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Influence of substance use on male reproductive health and offspring outcomes

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Introduction

The prevalence of ***substance use*** is rising, especially among men of ***reproductive*** age (~18–44 years old), and has been exacerbated by the COVID-19 pandemic–. The ***substances*** that are most popularly ***used*** include alcohol, cannabis, opioids and tobacco products. This trend in increasing ***use*** is concerning because men are often unaware of the potential adverse effects on their ***reproductive health***. Existing evidence indicates that ***substance use*** can ***influence*** spermatogenesis, ***reproductive*** hormone secretion via the hypothalamic–pituitary–gonadal (HPG) axis, and sexual function– (Box). As infertility is associated with a large emotional and economic burden,, identifying modifiable behavioural or lifestyle risk factors, such as ***substance use***, which can affect human fertility, is a considerable clinical issue and an important public ***health*** matter.

Emerging evidence also suggests that preconception paternal drug ***use*** can have adverse consequences for ***offspring*** (Box). Historically, the focus has mostly been on the effects of maternal ***substance use*** during pregnancy, whereas little is known regarding paternal contributions. The paucity of knowledge in this area is partly caused by the limitations of existing studies, such as confounding, recruitment bias and patient self-reporting, which make causal interpretations challenging. Results of studies in which the effect of preconception paternal ***substance use*** on ***offspring*** has been investigated have demonstrated that paternal exposure to alcohol, cannabis, opioids and tobacco can adversely ***influence offspring*** neurodevelopment and is associated with poor ***offspring*** mental ***health***, in particular hyperactivity, depression, attention-deficit hyperactivity disorder (ADHD) and addiction vulnerability,. The underlying cause is not well understood, but research has shown that preconception paternal ***substance use*** might alter ***offspring*** brain and neurobehavioural development through epigenetic mechanisms,–.

A comprehensive summary of the effects of ***substance use*** (alcohol, cannabis, opioids and nicotine) on ***male reproductive health*** and the short-term and long-term ***outcomes*** for ***offspring*** to guide ***health***-care providers is lacking. In this Review, we examine the ***influence*** of ***substance use*** on ***male*** fertility and the potential for preconception paternal ***use*** to affect the ***health*** of future ***offspring***. The preconception period is a crucial window for targeting education and counselling on the optimization of lifestyle factors, because motivation is often strong to achieve the desired ***health outcomes*** in preparation for pregnancy. Focusing public ***health*** efforts and ***health***-care provider counselling is important to improve patient awareness.

Box 1 Summary of ***substance use*** (that is, alcohol, cannabis, opioids and nicotine) on ***male reproductive health***

Effects of ***substances*** on ***male*** fertility can be measured ***using*** hypothalamus–pituitary–gonadal axis and semen parameter changes.

Alcohol — ↑ luteinizing hormone (LH) and/or follicle-stimulating hormone levels and sperm DNA fragmentation; ↓ testosterone levels, seminal volume and sperm count, motility and morphology.

Cannabis — ↓ LH and sperm count, motility and morphology; ↑ DNA fragmentation; ↓ or ↑ testosterone levels.

Opioids — ↓ gonadotropin-releasing hormone secretion, testosterone levels and sperm motility and morphology; ↑ sperm DNA fragmentation.

Nicotine — ↓ or ↑ LH and/or follicle-stimulating hormone; ↑ testosterone levels; ↓ sperm count, motility and morphology.

THC, Δ9 -tetrahydrocannabinol.

Box 2 Summary of paternal ***substance use*** (that is, alcohol, cannabis, opioids and nicotine) on ***offspring*** development

Effects on fetal development

Alcohol — increased intrauterine growth restriction

Cannabis — increased pregnancy loss

Opioids — decreased fetal weight

Nicotine — increased pregnancy loss

Effects on infant development (<1 year old)

Alcohol — increased birth defects, decreased birthweight

Cannabis — increased congenital cardiac anomalies

Opioids — increased withdrawal-like behaviour

Nicotine — increased testosterone levels

Effects on childhood and adolescent development (1–19 years old)

Alcohol — increased risk of cancers (leukaemia and brain tumours), psychopathological disorders and ***substance***-related disorders

Cannabis — increased behavioural issues

Opioids — increased risk of opioid addiction, delayed learning and impulsive behaviours

Nicotine — decreased sperm count, increased risk of neurodivergent behaviour (such as autism)

Male fertility

Unhealthy lifestyles, including consumption of alcohol, and ***use*** of tobacco or cannabis products, are universally recognized to negatively affect general ***health***, but their ***influence*** on ***male*** fertility is less well known. Studies are limited, but their results have shown that the most commonly ***used substances***, alcohol, cannabis, opioids and tobacco products, are associated with adverse ***reproductive health outcomes***.

Alcohol

Research on alcohol consumption and ***male*** fertility has largely demonstrated that it can alter ***male reproductive*** hormones,–, semen parameters,,, testicular volume, and sexual function, (Table). Results also suggest that these

changes follow an exposure–response relationship with an increased effect observed after heavy and chronic alcohol consumption,. Heavy drinking in men is often defined as ≥15 drinks per week, or binge drinking on each of ≥5 days in the past 30 days.

Effect of alcohol on ***reproductive*** ***health*** and ***offspring*** ***outcomes***

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
Reproductive health						
1992	***Male reproductive*** hormones	Rat (*n* = 24 total, 12 ethanol-treated and 12 control)	Experimental study	6% ethanol diet for 5 weeks	Ethanol exposure was associated with significantly lower serum and testicular testosterone than untreated animals (*P* < 0.01)	
1977	***Male reproductive*** hormones	Mouse (*n* = 28 total, 10 in control, 8 in ethanol-treated and 10 in sucrose-fed controls)	Experimental study	Intragastric administration of ethyl alcohol (1.24 g/kg)	Ethyl alcohol was associated with a transient decrease in plasma testosterone that recovered after 1 h	
2011	Semen parameters	Human (*n* = 209)	Retrospective study	Self-reported alcohol consumption	Heavy alcohol ***use*** (>10 drinks/week) was significantly associated with reduced sperm count (*P* = 0.04). No significant association between level of alcohol ***use*** and the high DNA stainability or DNA fragmentation index of sperm	
2018	Erectile dysfunction and sexual function	Human (*n* = 154,295)	Meta-analysis	Self-reported alcohol consumption	Light-to-moderate alcohol consumption (<21 drinks/week) correlated with a decreased risk of erectile dysfunction (OR 0.71, 95% CI 0.59?0.86, *P* = 0.000). Regular and heavy alcohol consumption (>21 drinks/week) had no significant effect on the prevalence of erectile dysfunction. A non-linear relationship was observed between alcohol consumption and risk of erectile dysfunction	
2004	Sexual function	Human (*n* = 2,112)	Observational study	Self-reported alcohol	Paternal consumption of >20 drinks/week before	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
				consumption	conception was associated with a significantly increased time to pregnancy (P < 0.001)	
2023	***Male reproductive*** hormones	Human (n = 23,258)	Meta-analysis study	Self-reported alcohol consumption	Alcohol consumption significantly decreased semen volume (SMD ?0.51, 95% CI ?0.77 to ?0.25), but was not significantly associated with changes in sperm density, mobility and morphologyAlcohol consumption was linked to decreased testosterone levels (SMD ?1.60, 95% CI ?2.05 to ?1.15), follicle-stimulating hormone (SMD ?0.47, 95% CI ?0.88 to ?0.05), luteinizing hormone (SMD ?1.35, 95% CI ?1.86 to ?0.83), but no effect on oestradiol, inhibin B and sex hormone-binding globulin	
2005	***Male reproductive*** hormones and semen parameters	Human (n = 66)	Observational study	Self-reported alcohol consumption	Alcohol consumption was associated with significantly (P < 0.001) increased follicle-stimulating hormone, luteinizing hormone, oestradiol levels, semen volume, sperm count, sperm motility and morphologically normal sperm, in addition to decreased testosterone and progesterone levels	
2006	***Male reproductive*** hormones	Human (n = 46)	Observational study	Self-reported alcohol consumption	Alcohol consumption was associated with significantly (P < 0.001) low plasma testosterone, luteinizing hormone and follicle-stimulating hormone	
2014	Semen parameters	Human (n = 8,344)	Cross-sectional study	Self-reported alcohol consumption	No consistent association between semen parameters and alcohol consumption. A positive linear association between total alcohol consumption and total or free testosterone was observed	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
2011	Semen parameters	Human (*n* = 29, 914)	Systematic review and meta-analysis	Self-reported alcohol consumption	Alcohol consumption is a risk factor for reduced semen volume and quality	
1994	Semen parameters	Human (*n* = 44)	Observational study	Family-reported alcohol consumption	Heavy alcohol consumption (>80 g per day) was associated with an increased risk of partial or complete spermatogenic arrest ($P < 0.001$) and Sertoli cell-only syndrome ($P < 0.05$)	
1985	Semen parameters and ***male reproductive*** hormones	Human (*n* = 20)	Experimental study	Alcohol dependence syndrome	Alcohol dependence syndrome was associated with a decrease in total semen volume, sperm concentration and testosterone, in addition to an increased percentage of morphologically abnormal sperm. No association of alcohol dependence syndrome and changes in luteinizing hormone, follicle-stimulating hormone and prolactin were observed	
2021	Erectile dysfunction and sexual function	Human (*n* = 216,461)	Meta-analysis	Self-reported alcohol consumption	Alcohol consumption was associated with erectile dysfunction (OR 0.89, 95% CI 0.81?0.97); light to moderate consumption (OR 0.82, 95% CI 0.72?0.94); heavy consumption (OR 0.82, 95% CI 0.67?1.00)	
2017	Semen parameters	Human (*n* = 16,395)	Systematic review and meta-analysis	Self-reported alcohol consumption	Alcohol consumption adversely affected semen volume and sperm morphology	
2013	Sperm parameters	Mouse	Experimental study	5% or 10% ethanol exposure	Paternal ethanol consumption was associated with decreased sperm count and motility, in addition to increased abnormal sperm morphology, apoptosis, DNA integrity and chromatin remodelling	
2018	Sperm parameters	Mouse (*n* = 18, 9	Observational study	Chronic ethanol consumptio	Paternal chronic ethanol exposure was associated	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
		ethanol-treated and 9 control)		n (vapour ethanol for 8 h per day, 5 days a week, for 5 weeks)	with altered sperm small non-coding RNAs and reduced epididymal expression of a tRNA-derived small RNA methyltransferase, *Nsun2*, known to directly regulate tRNA-derived small RNA biogenesis	
Offspring outcomes						
2019	Short-term and long-term ***offspring outcomes***	Mouse (*n* = 11 total, 6 alcohol-exposed and 5 control)	Experimental study	4-h nightly exposure to 10% ethanol solution	Paternal alcohol exposure before conception resulted in decreased ***offspring*** weight and increased insulin hypersensitivity in ***male offspring***	
2023	Short-term ***offspring outcomes***	Mouse (*n* = 192 total, 96 alcohol-exposed and 96 control)	Experimental study	Weight-based alcohol dosing (2.7 g/kg)	Paternal alcohol exposure before conception was associated with ***offspring*** craniofacial abnormalities and growth deficiencies that are dose dependent	
2021	Short-term ***offspring outcomes***	Human (*n* = 529,090)	Prospective, population-based study	Self-reported alcohol consumption	Paternal alcohol consumption before conception was associated with an increased risk of birth defects (OR 1.35, 95% CI 1.14?1.59; *P* < 0.001)	
2014	Short-term and long-term ***offspring outcomes***	Mouse (*n* = 123, 45 3.3 g/kg ethanol exposed, 39 1.1 g/kg ethanol exposed, and 39 control)	Experimental study	Intragastric ethanol exposure (0, 1.1, 3.3 g/kg)	Chronic paternal ethanol exposure (1.1 or 3.3 g/kg) before conception altered methylation of imprinted genes in sire sperm and in the ***offspring***?s cerebral cortices that are linked to delayed ***offspring*** cognitive performance, and increased anxiety and depression	
2007	Short-term and long-term ***offspring outcomes***	Mouse (*n* = 45 total, 15 ***males***, and 30 females). Single-case experimental design, same 15	Experimental study	Acute alcohol exposure (single dose 5 g/kg of 20% ethanol)	A single acute paternal alcohol exposure before insemination was linked to early ***offspring*** developmental delays and increased aggression	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
		males were exposed to saline and then to ethanol				
2018	Short-term ***offspring outcomes***	Human (*n* = 1,292)	Observational study	Self-reported alcohol consumption	Paternal alcohol consumption (amount not defined) 3 months before conception was associated with a shorter anogenital distance, a biomarker of ***reproductive*** hormone abnormalities, in ***offspring***, especially ***male offspring***	
1994	Short-term ***offspring outcomes***	Rats (*n* = 80 total, 20 ***male*** controls, 20 ***males*** at 1.25 g/kg, 20 ***males*** at 2.5 g/kg, and 20 ***males*** at 5 g/kg)	Observational study	Single acute alcohol exposure (saline, 1.25 g/kg, 2.5 g/kg, or 5 g/kg of 20% ethanol)	Paternal alcohol administration 24 h before breeding decreased the number of viable ***offspring*** and increased ***offspring*** mortality	
2009	Long-term ***offspring outcomes***	Human (*n* = 1,252)	Observational study	Self-reported alcohol consumption	Paternal alcohol dependence was associated with an increased risk of externalizing disorders and psychopathology in late adolescence in children	
2020	Short-term and long-term ***offspring outcomes***	Human (*n* = 4,726)	Observational study	Self-reported alcohol consumption	Paternal alcohol consumption (at least 50 ml per day) 3 months before conception was associated with an increased risk of ***offspring*** congenital heart disease (aOR 2.87, 95% CI 2.25?3.65)	
2022	Long-term ***offspring outcomes***	Human (*n* = 64,710)	Observational study	Self-reported alcohol consumption	Paternal alcohol consumption (20?100 g per week) was associated with an increased risk of ***substance***-related disorders in children. Children of fathers with the highest alcohol consumption increase were at a 63% higher risk	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					(HR 1.63, 95% CI 1.26?2.12) of ***substance***-related disorders	
2022	Long-term ***offspring outcomes***	Human (*n* = 796)	Observational study	Self-reported alcohol consumption	Preconception paternal alcohol consumption was associated with an increased risk of anxiety and depression in ***male offspring*** following at age 4 (RR 1.33, 95% CI 1.09?1.61) and 6 (RR 1.37, 95% CI 1.02?1.85) years	

aOR, adjusted odds ratio; HR, hazard ratio; OR, odds ratio; RR, risk ratio; SMD, standardized mean difference.

Male reproductive hormones

Alcohol consumption is reported to alter the regulation of the HPG axis and affects all three components of the axis (hypothalamus, pituitary and gonads), disrupting the production of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone,,,. Specifically, alcohol can stimulate the paraventricular nucleus of the hypothalamus to release corticotropin-releasing factor (CRF).

The effect of alcohol consumption on ***male*** fertility has been examined in preclinical and human studies, with varying results: results of the preclinical studies have largely demonstrated reduced levels of LH, FSH and testosterone, but the results of human studies have been conflicting,–. In 66 men aged 36.6 ± 5.7 years (mean ± standard deviation) who consumed a minimum of 180 ml of alcohol daily for at least 5 days per week for at least a year without polysubstance ***use***, elevated FSH, LH and oestradiol levels were observed. Testosterone and progesterone levels were also decreased. Similarly, ethanol intake of ~220 g daily for 4 weeks resulted in decreased testosterone levels and metabolism, independent of cirrhosis or nutritional factors, in 11 healthy men, 21–40 years of age. Taken together, these studies suggest that regular alcohol consumption, even up to 4 weeks, can alter ***male reproductive*** hormones and testosterone metabolism, which can affect fertility.

Contrary to these findings, another study of 45 men with alcoholism aged 20–40 years compared with 55 healthy men aged 22 to 32 years had significantly reduced levels of testosterone (4.96 ± 0.16 ng/ml versus 7.56 ± 0.13 ng/ml, $P < 0.001$), which correlated negatively with thiobarbituric acid reactive ***substances***. The authors hypothesized that because low testosterone was not accompanied by a rise in LH and FSH levels, but correlated with increased serum levels of oxidizing agents and decreased serum levels of reactive oxygen species, these results were in part attributable to an impaired HPG axis and increased oxidative stress. In addition, a duration-dependent decrease in serum testosterone levels was observed in alcohol users, which is important for ***health***-care providers to discuss with men, including those interested in conceiving. In 8,344 men (aged 30–80 years old) a linear association between total alcohol consumption and testosterone levels was observed, but no consistent association between alcohol consumption and serum inhibin B, FSH or LH levels was found. Interestingly, young men (aged 18–28 years) and fertile men (aged 18–45 years with pregnant partners) who consumed >20 alcoholic drinks per week had higher free testosterone than men consuming 1–10 drinks weekly, probably owing to changes in testosterone metabolism by the liver. This observation highlights that when testosterone is ***used*** alone as part of a fertility work-up it can be unreliable and should be combined with other ***reproductive health*** markers in alcohol users.

Research findings regarding the ***influence*** of alcohol consumption on ***male reproductive*** hormones are heterogenous, in part owing to expected intraindividual fluctuations in hormone levels and diurnal variation of sex hormones in men,. Testosterone cycles can fluctuate from increased in the morning to reduced in the evening,

which can affect study results depending on the time of day that hormonal sampling is performed. Thus, future studies need to harmonize timing of blood collection for ***male reproductive*** hormone assessment.

Semen parameters

Overall, animal and human studies suggest that alcohol ***use***, especially chronic and heavy intake, is associated with reduced sperm concentration and motility,,, increased abnormal sperm morphology,, and increased DNA damage, including defects in chromatin condensation,. In 2011, results of a meta-analysis of 57 studies including 29,914 participants aged ≥13 years showed a significant association between alcohol consumption by men and reduced semen volume (pooled mean difference (MD) −0.30, P = 0.007) in both healthy men and those with infertility. This meta-analysis was limited by heterogeneity between studies and inclusion of only cross-sectional studies, but it highlights modifiable lifestyle factors that can improve ***male*** fertility. In another study, 66 men (aged 36.6 ± 5.7 years) undergoing care at an addiction treatment centre, who consumed a minimum of 180 ml of alcohol per day for at least 5 days a week for 1 year, were found to have significantly decreased semen volume (1.56 ± 0.79 versus 2.17 ± 0.712), sperm count (51.99 ± 44.71 versus 132.97 ± 89.02), motility (30.38 ± 15.82 versus 56.10 ± 8.72) and morphologically normal sperm (67.17 ± 16.73 versus 82.00 ± 9.76) compared with healthy men (P < 0.001). An autopsy series including men (aged 49–61 years) who were light drinkers (n = 32, daily intake <10 g) and heavy drinkers (n = 44, daily intake> 80 g) reported that more than half of heavy drinkers (n = 23) had partial or complete spermatogenic arrest (P < 0.0001). Similarly, in 20 men (aged 25–42 years) with alcohol dependence syndrome, a decrease in semen sample volume (0.5–2.5 ml versus 3–4.5 ml), sperm concentration (less than 50 million/ml versus 60–164 million/ml), and normal sperm motility (20–45% versus >50%) was observed compared with men without a history of alcohol consumption. The authors of this study concluded that chronic alcohol consumption can ***influence*** spermatogenesis and spermiogenesis, resulting in oligozoopermia. By contrast, results of an international cross-sectional study including 8,344 healthy men (aged 18–45 years old) did not show any consistent association between semen parameters and low-to-moderate alcohol consumption (median weekly intake was 8 drinks).

The data are mixed, but the evidence largely supports an adverse effect of alcohol consumption on semen parameters that is probably dose dependent and time dependent. Contributing to the heterogeneity of the data is the variability in semen quality among healthy men and because studies varied in the degree of confounder adjustment. Moreover, moderate-to-heavy alcohol ***use*** could affect other physiology that can ***influence*** semen parameters and might account for the mixed evidence. To improve evaluation of the consequences of alcohol consumption on semen characteristics, future research must adequately adjust for confounding variables, especially polysubstance ***use***.

Testicular volume

Heavy alcohol ***use*** can result in testicular atrophy,, especially in men with advanced alcoholic cirrhosis, which can be caused by direct testicular damage secondary to an adverse effect on the HPG axis, and other common confounders such as polysubstance ***use*** or malnutrition. In a study including 55 men with cirrhosis of the liver, testicular atrophy was present in 70% of patients in whom the size of the testes were measured. Testicular atrophy, assessed ***using*** testicular tissue obtained as soon as possible post-mortem, has been reported to be primarily a result of decreased seminiferous tubule diameter and loss of germ cells. The loss of germinal tissue is thought to be secondary to primary testicular failure given the presence of elevated FSH in this study. Testicular shrinkage, in part owing to the loss of germ cells, can be associated with reduced sperm count and quality, which can adversely affect ***male*** fertility. Overall, the current literature suggests that alcohol consumption is associated with a dose-dependent effect on testicular volume, but more studies are needed to determine whether these changes are reversible with alcohol cessation.

Erectile dysfunction and sexual function

Evidence indicates that a relationship exists between alcohol intake and erectile dysfunction,,. A 2018 meta-analysis of 24 studies including 154,295 patients (aged 18–79 years) reported that light-to-moderate (<21 drinks weekly) alcohol consumption was linked to a protective effect against erectile dysfunction (odds ratio (OR) 0.71,

95% CI 0.59–0.86). However, regular and heavy alcohol intake (>21 drinks weekly) had no significant effect on the risk of erectile dysfunction (OR 0.99, 95% CI 0.81–1.22, P = 0.892). In this study, a non-linear relationship between alcohol intake and risk of erectile dysfunction was reported, potentially because of confounding ***influences*** from lifestyle factors. A major limitation of this meta-analysis was that it included only cross-sectional studies, limiting the strength of evidence of a causal relationship between alcohol and erectile dysfunction. Similarly, results of a meta-analysis from 2021 including 46 studies (n = 216,461) showed a protective effect between weekly alcohol intake and erectile dysfunction (OR 0.89, 95% CI 0.81–0.97); light to moderate (≤14 drinks per week, OR 0.82, 95% CI 0.72–0.94) and high (≥14 drinks per week, OR 0.82, 95% CI 0.67–1.00). A protective association possibly exists between alcohol consumption and erectile dysfunction, but the study was limited by high heterogeneity, selection and recall biases, as well as confounding variables.

Increased rates of sexual dysfunction have been reported in alcohol-dependent populations compared with social drinkers or healthy individuals. The most common issues reported include premature ejaculation, delayed ejaculation, decreased libido and reduced sexual potency,. In an observational study including 2,112 pregnant couples in the UK in which time to pregnancy (months) was assessed, paternal alcohol consumption significantly affected fecundity, especially if they consumed >20 alcoholic beverages a week (18.6, 95% CI 15.7–21.3, P < 0.001). This observation suggests a possible dose-dependent effect of alcohol consumption on fecundity and supports promotion of a healthy lifestyle among individuals planning or trying for pregnancy.

Alcohol consumption is associated with erectile dysfunction and sexual function, especially in exposure-duration and dose-dependent manners. Individuals that are sexually active would benefit from cessation of or reduced alcohol consumption, especially if they have sexual dysfunction already.

Summary

In general, preclinical and human research suggests that alcohol consumption negatively ***influences*** ***male*** ***reproductive*** ***health***, including ***male*** ***reproductive*** hormones, semen parameters, testicular volume and sexual function (Table). These effects seem to be linked to the duration and amount of alcohol consumed; regular or daily alcohol intake can negatively affect ***male*** fertility and make conception increasingly difficult, but occasional consumption has not been consistently shown to have an adverse effect. Currently, no guidelines exist regarding ***male*** fertility and a safe or preferred amount of alcohol to consume, but, importantly, ***health***-care providers need to screen their patients and counsel them regarding limiting the frequency and volume of alcohol exposure, and to avoid daily or binge drinking.

Cannabis

The prevalence of cannabis ***use*** is rising, especially among men of ***reproductive*** age, in part owing to growing societal acceptance and legalization,. Results from a 2021 United States national survey found that 22.1% (~27.2 million) men aged 18 years or older reported cannabis ***use*** in the past year, and prevalence was highest (36.6%, ~6.1 million) among those 18–25 years old. With regard to biological plausibility for cannabis negatively ***influencing*** ***male*** ***reproductive*** ***health***, the main psychoactive component of cannabis, ∆9-tetrahydrocannabinol (THC), binds to receptors in the endocannabinoid system (ECS) that are present in sperm and throughout the ***male*** ***reproductive*** tract (Box). The ECS has various roles in regulating the HPG axis, including control of gonadotropin secretion,, synthesis of testosterone in Leydig cells, spermatogenesis and function of sperm.

Overall, results of studies on cannabis and ***male*** fertility are variable but suggest that cannabis ***use*** adversely affects ***male*** ***reproductive*** ***health*** (Table). The data support a link between cannabis ***use*** and altered ***male*** ***reproductive*** hormones, semen parameters, libido, and erectile, ejaculation and orgasmic dysfunction,. The heterogeneity in results, especially in human studies, is partly a result of reliance on retrospective data, diversity of study populations, frequency and potency of cannabis ***use***, confounding variables including polysubstance ***use***, sociodemographic factors, and differences between cannabis products and modes of delivery. Cannabinoids have been shown to have varying effects on different ECS targets; thus, various types of cannabis products might have a diverse range of downstream effects. Limitations of preclinical studies include a focus on acute exposure to cannabis, doses and administration methods that are not representative of human usage, as well as intrinsic

differences between rodent and human physiology. This article focuses on the effects of cannabis only; cannabidiol is not discussed as it has a different side effects profile and affinity for cannabinoid receptors.

Effect of cannabis on ***reproductive health*** and ***offspring outcomes***

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
Reproductive health						
2019	***Male reproductive*** hormones	Non-human primates and human (7 clinical studies and 23 animal in vitro studies)	Systematic review	In vitro models, mammalian animal studies, and human studies reviewed	Long-term cannabis consumption was not consistently associated with hypothalamic?pituitary?gonadal axis hormones in human clinical studies. Negative or potentially negative effects of cannabis on hormones were noted in non-human and in vitro studies	
2022	***Male reproductive*** hormones	Human (*n* = 2,074)	Cross-sectional study	Self-reported cannabis ***use***	Men with previous cannabis ***use*** had significantly reduced testosterone compared with non-users (*P* = 0.03). No significant relationship with cannabis ***use*** and FSH or luteinizing hormone levels was observed	
1974	***Male reproductive*** hormones and semen parameters	Human (*n* = 20)	Observational study	Self-reported cannabis ***use***	Chronic users had significantly reduced testosterone compared with non-users (*P* < 0.001) and were at an increased risk of oligospermia. Reduced FSH levels were found in men with increased cannabis consumption (*P* < 0.01)	
2023	***Male reproductive*** hormones, semen parameters, and testicular volume	Non-human primate (*n* = 6 total)	Experimental study	Edible $?^{8}$-THC 2.5 mg/7 kg/day	Chronic THC consumption was associated with decreased testosterone levels and testicular volume, with partial reversal upon THC cessation. THC ***use*** was also associated with increased FSH (*P* = 0.01) that approached baseline upon THC cessation. Last, THC ***use*** also decreased semen volume	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
2015	Hormone levels; semen parameters	Human (*n* = 1,215)	Cross-sectional study	Self-reported cannabis ***use***	7% increased testosterone levels in those who smoked cannabis regularly. Cannabis smoking ?1/week was associated with reduced sperm concentration (*P* = 0.12) and sperm count (*P* = 0.17)	
2017	***Male reproductive*** hormones	Human (*n* = 1,577)	Cross-sectional study	Self-reported cannabis ***use***	No difference in testosterone levels based on ever ***using*** cannabis. Increased testosterone was associated with more recent ***use***, especially in the past month and year	
2021	***Male reproductive*** hormones and semen parameters	Human (*n* = 4,787)	Systematic revies	Self-reported cannabis ***use***	Significantly decreased FSH in men ***using*** cannabis (SMD ?0.142), but no significant differences in testosterone or luteinizing hormone. Among cannabis users, 45% had impaired semen parameters versus 25% in non-users; this result did not reach clinical significance (RR 1.16, 95% CI 0.84?1.60; *P* = 0.37)	
2022	Testicular volume	Non-human primate (*n* = 6)	Experimental study	Edible THC exposure (2.5 mg/7 kg/day)	Chronic daily THC ***use*** for 7 months was associated with decreased total bilateral testicular volume with exposure (mean decrease of 58%)	
2014	Semen parameters	Human (*n* = 1,970)	Observational study	Self-reported cannabis ***use***	Cannabis ***use*** in the past 3 months was associated with poor sperm morphology (OR 1.94, 95% CI 1.05?3.60)	
2020	Semen parameters	Human (*n* = 229)	Cross-sectional study	Self-reported cannabis ***use***	Recent (<6 weeks) users (OR 2.6, 95% CI 1.0?6.8) and heavy (>2 g) users (OR 4.3, 95% CI 1.1?15.9) were at an increased risk of having asthenozoospermia. Moderate users (1?2 g) were at an increased risk of teratozoospermia (OR	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
					3.4, 95% CI 1.5?7.9)	
2021	Semen parameters	Human (*n* = 409)	Cross-sectional study	Self-reported cannabis ***use***	Current users had increased odds of abnormal sperm morphology (OR 2.15, 95% CI 1.21?3.79), low semen volume (OR 2.76, 95% CI 1.19?6.42) but low odds of reduced motility (OR 0.47, 95% CI 0.25?0.91)	
1978	Semen parameters	Rat (*n* = 25 total, 9 controls, 4 placebo control, 6 at 0.4 mg/kg THC, and 6 at 3 mg/kg THC)	Experimental study	Cannabis smoke (0.4 mg/kg and 3 mg/kg THC)	Decreased epididymal sperm noted with heavy exposure (3 mg/kg THC), as well as increased dissociation of sperm head and tail	
1978	Semen parameters	Mice (*n* = 69 total, 15 control, 30 at 5 mg/kg, and 24 at 10 mg/kg)	Experimental study	Intraperitoneal injections of cannabinoids (5 mg/kg and 10 mg/kg THC)	Compared with controls, THC-exposed mice had an increased incidence of abnormal sperm and rate of translocations on cytogenetic assessment	
1979	Semen parameters	Human (*n* = 16)	Observational study	Self-reported cannabis ***use***	Significant decline in sperm concentration and count, as well as reduced motility and normal morphology with high exposure (8?20 cannabis cigarettes/day to cannabis ***use*** ($P < 0.01$)	
1985	Semen parameters	Mice (*n* = 48 ***males*** all THC-exposed)	Experimental study	THC (50 mg/kg) given by oral gavage	No significant increase in dominant-lethal or heritable translocation mutations	
2018	Semen parameters	Human (*n* = 24 total, 12 cannabis users and 12 non-users)Rat	Observational study (human)Experimental study (rat)	Self-reported cannabis ***use*** (human)Oral gavage of 2 mg/kg THC for 12 days (rat)	Significant differences in DNA methylation noted between users and non-users in both human and rodent sperm, particularly in Hippo signalling and cancer signalling pathways. Cannabis ***use*** compared with non-***use*** was associated with significantly lower sperm concentration (58.1 ± 26.5 vs 96.3 ± 49.7, $P < 0.05$)	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
2006	Semen parameters	Human (*n* = 78)	Experimental study	Sperm incubated with THC at various concentrations (0.032, 0.32 or 4.8 μM)	Dose-dependent decreased motility and spontaneous and induced acrosome reactions noted	
1977	Semen parameters	Canine (*n* = 10)	Experimental study	Daily administration of cannabis extract (12.5 mg/kg) for 30 days	Complete arrest of spermatogenesis and histological degeneration noted. Testicular weight was significantly lower in those exposed to cannabis than in controls ($P < 0.01$)	
2011	Semen parameters and testicular volume	Mouse (*n* = 18 total, 6 controls, 6 at 3 mg/kg/day, and 6 at 6 mg/kg/day)	Experimental study	Subjects given cannabis (3 mg/kg/day or 6 mg/kg/day) orally for 36 days	Daily cannabis intake is associated with decreased sperm count, viability and motility, as well as histological degenerative changes of the testes	
1974	Testicular volume	Mouse (*n* = 40 total, 10 control, 10 at 50 mg, 10 at 90 mg and 10 allowed to recover for 63 days)	Experimental study	Daily intraperitoneal injections of cannabis extract (10 mg/ml, 50 mg in 25 days and 90 mg in 45 days) given for 45 days	Significantly decreased testicular weight (515 mg ± 10 and 534 mg ± 51 with THC exposure versus 697 mg ± 28 control, $P < 0.05$) with shrinkage of the seminiferous tubules (155 μm ± 6 and 148 μm ± 3 with THC exposure vs 196 μm ± 2 control, $P < 0.001$) and seminal vesicles (293 mg ± 20 and 274 mg ± 29 with THC exposure vs 520 mg ± 38 control, $P < 0.001$)	
1982	Testicular volume	Rat (5 total groups with 8?10 ***males*** per group; group 1 at 25 mg/kg and vehicle, group 2 vehicle, group 3 at 25 mg/kg with sesame oil, group 4 sesame oil, and group 5	Experimental study	Oral administration of THC (1, 5 and 25 mg/kg/day) and cannabis extracts (3, 15 and 75 mg/kg/day)	Prostate, seminal vesicles and epididymal weights noted to be decreased in those with high dose levels	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
		untreated)				
1977	Testicular volume	Rat (*n* = 20 total, 5 THC-treated, 5 cannabidiol treated, 5 vehicle treated control, and 5 untreated control)	Experimental study	Subjects injected intraperitoneally with cannabinoids (2 mg/kg)	77% reduction in testicular weight in those exposed to cannabinoids was noted	
2018	Hormone levels; semen parameters; testicular volume	Mouse (*n* = 30 total, 10 control, 10 at 15 mg/kg/day and 10 at 30 mg/kg/day)	Experimental study	Cannabinoid (15 and 30 mg/kg/day) administered orally to subjects for 34 days	76% decrease in total circulating testosterone was observed in the high cannabinoid-exposure group, with a decreased number of sperm in the epididymis and increased abnormal morphology. No significant differences in testicular weight were noted	
2010	Testicular volume	Mouse (*n* = 60 total, 12 controls, 12 at 50 mg, 12 at 60 mg, 12 at 80 mg, 12 at 80 mg followed by cessation for 45 days)	Experimental study	Intraperitoneal injection of cannabis extract (40?60 mg)	Significant shrinkage of tubular diameter and regression of seminiferous epithelium in testes at low doses was noted (178.67 μm ± 0.98 at a 40-mg dose versus 136.20 μm ± 1.34 at a 60-mg dose versus 230.54 μm ± 3.47 in controls). Withdrawal was associated with an increase in testosterone levels	
2022	Testicular volume	Human (*n* = 316)	Cross-sectional study	Self-reported cannabis ***use***	Cannabis ***use*** was not significantly associated with testis volume	
2008	Sexual function	Human (*n* = 71 total, 64 men with erectile dysfunction and 7 healthy men)	Experimental study	Self-reported cannabis ***use***	Chronic cannabis ***use*** (at least weekly) can induce early endothelial damage in men with erectile dysfunction compared with non-users (12 ± 6 ml $min^{?1}$ versus 34 ± 5 l $min^{?1}$, *P* = 0.003)	
2019	Sexual function	Human (*n* = 3,395)	Systematic review	Self-reported cannabis ***use***	The odds of erectile dysfunction in cannabis users were significantly increased compared with non-users (OR 3.83, 95%	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
					CI 1.30?11.28; *P* = 0.02)	
2004	Sexual function	Human (*n* = 3,004)	Cross-sectional study	Self-reported cannabis ***use*** disorders	Cannabis ***use*** was associated with inhibited orgasm and painful sex	
2010	Sexual function	Human (*n* = 8,650)	Cross-sectional study	Self-reported cannabis ***use***	Daily cannabis ***use*** compared with no ***use*** was associated with increased odds for ?2 sexual partners in the prior year. In men, daily cannabis ***use*** compared with no ***use*** was associated with increased inability to reach orgasm (OR 3.94, 95% CI 1.71?9.07; *P* < 0.01), premature orgasm (OR 2.68, 95% CI 1.41?5.08; *P* < 0.01) and reaching orgasm too slowly (OR 2.05, 95% CI 1.02?4.12; *P* = 0.04)	
2019	Sexual function	Human (*n* = 216)	Cross-sectional study	Online questionnaire querying aspects of sexual experience	52.3% of respondents reported ***using*** cannabis to alter sexual experience, with 39% reporting improvement, 16% reporting mixed results and 5% reporting a worse experience. Many participants reported improved relaxation, increased touch sensitivity and intensity of feelings	
2023	Sexual function	Human (*n* = 811 total, 276 men)	Observational study	Self-reported cannabis ***use***	Cannabis ***use*** was perceived to increase sexual function and satisfaction, particularly increased desire and orgasm intensity. When ***using*** cannabis, 93.4% reported an increased ability to achieve an erection, 92.4% noted an increase in maintaining an erection and 70% reported a slightly or significantly increased orgasm intensity	
2020	Sexual function	Human (*n* = 325)	Cross-sectional study	Self-reported	Association between increased frequency of	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
				cannabis ***use***	cannabis ***use*** and increased ***male*** sexual function was noted	
2017	Sexual function	Human (*n* = 22,943)	Cross-sectional study	Self-reported cannabis ***use***	Cannabis users had significantly higher sexual frequency than never users	
2021	Sexual function	Human (*n* = 7,809)	Cross-sectional study	Self-reported cannabis ***use***	Cannabis ***use*** was associated with positive ADAM scores (52% versus 46%, *P* < 0.001) and increased odds of a positive ADAM score (OR 1.29, 95% CI 1.12?1.48). Cannabis users reported higher sexual frequency (8.8 ± 5.1 events/month versus 7.8 ± 4.9, *P* < 0.05)	
1994	Sexual function	Rat	Experimental study	Single oral dose of THC	Exposure to THC decreased the number of subjects exhibiting copulatory behaviour and increased periods to mounting and intromission	
2003	Sexual function	Rat	Experimental study	Oral THC over a 30-day period	Subjects exhibited decreased mounting behaviour, as well as decreased sperm count and rates of impregnation	
2018	Sexual function	Human (*n* = 22,943 men)	Observational study	Self-reported cannabis ***use***	Frequent weekly and daily cannabis ***use*** among ***male*** partners was positively associated with intercourse frequency (IRR 1.22, 95% CI 1.06?1.04, *P* = 0.006 and IRR 1.36, 95% CI 1.21?1.53, *P* < 0.001, respectively)	
2018	Sexual function	Human (*n* = 758)	Cross-sectional study	Self-reported cannabis ***use***	16.5% of men reported ***using*** cannabis while attempting to conceive. The ratio of time to pregnancy for non-users versus daily users in men was 1.08 (95% CI 0.79?1.47), showing no significant effect of cannabis ***use***	
1992	Sexual function	Mouse	Experimental study	10 mg/kg of THC over a 5-week	1/10 ***male*** mice in the THC group failed to mate	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
				period	with the females introduced. One mouse failed to sire ***offspring***	
1982	Sexual function	Mouse	Experimental study	Oral administration of cannabinoids	***Males*** exposed to cannabidiol impregnated fewer females than those not (60% versus 80% in control animals)	
2018	Sexual function	Mouse	Experimental study	Oral administration of cannabinoids was performed	***Males*** exposed to cannabinoids exhibited delayed time to first mount and intromission, reduced number of mounts and ejaculation. In the high-dose group, a 30% reduction in fertility was observed and a 23% reduction in the number of litters was observed	
1974	Sexual function	Human (*n* = 345)	Cross-sectional study	Self-reported cannabis ***use***	Variable effects of cannabis on sexual activity were observed, 39.1% of ***males*** noted an increase in desire and 59.8% reported an increase in sexual enjoyment. Desire and enjoyment was most increased after smoking one joint compared with smoking two or more joints	
Offspring outcomes						
1992	Short-term ***offspring outcomes***	Mouse (*n* = 80 total, 10 mice per group)	Experimental study	10 mg/kg of THC over a 5-week period	THC administration was not associated with pre-implantation loss or fetal mortality	
1982	Short-term ***offspring outcomes***	Mouse (*n* = 72 total, 18 oil, 18 THC, 18 cannabidiol and 18 cannabinol)	Experimental study	Oral administration of cannabinoids (oil, cannabis extract 25 mg/kg, THC 50 mg/kg and cannabinol 50 mg/kg)	THC exposure in ***males*** resulted in significantly more prenatal deaths than in the control group (37% versus 19%, $P < 0.05$). Similarly, cannabidiol exposure also resulted in significantly more prenatal and postnatal deaths than in controls (44% and 26% versus 19% and 5%, $P < 0.05$).THC and	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
					cannabidiol exposure resulted in increased rates of fetal loss	
2006	Short-term ***offspring outcomes***	Human (*n* = 221)	Observational study	Self-reported cannabis ***use***	Lifetime paternal cannabis ***use*** of 11?90 times was associated with a 15% decrease in infant birthweight (?0.16, 95% CI ?0.31 to ?0.01, *P* = 0.03) and >90 ***uses*** of cannabis was associated with a 23% decrease in infant birthweight (?0.27, 95% CI ?0.46 to ?0.07, *P* = 0.01). Paternal cannabis smoking in the past 15 years was associated with a 16% decrease in infant birthweight (?0.17, ?0.33 to ?0.02, *P* = 0.03)	
2009	Short-term ***offspring outcomes***	Human (*n* = 4,475)	Observational study	Self-reported cannabis ***use***	Paternal ***use*** of cannabis during pregnancy was not associated with fetal growth rates	
2021	Short-term ***offspring outcomes***	Human (*n* = 1,535)	Observational study	Self-reported cannabis ***use***	Paternal cannabis ***use*** ?1 time/week was linked to an increased risk of spontaneous abortion (HR 2.0, 95% CI 1.2?3.1) compared with no ***use***	
2001	Short-term ***offspring outcomes***	Human (*n* = 578)	Case?control study	Self-reported cannabis ***use***	Paternal cannabis ***use*** during conception and postnatally was associated with sudden infant death syndrome (OR 2.2, 95% CI 1.2?4.2; *P* = 0.01 and OR 2.8, 95% CI 1.1?7.3; *P* = 0.04, respectively)	
2019	Short-term and long-term ***offspring outcomes***	Rats (*n* = 17 total, 9 controls and 8 THC-exposed)	Experimental study	Sires were exposed to 2 mg/kg/day of THC for 12 days	THC exposure was associated with long-term impairment in attentional performance in ***offspring***. No significant differences in litter size, birthweight, survival or growth were found	
2020	Short-term and long-term ***offspring outcomes***	Rats (*n* = 32 total, 12 control, 10 at 2 mg/kg/day	Experimental study	THC (0, 2 or 4 mg/kg/day) administered subcutaneo	***Offspring*** of ***male*** rats exposed to THC showed significant locomotor hyperactivity (F(2,29) = 3.37, *P* < 0.05). These	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
		and 10 at 4 mg/kg/day		usly for 28 days	***offspring*** also showed decreased rates of interest in novel object recognition and radial-arm maze tasks	
2019	Short-term and long-term ***offspring outcomes***	Human (*n* = 5,903)	Observational study	Self-reported cannabis ***use***	Paternal cannabis ***use*** was associated with behavioural issues when ***using*** teacher-reported evaluations of children	
2022	Short-term and long-term ***offspring outcomes***	Rat (*n* = 36 total, three groups with *n* = 12 per group)	Experimental study	THC 4 mg/kg/day injected intraperitoneally	Significant methylation changes in F0 sperm were also seen in F1 sperm, including in the genes *Pxylp1* and *Mtss1l*. ***Offspring*** of rats exposed to cannabis had significantly increased rates of cardiomegaly (one-factor ANOVA (*P* = 0.0039)). Post hoc tests showed significantly increased heart weight relative to controls for both the early exposure ***offspring*** (*P* = 0.0013) and the late exposure ***offspring*** (*P* = 0.0099)	
1998	Short-term and long-term ***offspring outcomes***	Human (*n* = 7,868)	Case?control study	Self-reported cannabis ***use***	The attributable fraction for paternal cannabis usage in the transposition of the great arteries with an intact ventricular septum was found to be 7.8%	
1997	Short-term and long-term ***offspring outcomes***	Human (*n* = 4,190)	Case?control study	Self-reported cannabis ***use***	Paternal cannabis usage was significantly associated with ventricular septal defects (OR 1.36, 95% CI 1.05?1.76)	
2002	Congenital anomalies	Human (*n* = 3,627)	Case?control study	Self-reported cannabis ***use***	Paternal cannabis ***use*** was associated with a single ventricle	
1993	Congenital anomalies	Human (*n* = 644)	Case?control study	Self-reported cannabis ***use***	Paternal preconception cannabis ***use*** was associated with an increased risk of rhabdomyosarcoma (RR 2.0, 95% CI 1.3?3.3)	
2020	Short-term and long-	Human (*n* = 24)Rat (*n* =	Case?control, experiment	Self-reported	Cannabis ***use*** is associated with	

Year	Primary measures	Species	Study design	Conditions	Results	Ref.
	term ***offspring outcomes***	15)	al	cannabis ***use*** (human)Subcutaneously injected 4 mg/kg THC (rat)	substantial DNA methylation alterations, including in *DLGAP2*, a gene strongly implicated in autism.***Offspring*** of ***male*** rats exposed to THC still showed differences in DNA methylation for *Dlgap2* within the nucleus accumbens	
2018	Short-term and long-term ***offspring outcomes***	Human (*n* = 136)	Observational study	Self-reported cannabis ***use***	DNA methylation status in seven sites of *ANNK1*, *CNR1*, *DRD2* and *NCAM1* genes was examined. Increased rates of methylation in cannabis users were observed in two of the regions assessed: exon 8 of *DRD2* (*P* = 0.034) and the CpG-rich region of *NCAM1* (*P* = 0.0004), both genes involved in the dopaminergic pathway that can be associated with ***substance use***. Other regions assessed showed no statistically significant differences between cannabis users and non-users	

ADAM, androgen deficiency in the ageing ***male***; FSH, follicle-stimulating hormone; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, risk ratio; SMD, standardized mean difference; THC, tetrahydrocannabinol.

Box 3 The endocannabinoid system

The endocannabinoid system comprises the main endocannabinoid receptors CB1R (primarily in the central nervous system) and CB2R (primarily in the peripheral nervous system, especially immune cells), which are present throughout the ***male*** ***reproductive*** tract and in sperm.

Male ***reproductive*** hormones

Mixed results have been reported in preclinical and human studies regarding the effect of cannabis ***use*** on the HPG axis and ***male*** ***reproductive*** hormones. Findings from both preclinical and human studies show decreased, increased, or no effect on testosterone levels. Results of a systematic review of 91 studies (30 clinical studies and 61 animal or in vitro studies) showed that the effect of cannabis ***use*** on serum testosterone levels is variable. In 2,074 men undergoing evaluation for infertility, men with primary infertility who reported previous cannabis ***use*** had significantly reduced testosterone levels (median (interquartile range) 4.2 ng/ml (3.3–5.6 ng/ml)) compared with non-users (4.6 ng/ml (3.5–5.8 ng/ml)) (P = 0.03). A significant decrease in plasma testosterone levels was also observed in men who chronically ***used*** cannabis at least 4 days a week for a minimum of 6 months (416 ± 34 ng per 100 ml) versus those who had never ***used*** it (742 ± 29 ng per 100 ml) (P < 0.001). This observation is similar to those in a rhesus macaque model of chronic THC edible consumption (2.5 mg/7 kg/day — equivalent to a heavy

medical cannabis dose) that also showed partial reversal of testosterone levels with cessation of THC. By contrast, results of a large population study of 1,215 healthy men aged 18–26 years showed 7% higher serum testosterone levels in men who smoked cannabis regularly more than once per week than men who had never ***used*** cannabis. Similarly, in a study in which 2011–2016 National ***Health*** and Nutrition Examination Survey data from men in the USA were ***used***, THC ***use*** was associated with a small increase in serum testosterone. However, this observed rise in testosterone was not associated with the frequency of THC ***use***, suggesting that a dose-dependent response did not occur. Interestingly, no difference in serum testosterone between men who had previously ***used*** cannabis and those who had never ***used*** it was shown in other studies,, including a previous study ***using*** 2011–2012 National ***Health*** and Nutrition Examination Survey data. These findings suggest that cessation of cannabis ***use*** can reverse its effects on serum testosterone. Differing reported results could be a result of serum testosterone levels having diurnal fluctuation, peaking in the morning and decreasing throughout the day. Thus, the time of day when blood collection was performed can affect the results.

The reported effect of cannabis ***use*** on FSH levels has also been conflicting. Men who smoked >10 cannabis cigarettes a week had significantly lower FSH levels (7 ± 1 mIU per ml) than those only smoking 5–9 cannabis cigarettes weekly (12 ± 1 mIU per ml) ($P < 0.01$). Results of a systematic review showed a statistically significant decrease in FSH in men who ***used*** cannabis, but the standardized mean difference of 0.142 (95% CI −0.243 to 0.0425, $P = 0.005$) was not felt to be clinically significant. However, because of the limited and heterogenous studies included in the systematic review, an effect of cannabis on testicular function cannot be excluded. By contrast, chronic daily exposure to THC edibles in six ***male*** rhesus macaques resulted in a significant increase in FSH ($P = 0.01$) during THC consumption (0.17 ± 0.06 ng/ml to 0.33 ± 0.18 ng/ml) that almost returned to baseline (0.20 ± 0.10 ng/ml) after 4 months of THC cessation. These findings support the benefits of abstaining from THC ***use*** for ***male*** fertility.

Significantly reduced LH levels ($P < 0.05$) in four men following acute THC exposure from smoking cannabis have been reported. However, a dose-dependent effect of THC on serum LH levels is not apparent, possibly secondary to the small sample size studied. Furthermore, no significant difference in LH levels was observed in 20 men smoking 5–9 versus ≥10 cannabis cigarettes weekly, suggesting that no frequency-dependent effect was noted. Interestingly, significantly increased LH levels following chronic THC edible consumption (0.69 ± 0.18 ng/ml to 1.10 ± 0.35 ng/ml, $P < 0.001$) were observed in a rhesus macaque model that did not return to baseline after discontinuation of THC (0.98 ± 0.60 ng/ml). These findings suggest that cessation of THC might not reverse the effect on LH levels.

Overall, cannabis ***use*** seems to have variable effects on testosterone, FSH and LH levels and most consistently demonstrates an ***influence*** on testosterone levels. This observation highlights the potential association between cannabis ***use*** and ***male*** fertility. The variability observed is partly caused by the substantial increase in the potency and available formulations of cannabis over the past two decades; thus, comparing studies from different time periods is challenging. The National Institute on Drug Abuse, starting 10 May 2021, has also established 5 mg as the standard research unit for cannabis studies because this dose can produce a ‘high’ in both experienced and occasional users, and in some states it is ***used*** as the standard serving size in edible products that contain THC. However, it will be important to also develop a way of comparing different modes of cannabis delivery given that the drug is variable depending on the mode of delivery.

Semen parameters

Human sperm have been shown to express major receptors involved in the ECS, namely cannabinoid type 1 (ref.) and type 2 receptors (CB1R, CB2R) and transient receptor potential vanilloid 1 (TRPV1). Results of in vitro studies have shown the decreased motility and fertilizing ability of human sperm via CB1R activation and decreased motility via CB2R activation. Associations have been observed between cannabis ***use*** and abnormal sperm morphology,–, decreased volume, decreased sperm count and concentration,,,, and decreased motility. However, these findings were not consistently reported across studies and a systematic review did not demonstrate a significant relationship between cannabis ***use*** and abnormal semen parameters. The conflicting results are probably in part because of the high variability in semen analysis results within the same human subject.

Results of existing animal, and human studies, have suggested that cannabis ***use*** alters sperm morphology, but the literature is variable. Examination of lifestyle factors associated with poor sperm morphology in men recruited from fertility clinics across the UK showed that men aged ≤30 years who ***used*** cannabis 3 months before sample collection had an increased likelihood of having abnormal (<4% normal) sperm morphology (OR 1.94, 95% CI 1.05–3.60). By contrast, no significant change in sperm morphology from rhesus macaques was observed following daily THC (2.5 mg/7 kg/day) edible consumption for 7 months, but a dose-dependent increase in sperm DNA fragmentation, a marker of sperm DNA integrity important for fertilization and for the development of healthy ***offspring***, that partially reversed following 4 months of THC cessation, was observed. In a previous mouse study in which mice were exposed to high doses of THC (50 mg/kg) five times weekly for 6 weeks, no increase in lethal mutations or heritable translocations in ***offspring*** were found. This observation suggests that THC is not an efficient inducer of chromosome breakage in germ cells of ***male*** mice.

A strong association has been observed between cannabis exposure and decreased sperm count and concentration. An association between cannabis ***use*** and decreased sperm counts,,, and reduced sperm counts in individuals who ***used*** THC weekly compared with those who have never ***used*** THC, has been observed in several human studies,. In 16 healthy, chronic cannabis smokers with daily or near daily ***use*** over months to years, 4 weeks of high-dose cannabis ***use*** (8–20 cigarettes/day) resulted in a significant decrease in sperm concentration during the fifth (65% of baseline, $P < 0.001$) and sixth (70% of baseline, $P < 0.01$) weeks after exposure. The underlying aetiology is not well defined, but the observed cannabis-induced reduction in sperm count and concentration has been linked to arrested spermatogenesis. In a previous study, high doses of cannabis (12.5 mg of THC per kilogram of body weight) in canines over 30 days resulted in the total arrest of spermatogenesis. This observation suggests that cannabis at high doses daily for only a month can induce infertility.

In addition to altering sperm count and morphology, cannabis ***use*** has been reported to ***influence*** sperm motility. Following 4 weeks of exposure to high-dose cannabis (8–20 cigarettes with 2% THC per day), 16 healthy men, who smoked cannabis chronically, had a reduction in sperm motility that improved following cessation of chronic smoking, suggesting the potential for reversibility. Chronic cannabis ***use*** is typically defined as daily ***use*** for months to years. This effect was similarly observed ***using*** collected sperm incubated with THC at concentrations equivalent to therapeutic (0.032 µM) and recreational (0.32 µM and 4.8 µM) plasma levels, and was thought to be secondary to decreased mitochondrial transmembrane potential, mediated by CB1R activation. Results of previous studies have demonstrated CB1R on human sperm, showing that THC is a strong exogenous agonist for the CB1R, and observed that a reduction in mitochondrial function, or altered membrane potential, is associated with decreased sperm motility,,.

Overall, the evidence suggests that cannabis exposure can ***influence*** semen parameters, especially sperm count and concentration. However, the reported findings are inconsistent, potentially because in most studies only a single ejaculate was analysed, which might not reflect the degree of variation observed between multiple semen analyses in a single participant,. Owing to variation between semen collections, a second semen analysis is recommended by the WHO Laboratory Manual for the examination and processing of human semen to improve diagnostic reliability in the evaluation of ***male*** fertility,. Moreover, THC exposure has been variable in many studies, which will confound the true effect of THC on semen parameters. Thus, caution should be taken when comparing studies ***using*** single versus multiple ejaculates to assess semen parameters, and future research should evaluate semen characteristics over multiple collections.

Testicular volume

Preclinical studies in dogs and rhesus macaques have demonstrated an association between cannabis ***use*** and decreased testicular volume,, in addition to reduced prostate and seminal vesical weight,–. Variable effects of cannabis exposure on testicular volume in mice and rats have also been reported,, including histological changes such as degradation of seminiferous tubules, which can result in impaired sperm production, with only partial recovery after cannabis cessation,. The underlying mechanism for these changes in testicular volume is unknown, but has been previously linked to oxidative stress,. Testicular tissue and the ***male*** ***reproductive*** system are sensitive to oxidative stress, a major factor in the aetiology of ***male*** infertility,.

In rhesus macaques, chronic daily exposure to THC significantly lowered testicular volume by 11.8 cm3 (95% CI 8.3–15.4, P < 0.001) for every mg/7 kg/day increase in THC dosing. This observation was partly caused by decreased seminiferous tubule diameter and germ cell layers on histology that was partially reversed with cessation of THC. As the seminiferous tubules and germ cells are the site of spermatogenesis, this reduced diameter can affect sperm production, highlighting the potential benefit of stopping THC ***use*** to reverse these effects. In men aged 18–60 years, associations between regular cannabis ***use*** and decreased testicular volume have not been conclusively shown. However, the study was limited by a cross-sectional study design and lacked a matched control group of fertile 'healthy' men.

Overall, animal models have consistently demonstrated that cannabis ***use*** is linked to testicular atrophy, in part owing to decreased seminiferous tubule diameter and germ cell layers. These effects seem to be partly reversible with abstinence from THC, but studies with increased intervals of THC cessation are needed to determine whether full recovery is possible. Thus, ***health***-care providers should discuss the potential benefit of cessation for at least several months before conception in order to optimize fertility with their patients who are ***using*** cannabis and interested in conceiving.

Erectile dysfunction and sexual function

The ECS has been shown to have a role in erectile signalling and capacity and erectile dysfunction,,. Results of a study in rats demonstrated that an erection can be induced with administration of rimonabant, a cannabinoid receptor antagonist, secondary to activation of neuronal nitric oxide synthase in paraventricular oxytocinergic neurons mediating penile erection. Results of other studies ***using*** veno-occlusive plesmography to evaluate endothelium-dependent dilation of arteries in men with erectile dysfunction have suggested that THC might induce erectile dysfunction secondary to early endothelial damage. Veno-occlusive studies revealed impaired endothelium-dependent vasodilatation in men with erectile dysfunction who ***used*** cannabis regularly (at least weekly) compared with non-users (12 ± 6 ml min−1 versus 34 ± 5 ml min−1, P = 0.003). These findings indicate that men who ***use*** cannabis weekly or more frequently have impaired epithelium-dependent vasodilation compared with non-users, which can be modifiable with lifestyle changes, including discontinuing or reducing cannabis ***use***. Results of a systematic review and meta-analysis examining in which the prevalence and risk of erectile dysfunction in cannabis users versus non-users, including five case–control studies, showed that the odds ratio of erectile dysfunction in cannabis users was nearly four times that of non-users (OR 3.83, 95% CI 1.30–11.28, P = 0.02). The study had high heterogeneity (I2 = 90%), but the results suggest that men with erectile dysfunction would benefit from discontinuing cannabis ***use***. Similarly, results of other large survey studies in which the association between cannabis ***use*** and different sexual ***health outcomes*** was examined have also found associations between cannabis ***use*** and orgasmic dysfunction,. In one study, a telephone survey of 4,350 Australian men aged 16–64 years was conducted and showed that daily cannabis ***use*** versus no ***use*** was associated with increased inability to reach orgasm (OR 3.94, 95% CI 1.71–9.07, P < 0.01), reaching orgasm too quickly (OR 2.68, 95% CI 1.02–4.12, P = 0.04), and too slowly (OR 2.05, 95% CI 1.02–4.12, P = 0.04). The results of this study support that frequent cannabis ***use*** can ***influence*** the ability to orgasm as desired.

The effects of cannabis on human sexual function are complex and not conclusive, but some evidence suggests a role of the ECS in sexual function. Cannabis extracts have been commonly ***used*** to enhance sexual experience,. In a study including 276 ***male*** cannabis users aged 18–85 years, 93.4% reported no change or an increased ability to achieve an erection with cannabis ***use***, 92.4% noted no change or an increase in maintaining an erection when ***using*** cannabis, and 70% found that cannabis ***use*** slightly or significantly increased orgasm intensity. Results of a survey of 325 men visiting a cannabis dispensary showed that users had higher erectile function scores and satisfaction with intercourse than non-users. Those who ***used*** at least 3–5 times a week had a significantly higher International Index of Erectile Function (IIEF) score and intercourse satisfaction than those who ***used*** no more than twice a week (65.3 ± 68.02 versus 60.52 ± 13.84, P = 0.001 and 12.42 ± 2.26 versus 11.31 ± 3.37, P = 0.006, respectively). Increased rates of coital frequency have been associated with cannabis ***use*** compared with never ***use*** in a large cohort of 22,943 men (IRR 1.08, 95% CI 1.05–1.11, P < 0.001). Cannabis ***use*** in 993 men compared with 6,816 non-users has been linked to increased sexual frequency (8.8 events/month versus 7.8 events/month, P < 0.05), that is, not clinically significant. Conversely, in rats, both acute and chronic cannabis exposure have shown

to decrease libido and copulatory behaviour,. The conflicting results observed in humans compared with rats might be because of the much higher THC exposure in rats (5–10 g/kg),.

Some evidence is suggestive of a link between frequent cannabis ***use*** and difficulty achieving orgasm. In a survey of 8,656 men daily cannabis users were more likely to have orgasmic disorders, such as reaching orgasm too quickly (OR 2.68, 95% CI 1.41–5.08, P < 0.01), too slowly (OR 2.05, 95% CI 1.02–4.12, P = 0.04) or inability to orgasm (OR 3.94, 95% CI 1.71–9.07, P < 0.01), than non-users. Chronic cannabis ***use*** can result in increased orgasmic disorders, overall cannabis ***use*** has been linked to improved sexual experience secondary to increased erectile function and increased coital frequency.

In large human cohort studies, no relation between ***male*** cannabis ***use*** and fecundity has been found,. A prior study including 758 men participating in the National Survey of Family Growth across 121 geographic areas in the USA, time ratio to pregnancy of never users versus daily cannabis users was 1.08 (95% CI 0.79–1.47, P = 0.65). Similarly, in another study including 1,125 men at least 21 years old from the Pregnancy Study Online, a prospective cohort of North American couples, little association was found between ***male*** cannabis ***use*** and fecundability. The fecundability ratio, a ratio of fecundability in each exposure category compared with the reference category, for ***male*** cannabis ***use*** <1 and ≥1 time a week versus non-***use*** is 0.87 (95% CI 0.66–1.15) and 1.24 (95% CI 0.90–1.70) respectively. Similarly, in studies in mice, no difference in the number of fetuses sired per pregnancy in controls (12.0 ± 0.64) compared with mice administered 10 mg/kg THC orally every 2 days for 5 weeks (12.7 ± 1.41). These data indicate that cannabis ***use*** does not seem to affect fecundity, but these the effects of regular, heavy cannabis ***use*** for months to over a year were not examined.

The existing evidence suggests that cannabis has a dose-dependent effect on erectile dysfunction and sexual function. ***Use*** of high doses of cannabis in humans is linked to worsened erectile dysfunction and difficulty achieving orgasm, whereas low doses of cannabis are associated with increased sexual desire, frequency and rates of masturbation. Given the complex effects of cannabis ***use*** on erectile dysfunction and sexual function, patients must be appropriately counselled to make evidence-informed lifestyle decisions.

Summary

In general, cannabis ***use***, especially heavy and chronic ***use***, negatively affects ***male reproductive health***, but does not seem to ***influence*** fecundity in human cohorts (Table). Chronic or regular cannabis ***use*** is often defined as daily ***use*** for months to years, and heavy ***use*** is typically associated with daily or more frequent ***use***. Specifically, cannabis ***use*** has been linked to altered ***male reproductive*** hormones (such as testosterone, FSH and LH), semen parameters, testicular volume and sexual function (for example, libido and erectile dysfunction). For most individuals, cannabis will probably not affect their ability to conceive, but in those with subfertility or infertility, it could be a contributing factor and also exacerbate existing infertility issues, compounding their difficulty to conceive. The evidence also suggests that the effects seem to be dose dependent and potentially reversible,. This observation is concerning given that the potency of cannabis products has risen dramatically over the last few decades. Thus, ***health***-care providers should counsel men of ***reproductive*** age and those interested in conceiving towards cessation to avoid all potential risks, and to encourage reduced cannabis ***use*** in patients who are unable to abstain.

Opioids

Over the previous two decades, the ***use*** of opioids has risen dramatically across the USA and Canada, and abuse of fentanyl and synthetic, illicit opioids, has increased,. North America remains the centre of the opioid epidemic, but it has also become a public ***health*** issue for other countries, including the UK and Australia,. In 2015, 37% of American adults had been prescribed at least one opioid pain reliever, a rate that had tripled since the late 1990s. Overdoses, abuse and mortality has increased among many populations, including men of ***reproductive*** age. Accompanying these concerns, increasing evidence suggests that opioid ***use*** can affect ***male reproductive health*** (Table). Endogenous opioid peptides are present in the ***male reproductive*** tract and are involved in regulating ***reproductive*** physiology. Opioids, whether produced endogenously or exogenously, bind to opioid receptors in the hypothalamus, pituitary and testis and ***influence*** their function. Data are limited on whether a dose-dependent effect occurs, especially for the short-term ***use*** of opioids. Chronic, long-acting opioid ***use*** has been linked with an

increased risk of androgen suppression compared with similarly dosed short-acting opioids,. A previous retrospective case–control analysis including 357 men (94 chronic opioid users with at least 90 days of opioid ***use*** and 263 non-users) showed a significant, positive linear association between chronic opioid dose and the odds of developing hypogonadism in ***males*** (OR 1.44, 95% CI 1.16–1.78, P < 0.001). This observation suggests an increased risk of opioid-induced androgen deficiency and a negative effect on patient quality of life with chronic opioid ***use***. Thus, an increased index of suspicion can result in earlier recognition of symptoms in patients with chronic opioid ***use***.

Effect of opioids on ***reproductive*** ***health*** and ***offspring*** ***outcomes***

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
Reproductive health						
2013	***Reproductive*** hormones	Humans (*n* = 374)	Observational study	Self-reported opioid ***use***	Opioid ***use*** was associated with decreased testosterone levels and sperm parameters, including motility, density and morphology, but no change in FSH and LH. Opioid ***use*** was linked to increased sperm DNA fragmentation	
2018	Semen parameters and ***reproductive*** hormones	Humans (*n* = 60)	Case?control study	Self-reported opioid ***use***	Tramadol ***use*** was associated with elevated FSH, LH and prolactin, decreased androgen levels, low-quality semen profiles, decreased sperm viability and progressive motility, and increased incidences	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					of leukocytospermia and abnormal sperm morphology	
2016	Semen parameters and ***reproductive*** hormones	Mouse (*n* = 48, 8 groups with 6 animals in each group)	Experimental study	Morphine was intraperitoneally administered at 10 mg/kg daily on day 1 and then increased 2 mg/kg per day on days 2?30	Morphine administration decreased testosterone, LH, FSH, testis weight and sperm parameters, such as count, viability, morphology and motility	
2017	Erectile dysfunction and sexual function	Human (*n* = 8,829)	Systematic review and meta-analysis	Self-reported opioid ***use***	Opioid ***use*** was associated with an increased risk of erectile dysfunction	
2018	Sexual function	Human (*n* = 514)	Cross-sectional study	Self-reported opioid ***use***	Chronic opioid ***use*** diminished libido and impaired sexual performance	
Offspring outcomes						
2021	Long-term ***offspring outcomes***	Human (*n* = 8,410)	Population-based study	Self-reported opioid ***use***	Regular preconception paternal opioid ***use*** was independently associated with increased odds of overweight or obesity in ***offspring*** (aOR 1.76, 95% CI	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					1.15?2.71)	
2018	Short-term and long-term ***offspring outcomes***	Rat (*n* = 36, 19 morphine exposed and 17 saline exposed)	Experimental study	Escalating doses of morphine (2.5 mg/kg/day increased by 2.5 mg/kg per day to 25 mg/kg/day) for 10 days during postnatal days 31?40. Mating occurred 20 days after the last morphine injection	Transgenerational effect of paternal morphine exposure on adolescent ***offspring*** pain perception and the antinociceptive effect of morphine	
2021	Short-term and long-term ***offspring outcomes***	Rat (for F0, saline-treated *n* = 18, morphine treated *n* = 16; for F1, *n* = 14 and *n* = 11 for the saline-sired and morphine-sired group, respectively)	Experimental study	Escalating doses of morphine (2.5?25 mg/kg, subcutaneous injection) for 10 days	Paternal opiate exposure before conception impaired inhibitory control in ***male*** progeny; ***offspring*** exhibited delayed learning and impulsive behaviour	
2020	Short-term and long-term ***offspring outcomes***	Rat (for sires, *n* = 40 control and *n* = 39 morphine; for dams, *n* = 55 control and *n* = 58 morphine; ***offspring used*** in experiments varied between experimental approaches but was *n* = 8?14 animals per group)	Experimental study	Self-administered morphine	Paternal morphine exposure selectively disrupted novel object recognition in female but not ***male*** progeny, and did not change anxiety-like behaviour or stress-induced hypothalamic?pituitary?	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					adrenal axis activation in both ***male*** and female ***offspring***	
1991	Short-term and long-term ***offspring outcomes***	Rat (*n* = 70 total, 10 animals for each group ? weeks 1?6 ? and 20 animals for week 9	Experimental study	Implants with morphine (75 mg) or placebo pellets initially one on day 1, then two pellets at 4, 7 and 10 days. Pellets remain present for the following intervals: 1, 2, 3, 4, 6 and 9 weeks	Data suggest that paternal exposure to opiates ***influences offspring*** sexual maturation and can also have long-term, selective and gender-specific effects on endocrine function in their ***male offspring***	
2022	Short-term ***offspring outcomes***	Rat (*n* = 20 Sprague?Dawley, 10 ***males*** and 10 females; and *n* = 20 Long?Evans, 10 ***males*** and 10 females were ***used***)For multigenerational studies 18 Sprague?Dawley rats (9 ***males*** and 9 females) were ***used*** to produce a total of 112 F1 pups (***males***: 28 saline sired, 32 morphine sired; females: 22 saline sired, 30 morphine sired). Animals were randomly assigned to groups, with two to four rats from a single litter ***used*** in the studies)	Experimental study	Self-administered 3 mg/kg morphine sulfate in sterile 0.9% saline	Paternal preconception exposure to opioids increased the sensitivity of ***male offspring*** to the pain-relieving effects of morphine that correlated with gene expression changes within the regulator of G protein signalling family proteins	
2017	Short-term and long-term ***offspring outcomes***	Rat (*n* = 24 total, 12 morphine exposed and 12 saline exposed)	Experimental study	Morphine (10 mg/kg) or saline injected twice daily for 2 weeks	Paternal morphine exposure was associated with	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					significantly higher anxiety-like behaviour and enhanced voluntary consumption of morphine in morphine-derived compared with saline-derived ***male offspring*** ($P < 0.01$)	

aOR, adjusted odds ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Male reproductive hormones

In tandem with the drastic rise in opioid ***use***, the incidence of opioid-associated androgen deficiency has increased. Chronic opioid ***use*** results in suppression of the HPG axis through its central and peripheral effects, which results in secondary testosterone deficiency or opioid-associated androgen deficiency–. Opioids act directly on the hypothalamus by binding G protein coupled μ-opioid receptors and inhibiting the pulsatile release of GnRH, blocking the release of LH and FSH by the pituitary gland, and subsequently affecting testicular testosterone production. This syndrome is characterized by low levels of FSH and LH, leading to inadequate production of sex hormones, namely testosterone. A decrease in sex hormone levels, or interference in the pulsatory secretion of GnRH at the hypothalamic level, and the subsequent reduction in FSH and LH hormone secretion from the pituitary gland, are some known effects of opioids on the ***reproduction*** system. In men (n = 186, aged 20–50 years) ***using*** opioids, a negative effect of opioid ***use*** on testosterone levels was observed, but no change in serum FSH and LH levels was observed. Altered hormonal profiles were also noted in men (n = 30) abusing tramadol compared with age-matched non-users (n = 30), such as elevated FSH, LH and prolactin, and decreased androgen levels. These results suggest that opioid ***use*** can affect ***male reproductive*** hormones and negatively affect fertility, including time to conception.

Overall, opioid ***use*** is most consistently associated with decreased testosterone levels but has a more variable effect on other ***male reproductive*** hormones, such as FSH, LH and prolactin. The different types of opioid drugs and interindividual variability in hormone levels have probably contributed to the heterogeneity in the current data,. To overcome the limitations of the existing research, animal models with strong translational strength are needed to study the dose-dependent effect of chronic opioid ***use*** on ***male reproductive*** hormones and fertility potential.

Semen parameters

Opioids have been shown to increase free radical production, which can adversely affect spermatogenesis. In a case–control study men aged 20–40 years with morphine dependency (n = 30) had a significant decrease in both progressive (35.76% ± 15.95% versus 58.3% ± 10.93%, P = 0.038) and total sperm motility (46.13% ± 17.5% versus 71.36% ± 8.38%, P < 0.0001) compared with healthy men (n = 30)). In addition, morphine dependence was associated with decreased sperm chromatin condensation and increased rates of sperm apoptosis, although statistical significance was not observed. In a study investigating fertility and potential correlations with opioid abuse, opioid ***use*** correlated with decreased sperm parameters, including motility and morphology. Increased DNA fragmentation in patients ***using*** morphine was also observed. Similarly, in another study, long-term users of

tramadol had low-quality semen profiles, including low sperm viability, decreased progressive motility, increased incidence of leukocytospermia, and abnormal sperm morphology. Taken together, these findings suggest that regular opioid exposure adversely affects ***male*** fertility and follow-up studies are needed to determine if these effects are reversible with opioid abstinence.

Morphine has been shown to increase blood nitric oxide by regulating intracellular calcium and activating calcium/calmodulin-dependent nitric oxide synthase. A correlation between nitric oxide and sperm acrosome and tail defects in mice and humans has been observed, showing that nitric oxide reduces sperm motility by decreasing adenosine triphosphate (ATP) levels. Nitric oxide can also impair mitochondrial membranes in sperm, stimulating apoptosis. These observations suggest that morphine exposure can adversely affect sperm function and fertility through an inhibitory effect of nitric oxide on cellular respiration.

In general, opioid drug exposure, especially morphine dependency, is associated with an adverse effect on semen characteristics, including sperm count, motility, morphology and viability. The mechanism is not clear; however, reduced testosterone levels from opioid ***use*** have a role. For individuals interested in conceiving, discussing the potential ***influence*** that opioids have on semen parameters is important and abstaining or reducing the quantity of opioids ***used*** should be considered.

Testicular volume

Data regarding the effect of opioid exposure on testicular volume are lacking. Results of a case–control study of 100 men with opioid dependence and 100 healthy men showed that opioid ***use*** was associated with significantly reduced testicular volumes (11.2 ± 2.2 and 25.1 ± 2.7 cm3, $P < 0.001$). The underlying aetiology for this effect is unknown, but might be partly caused by opioid-induced alterations in ***male reproductive*** hormones, including decreased testosterone and altered LH and FSH levels. These alterations can result in decreased testicular growth because LH and FSH both have a crucial role in maintaining spermatogenesis,. The scant existing literature is probably because individuals with opioid dependence are less likely to be undergoing a fertility work-up, and testicular volume evaluation is not usually a part of the initial clinical assessment. Future research studies should include assessment of testicular volume when examining the effect of opioid ***use*** on ***male*** fertility and also assess the underlying mechanisms for the observed decrease in testicular size.

Erectile dysfunction and sexual function

Current studies consistently report a high prevalence of erectile dysfunction among ***males*** with opioid dependence,, partly caused by the inhibition of the HPG axis and decrease in testosterone levels, Erectile dysfunction is multifactorial and other potential contributing factors include depression, atherosclerosis, obesity, diabetes and trauma. Results of a systematic review and meta-analysis of 8,829 men from 10 studies showed that opioid ***use*** was associated with an increased risk of erectile dysfunction (risk ratio (RR) 1.96, 95% CI 1.66–2.32, $P < 0.001$). In another study including 63 men aged 30–50 years with an average of 11.9 ± 9.4 years of opioid ***use***, 34% reported erectile dysfunction. Common sequelae of chronic opioid ***use*** also include diminished libido and impaired sexual performance; thus, ***health***-care providers need to discuss with their patients when prescribing opioids.

Summary

In general, studies examining the effect of opioid ***use*** on ***male reproductive health*** are limited compared with other types of ***substance use*** and more studies are needed to guide evidence-based recommendations. The existing data suggest that opioid ***use*** is associated with a negative effect on testosterone, semen parameters, testicular volume and sexual function, including increased erectile dysfunction and decreased libido (Table). Based on the current safety data, ***health***-care providers should discuss with patients interested in conceiving the potential risks of opioid ***use*** to ***male*** fertility, including increased difficulty getting pregnant, recommend discontinuation of opioids before conception, and consider safer alternatives.

Nicotine

In 2019, the global number of current tobacco users was estimated to be one billion, making tobacco the second most commonly ***used*** psychoactive ***substance*** worldwide. Over the past decade, diversified commercial nicotine delivery systems or nicotine products (such as e-liquids, smokeless tobacco pouches and nicotine replacement therapies) have become increasingly popular. However, most of the world's nicotine exposure is still from combustible tobacco smoking, making nicotine and tobacco smoke a prevalent public ***health*** concern. Exposure to nicotine products has been shown to affect the ***male reproductive*** system directly by altering the testis and sperm, and indirectly by altering the endocrine system, (Table).

Effect of nicotine on ***reproductive health*** and ***offspring outcomes***

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
Reproductive health						
2012	***Male reproductive*** hormones	Human (*n* = 304)	Observational study	Self-reported smoking	Cigarette smoking was associated with increased morphological defects ($P < 0.0001$), reduced motility ($P < 0.001$), decreased sperm DNA integrity ($P = 0.006$), endocrine hormonal status, and the number of CAG repeats in the androgen receptor gene	
2016	***Male reproductive*** hormones	Human (*n* = 140)	Observational study	Self-reported smoking	Mild, moderate and heavy smokers displayed significant decreases in semen volume (2.7 ± 0.7, 2.2 ± 0.04, 2.6 ± 0.3 versus 3.37 ± 1.0) free (0.27 ± 0.1, 0.26 ± 0.1, 0.24 ± 0.1 versus 0.36 ± 0.1) and total testosterone (14.9 ± 3.2, 14.5 ± 5.7, 13.8 ± 5.6 versus 18.8 ± 4.6), follicle-stimulating hormone (6.9 ± 2.6, 6.8 ± 2.7, 5.8 ± 2.1 versus 8.56 ± 2.8) and sperm counts (sperm/ml 73.6 ± 21.6, 64.3 ± 19.8, 24.5 ± 12.1 versus 93.17 ± 22.1) motility (% immobile 35.1 ± 9.8, 36.2 ± 8.7, 34.5 ± 10.1 versus 7.64 ± 2.3) and morphology compared with non-smokers. No significant difference in luteinizing hormone, E_2 and prolactin was observed. Smokers also had an increased risk of developing oligospermia (OR 3.1, $P = 0.047$), asthenozoospermia (OR	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					4.2, *P* = 0.001) and teratozoospermia (OR 4.7, *P* = 0.0003)	
2009	***Male reproductive*** hormones	Human (*n* = 255)	Cross-sectional study	Self-reported smoking	Non-smokers and smokers displayed similar mean values for androgens, gonadotropins and sex hormone binding globulin	
2007	***Male reproductive*** hormones	Human (*n* = 3,427)	Observational study	Self-reported smoking	Significantly increased levels of total and free testosterone were found in smokers. Smokers had 15% higher total (*P* < 0.001) and 13% higher free (*P* < 0.01) testosterone levels than men who have never smoked	
2013	***Male reproductive*** hormones	Human (*n* = 76)	Observational study	Self-reported smoking and cotinine levels	Smoking cessation was not associated with a significant change in ***male*** total testosterone and sex hormone binding globulin levels	
2016	Semen parameters	Human (*n* = 5,865)	Systematic review and meta-analysis	Self-reported smokingCigarettes/day: mild (1?10); moderate (10?20); heavy (>20)	Smoking was associated with reduced sperm count (MD ?9.72 × 10^6/ml, 95% CI ?13.32 to ?6.12), motility (?3.48%, 95% CI ?5.53 to ?1.44) and morphology (?1.37%, 95% CI ?2.63 to ?0.11)	
2022	Semen parameters	Human (*n* = 90)	Experimental study	Self-reported smokingHeavy smokers (>20 cigarettes/day for over 1 year)	Smoking cessation for 3 months was associated with a significant increase in semen volume (2.48 ± 0.79 ml versus 2.90 ± 0.77 ml, *P* = 0.002), sperm concentration (18.45 × 10^6/ml ± 8.56 versus 22.64 × 10^6/ml ± 11.69, *P* = 0.001), and total sperm count (45.04 ± 24.38 × 10^6 versus 65.1 ± 34.9 × 10^6, *P* < 0.001)	
2013	Semen parameters	Human (*n* = 10)	Experimental study	Spermatozoa were exposed to nicotine (0, 1, 10 and 100 ng/ml) over 3 and 24 h	Nicotine decreased sperm progressive motility, reduced spermatozoa viability and increased levels of late apoptosis, altered chromatin compaction and DNA fragmentation in a concentration-	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					dependent manner	
2019	Semen parameters	Human (*n* = 340)	Observational study	Self-reported smoking ?1 cigarette/day for >10 years	Infertile smokers showed significant increases in sperm DNA fragmentation ($P < 0.001$) and abnormal sperm morphology ($P < 0.001$), and significant decreases in sperm counts and motility ($P < 0.001$) compared with fertile and infertile non-smokers	
2012	Semen parameters	Human (*n* = 160)	Observational study	Self-reported smoking	Compared with fertile non-smokers, fertile smokers showed significant increases in sperm DNA fragmentation (10.85 ± 2.37 versus 5.86 ± 1.38) and seminal reactive oxygen species 1,180.7 ± 633.18 versus 436.5 ± 270.7)	
2009	Semen parameters	Human (*n* = 13)	Observational study	Cigarette smoke extract (nicotine concentrations from 10 to 100 ?g/ml) at 3 and 24 h	Cigarette smoke extract negatively affects sperm motility and chromatin integrity in a dose-dependent and time-dependent manner	
2021	Testicular volume	Mouse	Experimental study	Nicotine (0.6 mg/kg) or saline for 14 days	Nicotine exposure induces testicular toxicity; it is associated with significantly decreased testicular weight ($P < 0.05$)	
2017	Testicular volume	Rat (*n* = 36 total, 12 control, 12 nicotine at 0.2 mg/kg, and 12 at nicotine 0.4 mg/kg	Experimental study	Nicotine (2 mg/kg or 4 mg/kg) or saline for 7 weeks	Nicotine exposure results in decreased testicular weight (2.210 g ± 0.14 versus 1.89 g ± 0.032, $P < 0.05$) and relative testes to body weight (0.98% ± 0.52 versus 0.72% ± 0.30, $P < 0.05$) compared with controls	
2012	Erectile dysfunction and sexual function	Human (*n* = 2,686)	Cross-sectional study	Self-reported smoking	Heavy smokers (?20 cigarettes/day) displayed a significantly increased risk of erectile dysfunction compared with never smokers (OR 1.23, 95% CI 1.03?1.49;	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					P = 0.02). Risk of erectile dysfunction was significantly increased in men smoking >23 years than never smokers (OR 1.60, 95% CI 1.22?2.09; *P* = 0.001)Comorbidities and lifestyle factors increased the association between smoking and erectile dysfunction risk: drinking alcohol (OR 1.32, 95% CI 1.01?1.74), physical inactivity (OR 1.33, 95% CI 1.05?1.67), history of hypertension (OR 1.71, 95% CI 1.11?2.62), dyslipidaemia (OR 1.39, 95% CI 1.06?1.81) and diabetes (OR 2.69, 95% CI 1.4?6.98)	
2005	Erectile dysfunction and sexual function	Human (*n* = 2,115)	Population-based study	Self-reported smoking	Current smokers in their 40s displayed the highest odds of erectile dysfunction (OR 2.74, 95% CI 0.44?16.89) compared with men in their 50s (OR 1.38, 95% CI 0.51?3.74), 60s (OR 1.70, 95% CI 0.82?3.51), and 70s (OR 0.77, 95% CI 0.27?2.21)	
2006	Erectile dysfunction and sexual function	Human (*n* = 8,367)	Cross-sectional study	Self-reported smoking	The aOR for erectile dysfunction in smokers was 1.24 (95% CI 1.01?1.52; *P* = 0.04) for those smoking ?20 cigarettes/day and 1.39 (95% CI 1.05?1.83; *P* = 0.02) for those smoking >20 cigarettes/day	
2005	Erectile dysfunction and sexual function	Human (*n* = 16,724)	Observational study	Self-reported smoking	The risk of erectile dysfunction was higher in current smokers (?10 cigarettes/day; aaOR 1.4, 95% CI 1.2?1.5; *P* < 0.0001) and former smokers (aaOR 1.3, 95% CI 1.2?1.5; *P* < 0.0001) than never smokers	
2004	Erectile dysfunction and sexual function	Human (*n* = 2,837)	Observational study	Self-reported smoking	Cessation of smoking for 1 year improves erectile dysfunction more than 25%, but improvement is less in older men. 19 men aged 30?39 years (38%),	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					9 men aged 40?49 years (27%) and 2 men aged 50?60 years (8%) had improved erectile dysfunction with smoking cessation for 1 year	
2022	Erectile dysfunction and sexual function	Human (*n* = 6,754)	Secondary analysis of a double-blind randomized control trial	Self-reported smoking	Compared with non-smokers, current smokers displayed greater mean total testosterone levels (485.4 versus 451.2 nmol/l, *P* < 0.001) and increased occurrence of low libido (25.6% versus 21.0%; OR 1.34, 95% CI 1.13?1.58; *P* = 0.001) and erectile dysfunction (31.6% versus 26.0%; OR 1.43, 95% CI 1.22?1.68; *P* = 0.001) with comparable sexual activity (81.7% versus 82.8%, *P* = 0.082)Compared with current smokers, former smokers had significantly reduced total testosterone (440.6 vs 485.4 nmol/l, *P* < 0.001) and reduced occurrence of low libido (OR 0.80, 95% CI 0.68?0.96; *P* = 0.013) and erectile dysfunction (OR 0.80, 95% CI 0.67?0.94; *P* = 0.006)	
2006	Erectile dysfunction and sexual function	Human (*n* = 819)	Cross-sectional study	Self-reported smoking	Current smokers who smoked >20 cigarettes/day displayed increased dissatisfaction, erection difficulty and erectile dysfunction compared with never smokers, which increased significantly with age (*P* < 0.05; aaOR 1.47, 95% CI 1.00?2.16)	
Offspring outcomes						
2021	Short-term ***offspring outcomes***	Human (meta-analysis of 8 studies)	Systematic review and meta-analysis study	Self-reported smoking	Paternal smoking of >10 cigarettes/day before conception increased the risk of pregnancy loss (pooled risk estimates; 1.12, 95% CI 1.08?1.16	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					for 11?19 cigarettes/day; 1.23, 95% CI 1.17?1.29 for ?20 cigarettes/day)	
2020	Short-term ***offspring outcomes***	Human (*n* = 566,439 couples)	Prospective, population-based study	Self-reported smoking	Increased risk of birth defects was found in ***offspring*** of fathers who continued smoking (OR 1.87, 95% CI 1.36?2.56; *P* < .001) and decreased smoking (OR 1.41, 95% CI 1.10?1.82; *P* = 0.007). Reduced risk of congenital heart diseases, limb abnormalities, digestive tract anomalies and neural tube defects were found in infants whose fathers stopped (OR 0.32, 95% CI 0.15?0.67; *P* = 0.003) or decreased smoking (OR 0.25, 95% CI 0.13?0.49; *P* = 0.000) before conception	
2019	Short-term and long-term ***offspring outcomes***	Rat (Sprague?Dawley, *n* = 18 breeding pairs total, 9 pairs for the controls and 9 for the treatment group)	Experimental study	0 or 2 mg/kg/day nicotine for 56 consecutive days	Paternal nicotine exposure had no effect on ***offspring*** viability, ***health*** or growth, but chronic paternal nicotine exposure was linked to altered ***offspring*** behaviour, locomotor hyperactivity and impaired habituation	
2022	Long-term ***offspring outcomes***	Human (*n* = 48) and mouse (*n* = 20 ***male offspring*** in the treatment group, *n* = 15 ***male offspring*** in the control group)	Observational study (human); experimental study (mouse)	Self-reported smoking (human); water containing 2 mg/ml of cigarette smoke extract (mouse)	Tobacco smoking was associated with significantly increased sperm DNA-methylation changes (2.44 ± 0.16 versus 1.94 ± 0.16), especially hypermethylation in the *DLK1* locus (*P* < 0.01) in normozoospermic non-smokers compared with normozoospermic smokersCigarette smoking extract was associated with significantly increased global DNA methylation levels in spermatozoa and an increased risk of long-term metabolic dysfunction in F1 ***offspring***. In ***offspring***,	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
					differentially methylated regions of *Dlk1*, significantly increased *Dlk1* expression in their livers, significantly increased glucose levels ($P < 0.001$), and significant reduced LDL ($P < 0.01$). An increased accumulation of liver fat was also observed ($P < 0.05$)	
2021	Long-term ***offspring outcomes***	Mouse (*n* = 10?12 animals per group)	Experimental study	0.9% sterile saline or nicotine hydrogen tartrate salt (12.6 mg/kg/day, free base weight, dissolved in 0.9% sterile saline) for 28 days	Paternal nicotine exposure enhances fear memory, reduces nicotine administration and alters hippocampal genetic and neural function in F1 and F2 ***offspring***	
2021	Long-term ***offspring outcomes***	Mouse (cohort A nicotine sired *n* = 15; saline sired *n* = 20; cohort B nicotine sired *n* = 7; saline sired *n* = 8)	Experimental study	Nicotine (12.6 mg/kg/day) or 0.9% saline for 28 days	Parental nicotine exposure was associated with decreased risk of nicotine addiction-related phenotypes in ***offspring***	
2018	Long-term ***offspring outcomes***	Mouse (*n* values varied between assay but overall ranged from F1 water ***males*** *n* = 3?18; F1 nicotine ***male*** *n* = 4?12; for F2 studies: F2 water ***male*** *n* = 10; F2 female-derived nicotine ***male*** *n* = 11; F2	Experimental study	Nicotine (200 ?g/ml in drinking water) for 12 weeks	Paternal nicotine exposure produces behavioural changes in F1 and F2 ***offspring***, and is linked to nicotine-induced changes to paternal spermatozoa DNA methylation	

Year	Primary measure	Species	Study design	Conditions	Results	Ref.
		male-derived nicotine ***male*** *n* = 5; F2 water female *n* = 9; F2 female-derived nicotine female *n* = 9; F2 ***male***-derived nicotine female *n* = 5)				
2012	Long-term ***offspring outcomes***	Human (*n* = 39)	Observational study	Newborn umbilical cord blood and maternal peripheral blood	Paternal preconception smoking (% tail DNA: *P* > 0.032; yH2AX foci: *P* > 0.018) induced DNA damage in the F1 ***offspring*** cord blood	
2013	Long-term ***offspring outcomes***	Human (*n* = 295)	Observational study	Self-reported smoking	In ***offspring*** of non-smoking mothers, paternal smoking was associated with 46% (95% CI 21?64%) reduced total sperm count	

aaOR, age-adjusted odds ratio; aOR, adjusted odds ratio; MD, mean difference; OR, odds ratio.

Male reproductive hormones

The evidence concerning the effects of tobacco smoke on ***male reproductive*** hormones is conflicting. In one study, serum levels of FSH, LH and testosterone among 126 non-smoking men and 178 men who smoked cigarettes for over 6 months (98 men smoked 1–20 cigarettes per day, 80 men smoked >21 cigarettes per day) showed that heavy smokers (>20 cigarettes per day) had significantly lower testosterone levels (P < 0.0001) and significantly higher FSH (P < 0.0001) and LH levels (P < 0.001) than non-smokers. These findings suggest that heavy smoking can be associated with impaired ***male*** fertility, an elevated FSH is indicative of abnormal spermatogenesis and primary testicular failure. Conversely, in 95 men who smoked cigarettes (30 mild smokers: <5 cigarettes per day, 30 moderate smokers: 5–10 cigarettes per day, 35 heavy smokers: >10 cigarettes per day), smoking significantly reduced both total testosterone and FSH in a dose-dependent fashion compared with 45 non-smoking men. The results of this study demonstrated that a reduction in total testosterone (18.8 nmol/l ± 4.6 versus 14.9 nmol/l ± 3.2 versus 14.5 nmol/l ± 5.7 versus 0.24 nmol/l ± 0.1, P = 0.0.21) and FSH (8.56 IU/l ± 2.8 versus 6.90 IU/l ± 2.6 versus 6.80 IU/l ± 2.7 versus 5.80 IU/l ± 2.1, P = 0.007) was inversely proportional to the number of cigarettes smoked per day (non-smoker, mild, moderate and heavy). These observed findings suggest that in men who are unable to quit smoking, cutting down on the number of cigarettes smoked might be beneficial to their fertility. By contrast, in another study including 90 men who smoked cigarettes and 165 men who did not (aged 30–70 years), no difference in LH (P = 0.573), FSH (P = 0.693) or total testosterone (P = 0.580) was observed, regardless of pack-years of smoking; whereas, in 3,427 men who smoked cigarettes, total testosterone increased 15% compared with men who did not smoke (P < 0.001). These inconsistent ***outcomes*** across studies provide challenges to counselling patients regarding the potential risks of cigarette smoking and ***male*** fertility.

To determine whether tobacco cessation is beneficial, cessation of smoking for 1 year was analysed in 76 men who smoked cigarettes (average 24 ± 10 cigarettes per day) and found no significant differences in testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulphate, cortisol or sex hormone-binding globulin during a 1-year cessation from smoking. This observation suggests that impaired ***male*** fertility associated with chronic cigarette smoking might not be reversible with cessation.

Overall, the scientific literature focused on nicotine ***use*** and ***male reproductive*** hormones is heterogenous but suggest a potential effect on testosterone, FSH and LH with heavy smoking that might not be reversible with smoking cessation. This possibility highlights the importance of increased public awareness and ***health***-care provider counselling regarding the potential adverse effect on ***male*** fertility associated with smoking and the benefit of smoking abstinence or limiting the amount smoked. The conflicting results are partly caused by the range of tobacco products available and the diurnal variation of ***male reproductive*** hormone levels. Relevant animal models with strong translation are needed to address this by limiting confounding variables, controlling the amount of tobacco exposure and timing hormonal assessments. Ideally, this research would be performed ***using*** a single-case study design in which each subject can serve as their own control to minimize inter-animal variability.

Semen parameters

Many studies within the last three decades have shown positive correlations between nicotine and cigarette smoke exposure and altered semen parameters–. Existing evidence also largely demonstrates that exposure to tobacco smoking increases sperm DNA fragmentation, which has been linked to the polycyclic aromatic hydrocarbons present in tobacco smoke–. In a meta-analysis of 20 studies including 5,865 ***male*** participants (at least 13 years of age), exposure to cigarette smoke was significantly associated with reductions in sperm count (MD 9.72 × 106ml, 95% CI 13.32–6.12, P < 0.001), sperm motility (MD 3.48%, 95% CI 5.53–1.44, P < 0.001) and normal sperm morphology (MD 1.37%, 95% CI 2.63–0.11, P = 0.03). Evidence has shown a deleterious effect of nicotine and tobacco smoke exposure on semen parameters, but a few studies have examined the potential benefits of smoking cessation. In a 2022 study, semen parameters in 48 men (aged 28–41 years) who smoked an average of 30 cigarettes per day before and after smoking cessation for 3 months were compared, and significant increases in semen volume (2.48 ml ± 0.79 ml versus 2.90 ml ± 0.77 ml, P = 0.002), sperm concentration (18.45 × 106/ml ± 8.56 versus 22.64 × 106/ml ± 11.69, P = 0.001) and total sperm count (45.04 × 106/ml ± 24.38 versus 65.1 × 106/ml ± 34.9, P < 0.001) were found, with positive yet insignificant trends in sperm motility (20.54% ± 15.72 versus 21.41 ± 14.97, P = 0.190) and sperm morphology (2.22% ± 1.69 versus 2.43 ± 1.47, P = 0.120). In isolated spermatozoa from 10 non-smoking men with normozoospermia, results of a previous study showed that in vitro nicotine exposure suppressed sperm motility in a dose-dependent manner, even when the lowest concentration was ***used*** (1 ng/ml, P < 0.05),. The results of this study demonstrated that nicotine, the main component of cigarette smoke, can independently alter sperm motility in a dose-dependent manner, so counselling patients who are unable to or unwilling to quit smoking regarding the benefits of limiting nicotine exposure is important.

In general, evidence suggests that nicotine ***use*** adversely affects semen characteristics, potentially in a dose-dependent manner. However, the mixed results reported are likely a result of confounding factors, including combustible products from tobacco smoke, the type and duration of ***use***, and the time at which semen samples were collected. Future studies should include the type, frequency and duration of tobacco products ***used***, and attempt to coordinate semen collections at a similar time of day across participants.

Testicular volume

Studies assessing the effect of nicotine on testicular volume are preliminary in nature; however, two studies in both mice and rats suggest that nicotine administration significantly reduces total testicular weight relative to total body weight,. In the mice, nicotine was injected intraperitoneally (0.6 mg/kg) for 14 days and nicotine decreased testicular weight significantly (P < 0.05). Similarly, rats were injected intraperitoneally with saline (0.2 ml) or high-dose (0.4 mg/kg) nicotine and notable decreases in testicular weight (2.210 g ± 0.14 versus 1.89 g ± 0.032, P < 0.05) and relative testes-to-body weight (0.98% ± 0.52 versus 0.72% ± 0.30, P < 0.05) were observed. These findings are concerning; at this time, data are insufficient to conclude that nicotine ***use*** negatively ***influences*** testicular volume

and further animal studies with strong translational relevance, recapitulating typical human ***use*** and mimicking the ***male*** HPG axis, are needed.

Erectile dysfunction and sexual function

The ***use*** of nicotine and cigarettes has been linked to erectile dysfunction, but many men are unaware of this risk,. The underlying aetiology is largely thought to be secondary to vascular mechanisms, primarily depletion of nitric oxide (an important neurotransmitter found in cigarette smoke) that regulates penile vessel constriction and relaxation of the corpora cavernosa to achieve penile erection. Men with vascular risk factors such as hypertension or diabetes and who smoke are at increased odds of developing erectile dysfunction.

In a cross-sectional study, ~23% of instances of erectile dysfunction were associated with cigarette smoking. In this study of 2,686 men (22.9% smoked <20 cigarettes per day and 31.5% smoked ≥20 cigarettes per day), individuals who smoked for >23 years had a significantly higher risk of erectile dysfunction than never smokers (OR 1.23, 95% CI 1.03–1.49, P = 0.02). In another population-based study including 1,329 men with a regular sexual partner (173 current smokers and 836 had previously smoked) in which former and never smokers were compared, the risk of erectile dysfunction was highest among current smokers in their 40s (OR 2.74, 95% CI 0.44–16.89, P < 0.09). In addition, non-smoking men were significantly less likely to experience erectile dysfunction than men who were current (OR 1.17, 95% CI 0.71–1.94, P < 0.09) or ever smokers (OR 1.46, 95% CI 1.05–2.02, P < 0.09). Results of a cross-sectional study of 8,367 men (8.8% non-smokers, 9.4% ≤20 cigarettes per day, 14.7% >20 cigarettes per day) also reported that smoking was significantly associated with the occurrence of erectile dysfunction following a dose-dependent pattern. Compared with non-smokers, the adjusted odds ratio for erectile dysfunction was 1.24 (95% CI 1.01–1.52, P = 0.04) in men smoking ≤20 cigarettes per day and 1.39 (95% CI 1.05–1.83, P = 0.02) for those smoking >20 cigarettes per day. Results of similar studies also demonstrated a positive association between smoking frequency/duration and erectile dysfunction,. Some evidence shows that smoking cessation improves erectile dysfunction rates, but is mostly limited to men under the age of 50 years lacking comorbidities and with minor smoking histories. In a prospective study of 2,837 smokers (aged 30–60 years), 637 (22.5%) reported having erectile dysfunction, which correlated with the level of exposure to smoking. Of the 118 patients who stopped smoking, erectile dysfunction improved after a year in >25%; however, older individuals experienced less improvement. Overall, 19 of men aged 30–39 years (38%), 9 of men aged 40–49 years (27%), and 2 of men aged 50–60 years (8%) had improved erectile dysfunction with smoking cessation for 1 year.

Sexual function increased following smoking cessation in 6,754 men aged 50–75 years and grouped into non-smokers (3,069; 45.4%), former smokers (2,673; 39.6%) and current smokers (1,012; 15%). Current smokers had a higher prevalence of low libido than former and non-smokers (25.6% versus 21.0%, P = 0.002) with comparable sexual activity (81.7% versus 82.8%, P = 0.420). Cigarette smoking is associated with worse sexual ***health*** than in non-smokers; the decrease in libido was not enough to reduce the frequency of sexual activity. In 819 men aged 31–60 years, current smokers who smoked ≥20 cigarettes had greater sexual dissatisfaction than never smokers. These findings highlight cigarette smoking as a modifiable lifestyle behaviour in men with sexual dissatisfaction and dysfunction.

Overall, nicotine ***use*** is associated with erectile dysfunction and decreased sexual function, including low libido and sexual satisfaction. These ***outcomes*** seem to be dose dependent, based on the number of cigarettes smoked or amount of tobacco product ***used*** per day, and are at increased likelihood in men with underlying vascular conditions, such as diabetes, than in those without. Thus, counselling patients undergoing evaluation for sexual dysfunction to cut back or abstain from nicotine ***use*** is important.

Summary

Nicotine ***use*** is highly prevalent and evidence largely suggests that it negatively affects ***male reproductive health***, especially semen parameters and sexual function (Table). The availability of different tobacco products and inconsistent adjustment of confounders, including polysubstance ***use***, contribute to mixed findings. ***Health***-care providers must discuss with patients that nicotine ***use*** could adversely affect ***male*** fertility and the benefits of cessation or limited ***use***.

Paternal ***health*** and behavioural lifestyles, such as ***substance use***, can affect ***male reproductive*** and ***offspring outcomes***. ***Substance use***, especially among ***reproductive***-age men, continues to be an ongoing issue partly owing to the lack of awareness regarding the potential ***influence*** on ***reproductive health***. Research has shown that ***substance use*** can affect semen parameters, ***male reproductive*** hormone secretion and sexual function. Thus, identifying these modifiable lifestyle paternal factors with regard to ***reproductive outcomes*** is important. This intervention is especially urgent considering the growing evidence highlighting that preconception paternal ***substance use*** is linked to adverse ***offspring*** development, including congenital anomalies, low birthweight, and metabolic and neurodevelopmental disorders,,–.

Offspring outcomes

Accumulating evidence suggests that preconception paternal ***substance use*** can result in adverse consequences for ***offspring***, including abnormal brain development, neurobehavioural dysfunction and worsened mental ***health***. Increased ***offspring*** morbidity can occur both in the short term (that is, the neonatal period and infancy) in addition to the long term (that is, childhood through to adulthood). The most common ***substances used*** include alcohol, cannabis, opioids and nicotine.

Alcohol

Paternal alcohol consumption is associated with negative ***influences*** on ***offspring*** growth, development, neurodevelopment and sociobehaviour that might have a greater effect on boys than on girls,– (Table).

Short-term ***outcomes***

In animal studies, preconception paternal alcohol consumption has been linked to intrauterine growth restriction,, craniofacial growth deficiencies, low birthweight,, limited growth and altered ***reproductive*** development in ***offspring***. Affected growth patterns have been reported as sex specific, with an increased effect on ***male offspring***. In ***male*** mice, preconception paternal alcohol exposure (10% ethanol for 4 h daily) for 70 days before mating was associated with a significantly increased incidence of intrauterine growth restriction (25% reduction in body weight, $P = 0.004$) and ***male offspring*** were more greatly affected than females (15% reduction in body weight, $P = 0.017$). In another study of adult ***male*** mice exposed daily to 10% ethanol (2.7 g/kg), 2D imaging on collected fetal heads post-delivery demonstrated that preconception ***male*** alcohol exposure induces a significant increase in craniofacial growth deficiencies in ***offspring*** ($P < 0.0001$). The results of these studies suggest that paternal alcohol ***use*** before conception can affect ***offspring*** development. A prospective cohort study of 1,292 pregnancies through in-person interview demonstrated that ***offspring*** in the paternal-exposed group (exposure to alcohol within the 3 months before conception) had a shorter anogenital distance than the unexposed group at birth and at 6 months, especially in boys ($P = 0.01$ and $P = 0.02$, respectively) compared with girls ($P = 0.04$ and $P = 0.04$, respectively). This observation indicates that paternal alcohol consumption can have an adverse effect on ***offspring reproductive*** development. In rats, acute paternal alcohol exposure (intraperitoneal injection with alcohol 5 g/kg) compared with saline exposure 24 h before breeding resulted in a ~50% reduction in viable ***offspring***. These results suggest that even acute paternal alcohol ***use*** can adversely affect fertility and fetal ***outcomes***. A large population study involving 529,090 couples from the National Free Preconception ***Health*** Examination Project determined that the risk of birth defects was increased with paternal alcohol consumption (drinking at least once per week) (OR 1.35, 95% CI 1.14–1.59, $P < 0.001$), especially the risk of cleft lip or palate (OR 1.55, 95% CI 1.04–2.30, $P = 0.03$). This study only reported the frequency, but not the amount, of alcohol consumed but it suggests that future fathers should be counselled to modify their alcohol intake before conceiving.

Long-term ***outcomes***

Preclinical studies have shown that preconception paternal alcohol consumption can alter the sperm genome and epigenome, including changes in DNA methylation, chromatin structure modifications and small non-coding RNAs,. In a study of adult mice exposed to vapour ethanol or room air (8 h a day for 5 days per week) over 5 weeks, significantly altered expression of several small non-coding RNA species ($P < 0.05$) in sperm was reported. As small non-coding RNAs in sperm can induce heritable phenotypes in ***offspring***, these findings suggest a potential underlying mechanism for how paternal alcohol consumption might affect ***offspring*** development and ***health***.

Results of another study of ***male*** mice showed that exposure to 10% ethanol compared with saline ad lib for 35 days can significantly disturb sperm DNA integrity and chromatin remodelling ($P < 0.05$). These changes could contribute to abnormal ***offspring*** neurodevelopment including anxiety, depression, cognitive impairment and ADHD,,. In the prospective Shanghai-Minhang Birth Cohort Study of 796 children, preconception paternal alcohol consumption was associated with an increased risk of anxiety and depression in ***male offspring*** at age 4 years (RR 1.33, 95% CI 1.09–1.61) and 6 years (RR 1.37, 95% CI 1.02–1.85). In a study of ***male*** mice (n = 15) injected intraperitoneally with 20% ethanol (5 mg/kg) compared with saline before mating, alcohol-sired pups had delayed motor milestones ($P < 0.05$), decreased frequency of risk assessment behaviour ($P < 0.001$), increased aggressive behaviours ($P < 0.001$) and increased defensive behaviours ($P < 0.0001$). Results of a study of mice exposed to ethanol via oral gavage (3.3 g/kg ethanol or 1.1 g/kg ethanol) demonstrated that ***offspring*** of paternally ethanol-exposed mice had greater anxiety-like behaviour, and decreased learning ability and memory ($P < 0.05$), than mice that received saline for 1 month.

Similarly, a link between paternal drinking and an increased incidence of externalizing psychopathological disorders,, congenital heart defects and cancer (such as leukaemia, brain tumours and neuroblastoma) in children. Data from the Minnesota Twin Family Study, a community-based investigation through structured interviews of adolescents (age 17 years, n = 1,252) and their parents, demonstrated that parental alcohol dependence (both or one parent) was associated with an increased risk of externalizing psychopathology in late-adolescent ***offspring***, including ADHD (OR 2.77, 95% CI 1.18–6.46, $P < 0.05$), oppositional defiant disorder (OR 2.28, 95% CI 1.46–3.56, $P < 0.001$), conduct disorder (OR 1.85, 95% CI 1.27–2.68, $P < 0.01$), adult antisocial behaviour (OR 2.25, 95% CI 1.22–4.14, $P < 0.01$), nicotine dependence (OR 1.96, 95% CI 1.27–3.05, $P < 0.01$), alcohol dependence (OR 2.18, 95% CI 1.32–3.61, $P < 0.01$) and drug dependence (OR 2.25, 95% CI 1.09–4.62, $P < 0.05$).

A population-based case–control study ***using*** data from the Guangdong Registry of Congenital Heart Disease, an ongoing WHO population-based surveillance system, showed that paternal alcohol consumption was associated with an increased risk of congenital heart disease (aOR 2.87, 95% CI 2.25–3.65). The most common congenital heart defects associated with paternal alcohol consumption were left ventricular outflow tract obstruction (12.7%), atrial septal defect (9.1%), tetralogy of Fallot (6.9%) and transposition of the great arteries (6.7%). In addition, results of a prospective cohort study including 4,710 men (aged 18–20 years) demonstrated that paternal alcohol consumption, even in moderate amounts (20–60 g of alcohol consumed per week), is linked to an increased risk of ***substance***-related disorders in their children. Paternal volume of alcohol consumed was associated with the risk of ***offspring substance***-related disorders; the risk ranged from HR 1.11 (95% CI 0.84–1.45) for the lowest drinking quintile (up to 20 g alcohol per week) to HR 2.02 (95% CI 1.56–2.62) for the highest drinking quintile (80–100 g alcohol per week). These observations suggest that paternal alcohol consumption, especially quantity consumed, can ***influence offspring*** risk of addiction.

Summary

In general, results preclinical and human studies have shown that preconception paternal alcohol consumption can adversely affect ***offspring*** development and function (Table). Prenatal alcohol exposure from maternal ***use*** receives increased focus, but counselling men interested in conceiving and recommending cessation of paternal alcohol consumption before conception is equally important.

Cannabis

Paternal cannabis ***use*** has been linked to adverse ***offspring outcomes*** including increased miscarriage rates and altered neurobehavioural ***outcomes*** such as hyperactivity and poor attention, (Table). In preclinical studies, cannabis exposure has also been inconsistently associated with congenital anomalies.

Short-term ***outcomes***

The effects of cannabis ***use*** on ***offspring outcomes*** have been most frequently studied in relation to maternal exposure, but growing evidence suggests that paternal exposure might also have deleterious effects. Paternal cannabis ***use*** and perinatal ***outcomes*** in mice and rats have been the focus of several studies. Impairments in placental development and ***offspring*** growth were noted in those with sires exposed to a CB2R agonist for 5

weeks. Additionally, ***offspring*** from ***male*** mice exposed to THC (50 mg/kg) orally three times a day for 5 weeks were significantly more likely to be lost during pregnancy (37% versus 19%, $P < 0.05$) than those given oil, and the sperm from these mice was found to have an increased prevalence of chromosomal abnormalities such as aneuploidy (9.66 versus 0.27, $P < 0.05$), polyploidy (5.4 versus 3.88, $P < 0.05$), and translocation events (0.54 versus 3.12, $P < 0.05$). A dose of 50 mg/kg THC in mice corresponds to an oral dose of approximately 4 mg/kg in humans, equivalent to three cannabis cigarettes containing 1% THC. However, in another mouse study ***using*** a similar duration of THC exposure (every other day for 5 weeks), but a much lower THC dose (10 mg/kg versus 50 mg/kg body weight), was not able to recapitulate the findings of fetal loss. These findings suggest a dose-related effect with considerably adverse ***offspring*** ***outcomes*** most associated with heavy, daily cannabis ***use*** before conception.

In human populations, increased paternal ***use*** of cannabis preconception has been linked to decreased infant birthweight in couples undergoing in vitro fertilization. Results of a prospective study including 221 couples undergoing in vitro fertilization showed that men who ***used*** cannabis a year before the procedure had 1 less embryo transferred (95% CI −1.25 to −1.02, $P = 0.04$). In addition, the lifetime amount of cannabis smoked before in vitro fertilization was associated with decreased infant birthweight, moderate ***use*** (11–90 times) was associated with a 15% decrease (95% CI −0.3 to −0.01, $P = 0.03$) and heavy ***use*** (>90 times) was associated with a 23% decrease (95% CI −0.46 to −0.07, $P = 0.01$) in infant birthweight. By contrast, no association was found in a large cohort study of 2,642 men (115 cannabis users and 2,527 non-users) between paternal cannabis ***use*** and changes in birthweight (40.68; 95% CI −56.71 to 138.06, $P = 0.41$), but only paternal cannabis usage during pregnancy rather than the preconception period was examined. These results suggest that the timing of paternal cannabis ***use***, especially before conception, can ***influence*** the potential for adverse ***offspring*** ***outcomes***. Regarding fetal loss, a large prospective study of 1,535 couples (9% reported ***male*** cannabis ***use*** less than once a week and 8% reported cannabis ***use*** at least once a week, with half ***using*** daily) conducted online found that couples in which the man ***used*** cannabis at least once per week were at an increased risk of experiencing spontaneous abortion (hazard ratio 2, 95% CI 1.2–3.1). Associations between paternal cannabis usage before conception, during pregnancy, and postnatally with sudden infant death syndrome (SIDS) have also been reported in a case–control study. In a study involving 239 infants who died of SIDS matched to 239 healthy infants, an increased risk of SIDS was associated with fathers who ***used*** cannabis during conception (OR 2.2, 95% CI 1.2–4.2, $P = 0.01$), during pregnancy (OR 2, 95% CI 1.0–4.1, $P = 0.05$) and postnatally (OR 2.8, 95% CI 1.1–7.3, $P = 0.04$). The findings of this study underscore the role of paternal ***substance use***, specifically the relationship between cannabis ***use*** and SIDS.

Long-term ***outcomes***

Evidence from animal studies has largely highlighted that paternal cannabis ***use*** might ***influence*** ***offspring*** development and behaviour. In a rat model, paternal exposure to THC (0 or 2 mg/kg/day oral gavage) for 12 days was associated with significantly reduced attentional performance ($P < 0.025$). In another study in ***male*** rats, THC (0, 2 or 4 mg/kg/day subcutaneously) for 28 days adversely affects ***offspring*** behavioural effects, including increased locomotor hyperactivity in adolescent and adult ***offspring*** ($P < 0.05$). These findings support the ***influence*** of paternal cannabis ***use*** on ***offspring*** development, particularly behaviour. Corresponding data in humans are comparatively limited, but associations between paternal cannabis ***use*** and ***offspring*** behavioural problems have been described. A population-based birth cohort study (n = 5,903) noted that paternal cannabis ***use***, through smoking, reported by questionnaire, was associated with child externalizing problems by 7–10 years old (B = 0.36, 95% CI 0.22–0.49) but not internalizing problems measured by validated teacher, child and mother reports. Externalizing behaviour has been shown to have common genetic and environmental origins and although the literature often focuses on maternal contributions, these reported observations reflect the important role of paternal contributions to ***offspring*** development.

Paternal cannabis ***use*** has also been inconsistently linked to ***offspring*** congenital anomalies. In a study of rats, ***offspring*** born to cannabis extract-exposed fathers (intraperitoneal injection of 4 mg/kg/day THC) exhibited significant rates of cardiomegaly relative to those born to control fathers ($P = 0.0013$). These cardiac findings in ***offspring*** were associated with altered sperm DNA methylation of genes associated with early developmental processes in the cannabis extract-exposed father. This observation supports the theory of paternal origins of ***health*** and disease, in which paternal environmental exposures can disrupt early ***offspring*** development and the

importance of ***health***-care provider counselling for individuals interested in conceiving. Furthermore, results of several studies based on the Baltimore-Washington Infant Study, a regional epidemiological study of congenital heart disease, and the Atlanta Birth Defects Case–Control Study showed associations between paternal cannabis ***use*** with transposition of the great arteries (RR 1.4, 95% CI 2.8–12.7, P = 0.05), ventricular septal defects (OR 1.36, 95% CI 1.05–1.76) and single-ventricle defect (OR 2.2, 95% CI 1.0–5.2),. Taken together, these findings highlight the need to consider paternal environmental factors in the pathogenesis of fetal cardiac abnormalities and the importance of preconception counselling. In addition, an increased risk of rhabdomyosarcoma by two-fold (95% CI 1.3–3.3) in the child has also been associated with the paternal ***use*** of cannabis during the year before their child's birth. This observation suggests that paternal cannabis ***use*** before conception can increase ***offspring*** risk of rhabdomyosarcoma and that lifestyle modification might be beneficial in ***reproductive***-age men to reduce ***offspring*** morbidity.

The underlying mechanisms by which paternal cannabis exposure might ***influence*** ***offspring*** ***outcomes*** are not fully understood; emerging evidence suggests that epigenetics, including DNA methylation, might have a role in the transmission of ***outcomes***. In recreational cannabis users, widespread alterations in sperm DNA methylation were found compared with non-users, including hypomethylation of DLGAP2 (ref.), a gene that has been associated with or implicated in the pathogenesis of autism spectrum disorders,. Sperm from ***male*** rats exposed to cannabis demonstrated changes in methylation that were also found to be present in their ***offspring***, suggesting the potential for transmissibility. Similarly, alterations in DNA methylation patterns noted in mouse sperm exposed to synthetic cannabinoids were transmitted to placental tissues, with some of the affected genes known to be involved in placental and embryonic development. The importance of these findings is that paternal selective activation of cannabinoid receptors in the sperm epigenome can affect pregnancy ***outcomes***. ***Male*** cannabis users (n = 30) had increased incidence of hypermethylation in DRD2 and NCAM1, genes that are involved in dopaminergic pathways and that have been associated with ***substance use*** disorders, including nicotine and alcohol dependence–. However, whether these changes are transmissible to ***offspring*** in a clinically meaningful way has yet to be demonstrated and will require further investigation. If transmissible, concern for increased ***offspring*** addiction risk would exist and preventative interventions would be beneficial, including early referral to support services.

Summary

Preclinical and human studies suggest that paternal cannabis ***use*** might increase pregnancy loss and can adversely affect short-term and long-term ***offspring*** ***outcomes***, including development and behaviour (Table). The underlying mechanism for these observations is not well understood but could be a result of inherited epigenetic alterations. Additional research in relevant animal models is needed to overcome the limitations and confounding variables of human studies, to better examine the relationship between paternal cannabis ***use***, including dose, frequency and duration ***used***, and ***offspring*** development and ***outcomes***.

Opioids

Research on the effect of paternal opioid ***use*** on ***offspring*** ***health*** ***outcomes*** is limited, especially regarding a dose-related effect. Dose–response studies would provide information regarding the safest effective dose. Existing evidence suggests that it is associated with changes in ***offspring*** weight, neurobehaviour, pain perception and vulnerability to opioid abuse,– (Table). In preclinical studies, ***offspring*** with fathers who ***used*** opioids, especially ***males***, demonstrated increased withdrawal-like behaviours, sensitivity to the antinociceptive properties of opioids, delayed learning and impulsivity,–.

Short-term ***outcomes***

Little is known about the effect of chronic opioid exposure on the next generation, let alone from paternal preconception opioid ***use***. Much of the existing research on the transgenerational ***influence*** of paternal opioid ***use*** has been studied in conjunction with maternal opioid exposure. Existing evidence on paternal preconception opioid ***use*** suggests an ***influence*** on fetal organ weights (such as adrenal gland and thymus) and ***offspring*** hormone levels (including testosterone) that are involved in growth-regulation and neurotransmitter function. A study of ***male*** rats subcutaneously injected with methadone (5 mg/kg) for 4 days before undergoing mating compared with

untreated ***males*** had ***offspring*** notable for significantly heavier adrenal glands (29.02 mg ± 0.81 versus 23.75 mg ± 1.05, P < 0.05) and lighter thymus glands (65.37 mg ± 4.18 versus 72.56 mg ± 2.26, P < 0.05). Results of another study of ***male*** rats implanted with morphine pellets before conception were notable for ***offspring*** with significantly decreased serum testosterone levels (3.18 ng/ml ± 0.27 versus 4.37 ± 0.37, P < 0.01). These results indicate that paternal opioid ***use*** can affect ***offspring*** development and endocrine function. In a study involving 8,410 parent–***offspring*** pairs, regular preconception paternal opioid ***use*** was independently associated with increased odds of ***offspring*** being overweight (adjusted OR (aOR) 1.76, 95% CI 1.15–2.71). These observations suggest that paternal opioid ***use*** before conception can ***influence*** ***offspring*** metabolic ***health*** and given the obesity pandemic, suggests that opioid ***use*** is a modifiable lifestyle factor to consider.

Long-term ***outcomes***

Emerging evidence shows that preconception paternal opioid exposure might ***influence*** developmental trajectories across multiple generations,,,. Preclinical studies suggest that paternal opioid ***use*** can affect ***offspring*** behaviour and neurobiological characteristics, including increased withdrawal-like behaviours, synaptic plasticity deficits and altered sensitivity to the antinociceptive properties of opioids. In addition, findings suggest that paternal opioid ***use*** might increase ***offspring*** vulnerability to opioid abuse in a sex-dependent manner, with ***males*** often more affected. In a study of ***male*** rats injected with morphine (25 mg/kg) the day before mating, ***male*** ***offspring*** of morphine-exposed fathers had a significantly enhanced sensitivity to the antinociceptive effects of morphine (P < 0.01) compared with ***male*** ***offspring*** of unexposed sires; however, no significant effect was seen in female ***offspring***. In another study of ***male*** rats injected with morphine twice daily (10 mg/kg every 12 h) for 2 weeks, significantly higher anxiety-like behaviour and enhanced voluntary consumption of morphine in ***male*** ***offspring*** of morphine-exposed fathers than in those whose fathers were exposed to saline (P < 0.01). These findings are concerning and support the ***influence*** of paternal opioid ***use*** on ***offspring*** development, with the greatest effect on ***male*** ***offspring***.

In a rat model, paternal preconception exposure to opioids has been shown to increase sensitivity to the pain-relieving effects of morphine in ***male*** ***offspring***. An intergenerational effect of paternal morphine exposure during adolescence on pain perception and the antinociceptive effect of morphine in rat ***offspring*** have also been demonstrated. In adolescent ***male*** rats receiving subcutaneous morphine (2.5 mg/kg initially and increased to 25 mg/kg over 40 days) compared with saline before mating, ***offspring*** had significantly decreased pain-related behaviours and an antinociception effect (P < 0.001). A paternal opioid self-administration rat model (0.75 mg/kg/infusion of morphine over 5 s for 3 h a day) to mimic the human condition of voluntary consumption showed that paternal morphine exposure compared with saline-exposed controls selectively disrupts novel object recognition in female (P =0.011) but not ***male*** (P = 0.965) progeny. However, anxiety-like behaviour or stress-induced hypothalamic–pituitary–adrenal axis activation was changed in neither ***male*** nor female ***offspring***. In another study, ***male*** Wistar rats received escalating subcutaneous doses of morphine (2.5–25 mg/kg) or saline for 10 days. ***Offspring*** sired by rats that had received morphine exhibited delayed learning (P = 0.002) and impulsive behaviour (P < 0.001) compared with ***offspring*** sired by control rats. Taken together, the findings of these studies suggest that paternal opioid exposure can affect socioemotional behaviour and response to pain in progeny.

Summary

Evidence examining the ***influence*** of paternal opioid ***use*** on ***offspring*** ***health*** ***outcomes*** is lacking. Results of preclinical and human studies have shown that paternal opioid ***use*** is associated with adverse effects on ***offspring*** weight, neurodevelopment, sociobehaviour, sensitivity to pain and addiction vulnerability, with ***male*** ***offspring*** more likely to be affected than female ***offspring*** (Table). The social consequences of paternal opioid ***use*** can result in an increased prevalence of mental ***health*** and addiction disorders, which can be associated with increased morbidity and mortality. More research is needed to uncover the mechanisms underlying these observations so that potential intervention or targeted therapies can be developed.

Nicotine

Overall, evidence regarding paternal nicotine product ***use*** and pregnancy and ***offspring*** ***outcomes*** is limited. Paternal nicotine product ***use*** has been linked to increased pregnancy loss, birth defects and abnormal ***offspring***

neurobehaviour, (Table). Some of these adverse effects seem to be dose dependent and potentially mitigated by a reduction or cessation of paternal nicotine ***use***.

Short-term ***outcomes***

Most research on the intergenerational effects of parental nicotine product ***use*** has focused on maternal exposure, with little known about paternal ***use***. Evidence from human studies and animal models has shown a potential link between paternal preconception nicotine exposure and ***offspring*** ***health***. In a rat model of chronic nicotine exposure, paternal nicotine exposure did not affect ***offspring*** viability, ***health*** or growth. By contrast, results of a systematic review and meta-analysis of eight human studies including men and women showed that, after adjusting for maternal smoking status, preconception paternal smoking of >10 cigarettes daily was linked to an increased risk of pregnancy loss in a dose-dependent manner. No adverse effects were found with paternal smoking of 1–10 cigarettes per day. In a prospective, population-based study, pregnancy ***outcomes*** of 566,439 couples based on preconception paternal smoking habits were investigated. A significantly higher prevalence of birth defects was observed in children of couples with continued (OR 1.87, 95% CI 1.36–2.56, P < 0.000) or reduced (OR 1.41, 95% CI 1.10–1.82, P = 0.007) paternal smoking during pregnancy. Interestingly, in the 1:1 case–control (birth defects compared with normal pregnancy) analysis, reduced risks of congenital heart diseases, limb and digestive tract anomalies, and neural tube defects were observed in couples with decreased (OR 0.025, 95% CI 0.13–0.49, P = 0.000) or ceased (OR 0.32, 95% CI 0.15–0.67, P = 0.003) paternal smoking during pregnancy. These results suggest that changes in smoking behaviour, including cessation or reduction, might reduce the risk of miscarriage and ***offspring*** birth defects.

Long-term ***outcomes***

Existing evidence suggests that paternal nicotine exposure can induce epigenetic changes, including alterations in DNA methylation (both hypomethylation and hypermethylation) and histone modification, that might result in ***offspring*** neurobehavioural and metabolic effects–. Results of studies in rats have shown that chronic paternal nicotine exposure can substantially alter ***offspring*** behavioural function, including impaired habituation and locomotor hyperactivity. In ***male*** rats exposed to saline or 2 mg/kg/day nicotine subcutaneously for 56 days, paternal nicotine exposure was associated with a significant (P < 0.025) degree of locomotor hyperactivity in juvenile ***male*** ***offspring*** (41.1 ± 1.7) compared with ***male*** controls (34.5 ± 1.7). In addition, ***offspring*** of nicotine-treated ***males*** demonstrated a pattern of slower habituation of locomotor behaviour than those with saline-exposed fathers (P < 0.05). In both humans and a mouse model, paternal exposure to cigarette smoke altered sperm DNA methylation in the F1 generation at genes, including DLK1, that are involved in metabolic function. Taken together, the findings of these studies suggest that paternal exposure to cigarette smoke can result in behaviour and epigenetic changes in ***offspring*** that might affect long-term ***outcomes***, including metabolic function and behavioural ***health***.

In a C57BL6/J mouse model, paternal nicotine exposure was potentially shown to have a multigenerational effect of increasing ***offspring*** susceptibility to anxiety disorders such as post-traumatic stress disorder, but might also result in decreased susceptibility to nicotine addiction-related phenotypes. Paternal preconception smoking also resulted in significantly increased spontaneous locomotor activity (10,173 ± 5,371.4 versus 5,655 ± 2,041.99 and 14,571 ± 6,248.4 versus 9,995 ± 4,153.6, P < 0.05) and significantly decreased reversal learning (16.41 ± 8.31 versus 8.19 ± 4.87 and 14.05 ± 7.41 versus 4.13 ± 4.46, P < 0.01) of F1 ***male*** and female mice, respectively, which could relate to the increased occurrence of neurobehavioural disabilities such as ADHD and autism. These findings also highlight the potential differences in sensitivity of ***male*** versus female ***offspring*** to nicotine exposure. F1 ***male*** ***offspring*** were also observed to have significantly reduced attention, brain monoamine (for example, dopamine, noradrenaline and metabolites) levels, and dopamine receptor mRNA expression (P < 0.05).

Analysing the effects of paternal preconception tobacco smoke exposure on human ***offspring*** has been a challenge because the separation of preconception and gestational exposures are difficult to control. ***Offspring*** cord blood analysed for genomic stability contained predictors of increased single-strand and double-strand DNA breaks with paternal smoking. Thus, paternal smoking habits could provide a mechanistic basis for genetic instability in ***offspring*** and preconception and gestational cigarette smoking could have an intergenerational risk of

the induction of DNA damage in human ***offspring***. Spermatozoa DNA damage can increase the likelihood of unsuccessful fertilization, miscarriage, impaired embryo quality and altered embryonic development. The semen parameters of 295 adolescent men showed that those with fathers exposed to cigarette smoke displayed 46% lower total sperm counts and lower sperm concentrations, which might adversely affect their fertility and ability to conceive.

Summary

The evidence is conflicting, but overall suggests that paternal nicotine ***use*** can negatively affect short-term and long-term ***offspring*** ***health*** and that adverse ***outcomes*** are probably dose dependent (Table). Inconsistent adjustment of confounders, including tobacco smoke and maternal nicotine ***use***, probably contributed to the variability in study findings. Future research needs to also focus on understanding the benefits of cessation in addition to the effects of dose, frequency and duration of exposure on ***offspring*** ***outcomes*** to improve counselling of patients regarding paternal nicotine ***use***.

Public ***health***

The ***influence*** of paternal ***health*** and behavioural lifestyles, such as ***substance use***, on ***male*** fertility and ***offspring*** ***outcomes*** is an understudied and underappreciated topic in ***reproductive*** ***health***. Existing ***health*** campaigns by large organizations, including the Centers for Disease Control and Prevention, the March of Dimes, the ***Substance*** Abuse and Mental ***Health*** Services Administration, National Institutes of ***Health*** and the WHO, are focused on improving maternal ***health***; similar measures targeting paternal ***health*** and lifestyle are largely unavailable. Few guidelines and recommendations exist to direct ***health***-care providers in discussing ***substance use*** with patients intending to conceive owing to limited safety data. The American Society of ***Reproductive*** Medicine and the American Urological Association have issued committee opinions to assist practitioners in optimizing fertility, including ***substance use*** counselling, but highlight the need for more evidence-supported recommendations,. Thus, additional research is urgently needed to inform guideline development, prevention campaigns and programme implementation to promote ***male*** ***reproductive*** ***health***. To achieve this aim, heightened awareness and recognition of the paternal role in achieving successful healthy ***offspring*** is needed. Currently, well-established public ***health*** policies exist advising future mothers not to consume alcohol, smoke or eat unhealthily to benefit their ***offspring***. However, appreciation by the general population that paternal contributions are evidently relevant and can adversely affect ***male*** fertility in addition to prenatal ***health*** ***outcomes*** is lacking. Increased public understanding regarding the potential adverse effect of paternal ***substance use*** on future ***offspring*** ***health*** will encourage professional and parent-implemented early intervention strategies to help to decrease developmental delays or disabilities and maximize developmental potential,.

Patient counselling

Crucially, ***health***-care providers need to counsel men of ***reproductive*** age and men and couples undergoing ***reproductive*** decisions regarding the negative effects of ***substance use*** on ***male*** fertility and ***offspring*** development, and the potential benefit of cessation of or reducing ***substance use***. The growing prevalence of ***substance use*** can partly be attributed to perceptions of safety because insufficient evidence exists regarding its risks and patient counselling by ***health***-care providers is lacking. To mitigate the potential adverse effects of ***substance use***, ***health***-care providers must engage in evidence-informed discussions with patients about the ***reproductive*** ***health*** effects of ***substance use***. However, many providers have cited a lack of training, clarity of the evidence on ***health*** effects, and limited practice talking to patients about these topics as barriers to discussing ***substance use***. Thus, a crucial need exists to design and disseminate educational strategies and resources to teach clinicians so that they can effectively provide information and appropriate counselling. In addition, professional ***health***-care societies should focus on providing more directive and up-to-date guidelines for practitioners to follow.

Overall, safe limits for consumption are not known so the safest option to avoid harmful effects to fertility and ***offspring*** ***health*** is cessation. For patients who are not ready to stop their ***substance use*** or feel that stopping is not the best option for them, the goal should be harm reduction. Harm-reduction strategies include considering

safer alternatives to the ***substance used***, ***using*** reduced amounts, and decreasing frequency of ***use*** given that a dose-dependent and/or duration-dependent response is often observed. ***Substance use*** is an important modifiable lifestyle risk factor that can be optimized before conception to improve fecundity, and pregnancy, birth, and short-term and long-term ***outcomes*** in ***offspring***.

Future directions

Additional research is needed to further understand the magnitude of the effects of ***substance use*** on ***male*** fertility, especially to determine whether a dose-dependent effect exists, and if the changes are reversible or permanent. Also, as the prevalence of the co-***use*** of marijuana or opioids with nicotine and/or alcohol consumption is high, preclinical studies need to reflect real-world ***use*** and elucidate the effects of each ***substance*** individually as well as in combination. Characterizing the role and contributions of paternal origins of disease on short-term and long-term ***offspring health outcomes*** is also crucial, including neurodevelopmental and sociobehavioural ***outcomes***. This characterization would highlight the importance of paternal lifestyle, diet and other environmental exposures on future ***offspring health***. Research is also needed to determine the underlying mechanisms of potential intergenerational transmissibility. DNA methylation is one of the most frequently studied means of potential paternal transmission of non-genetic characteristics to ***offspring***, but future work should investigate the role of retained histone proteins and other non-genetic components of epigenetic inheritance because of their ***influence*** on key developmental processes.

Evidence-based counselling is also needed for individuals or couples intending to conceive, to inform preconception lifestyle modifications. As studies have shown that many ***health***-care providers do not address the safety of cannabis ***use***, in part owing to a lack of training and the clarity of the evidence on ***health*** effects, a crucial need to educate ***health***-care providers exists so that they can effectively provide information and appropriate counselling to patients ***using*** cannabis. Furthermore, rational developmental screening strategies for exposed ***offspring*** are needed, as well as personalized therapeutic strategies, including cognitive behavioural therapy and targeted behaviour interventions, to mitigate the potential adverse effects of early environmental risk factors.

Conclusions

Substance use has been rising, especially during the COVID-19 pandemic. The accumulating data supporting adverse effects of paternal ***substance use*** on ***male reproductive health*** and short-term and long-term ***offspring health outcomes*** are concerning. These findings are important as they support the notion that paternal — not only maternal — preconception exposure history can contribute substantially to successful and healthy conception, as well as to future ***offspring health***. Comprehensive counselling by ***health***-care providers, improved patient education and improved public ***health*** measures (especially targeting individuals interested in conceiving) focused on how paternal ***substance use*** can affect not only a patient's ***health*** but also the ***health*** of their future ***offspring*** are all needed.

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