan M, Duval K, Farrah J, et al. Anthropometric and lifestyle changes in male partners of infertile couples in which the women is obese are associated with pregnancy – preliminary results. *Can J Diabetes*. 2015;39(006):529-530.
- Bender Atik R, Christiansen OB, Elson J, et al. ESHRE guideline: recurrent pregnancy loss. *Human Reprod Open*. 2018;2018(2):hoy004.
- Cooper TG, Noonan E, Von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010;16(3):231-245.
- Canagasaby A, Vinson DC. Screening for hazardous or harmful drinking using one or two quantity-frequency questions. *Alcohol Alcohol.* 2005;40(3):208-213.
- Tuomela J, Kaprio J, Sipila PN, et al. Accuracy of self-reported anthropometric measures – findings from the Finnish Twin Study. *Obes Res Clin Pract*. 2019;13(6):522-528.
- Dekkers JC, vanWier MF, Hendriksen IJ, Twisk JW, vanMechelen W. Accuracy of self-reported body weight, height and waist circumference in a Dutch overweight working population. BMC Med Res Methodol. 2008;8:69.
- Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr.* 2004;79(3):379-384.

- Hammiche F, Laven JS, Twigt JM, Boellaard WP, Steegers EA, Steegers-Theunissen RP. Body mass index and central adiposity are associated with sperm quality in men of sub-fertile couples. *Hum Reprod.* 2012;27(8):2365-2372.
- Eisenberg ML, Kim S, Chen Z, Sundaram R, Schisterman EF, Buck Louis GM. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. *Hum Reprod*. 2014;29(2):193-200.
- Action on Smoking and Health. Smoking statistics factsheet November 2018. Available at http://ash.org.uk/category/infor mation-and-resources/fact-sheets/. Accessed 23 March, 2019.
- NHS Choices. Cannabis: The Facts Live Well NHS Choices. Available at http://www.nhs.uk/livewell/drugs/pages/cannabisfacts.aspx. Accessed 23 March, 2019.
- 35. Ricci E, Viganò P, Cipriani S, et al. Coffee and caffeine intake and male infertility: a systematic review. *Nutr J.* 2017;16(1):37.
- Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Human Repro Update*. 2017;23(6):646-659.
- Sloter E, Schmid TE, Marchetti F, Eskenazi B, Nath J, Wyrobek AJ. Quantitative effects of male age on sperm motion. *Hum Reprod*. 2006;21(11):2868-2875.
- Belloc S, Cohen-Bacrie M, Amar E, et al. High body mass index has a deleterious effect on semen parameters except morphology: results from a large cohort study. *Fertil Steril*. 2014;102(5):1268-1273.
- Yousefniapasha Y, Jorsaraei G, Gholinezhadchari M, Mahjoub S, Hajiahmadi M, Farsi M. Nitric oxide levels and total antioxidant capacity in the seminal plasma of sub-fertile smoking men. *Cell J*. 2015;17(1):129-136.
- Hammadeh ME, Hamad MF, Montenarh M, Fischer-Hammadeh C. Protamine contents and P1/P2 ratio in human spermatozoa from smokers and non-smokers. *Hum Reprod*. 2010;25(11):2708-2720.
- Mitra A, Chakraborty B, Mukhopadhay D, et al. Effect of smoking on semen quality, FSH, testosterone level, and CAG repeat length in androgen receptor gene of infertile men in an Indian city. Syst Biol in Reprod Med. 2012;58(5):255-262.
- Collodel G, Capitani S, Pammolli A, Giannerini V, Geminiani M, Moretti E. Semen quality of male idiopathic infertile smokers and nonsmokers: an Ultrastructural Study. J Androl. 2010;31(2):108-113.
- 43. Safarinejad MR, Asgari SA, Farshi A, et al. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. *Reprod Toxicol.* 2013;36:18-23.
- Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. J Androl. 2012;33(4):515-528.
- Gaur DS, Talekar MS, Pathak VP. Alcohol intake and cigarette smoking: Impact of two major lifestyle factors on male fertility. *Indian J Pathol Microbiol.* 2010;53(1):35-40.
- Anderson RA, Willis BR, Oswald C, Zaneveld LJ. Ethanol-induced male sub-fertility: impairment of spermatozoa. J Pharmacol Exp Ther. 1983;225(2):479-486.
- 47. Dias TR, Alves MG, Martins BRL, et al. Dose-dependent effects of caffeine in human Sertoli cells metabolism and oxidative profile: relevance for male fertility. *Toxicology*. 2015;328:12-20.
- Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male sub-fertility. *Repro Biomed Online*. 2014;28(6):684-703.
- 49. Cochrane SH. Fertility and education: what do we really know? World Bank staff occasional papers; no. OCP 26. Baltimore, MD: Johns Hopkins University Press; 1979.
- Faure C, Dupont C, Baraibar MA, et al. In subfertile couple, abdominal fat loss in men is associated with improvement of sperm quality and pregnancy: a case-series. *PLoS ONE*. 2014;2:e86300.
- 51. Guthauser B, Boitrelle F, Plat A, Thiercelin N, Vialard F. Chronic excessive alcohol consumption and male fertility: a case report

- 52. Sermondade N, Elloumi H, Berthaut I, et al. Progressive alcohol-induced sperm alterations leading to spermatogenic arrest, which was reversed after alcohol withdrawal. *Reprod Biomed Online*. 2010;20(3):324-327.
- Vicari E, Arancio A, Giuffrida V, D'Agata R, Calogero AE. A case of reversible azoospermia following withdrawal from alcohol consumption. J Endocrinol Invest. 2002;25(5):473-476.
- Kuller LH, May SJ, Perper JA. The relationship between alcohol, liver disease, and testicular pathology. *Am J Epidemiol.* 1978;108:192-199.
- Braga DP, Halpern G, Figueira RC, et al. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. *Fertil Steril*. 2012;97(1):53-59.
- Anderson RA Jr, Willis BR, Oswald C, Zaneveld LJ. Partial reversal of ethanol-induced male reproductive pathology following abstinence. *Alcohol Alcohol.* 1985;20:273-286.
- 57. Boeri L, Capogrosso P, Ventimiglia E, et al. Heavy cigarette smoking and alcohol consumption are associated with impaired sperm parameters in primary infertile men. *Asian J Androl.* 2019;21:478-485.
- Peng Y, Chang W, Zhou H, Hu H, Liang W. Factors associated with health-seeking behavior among migrant workers in Beijing. *China*. *BMC Health Serv Res.* 2010;10:69.
- Richardson A, Allen JA, Xiao H, Vallone D. Effects of race/ethnicity and socioeconomic status on health information-seeking, confidence, and trust. J. Health Care Poor Underserved. 2012;23(4):1477-1493.

- Scribani M, Shelton J, Krupa CD, et al. Comparison of bias resulting from two methods of self-reporting height and weight: a validation study. JRSM Open. 2014;5(6):204253331351404.
- Bhanji S, Khuwaja AK, Siddiqui F, Azam I, Kazmi K. Underestimation of weight and its associated factors among overweight and obese adults in Pakistan: a cross sectional study. BMC Public Health. 2011;11:363.
- 62. Williams R, Vinson DC. Validation of a single screening question for problem drinking. *J Fam Pract*. 2001;50(4):307-312.
- 63. Coulton S, Perryman K, Bland M, et al. Screening and brief interventions for hazardous alcohol use in accident and emergency departments: a randomised controlled trial protocol. *BMC Health Serv Res.* 2009;9:114.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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