

# Beyond body mass index: a synthesis of lifestyle factors that may influence in vitro fertilisation outcomes

## Abstract

There are several lifestyle factors that are thought to potentially impact in vitro fertilisation outcomes, including body mass index, smoking, alcohol consumption, caffeine, dietary patterns and physical activity. Eligibility criteria for in vitro fertilisation in England often require individuals to be non-smokers, drug free and have a body mass index  $<30\text{kg}/\text{m}^2$ . Some researchers have questioned the scientific and ethical basis for the use of body mass index thresholds in fertility treatment, citing evidence that other factors may have a greater effect on the chance of success of in vitro fertilisation. This article aims to briefly synthesise the current evidence on how other factors such as smoking, alcohol, recreational drugs, smoking, caffeine, dietary patterns and physical activity may impact in vitro fertilisation outcomes.

## Keywords

Assisted reproductive technology | Body mass index |  
In vitro fertilisation | Obesity | Pregnancy rate

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Body mass index is used globally to determine access to fertility treatment, including in vitro fertilisation, with different countries imposing diverse limits (De Wert et al, 2014; Tremellen and Savulescu, 2016; Koning et al, 2017). Guidance in the UK imposes an in vitro fertilisation body mass index threshold of  $30\text{kg}/\text{m}^2$ , with those with obesity advised to lose weight in order to restore ovulation, increase their response to ovulation induction agents and improve pregnancy outcomes (Emokpae and Brown, 2021; NHS, 2022a, b; 2023). A systematic review suggested that women with a body mass index  $>30\text{kg}/\text{m}^2$  (classified as obese) have a clinical and statistically significant decreased probability of live birth following in vitro fertilisation, compared with women of healthy weight (body mass index:  $18.5\text{--}24.9\text{kg}/\text{m}^2$ ) (Sermondade et al, 2019). However, some researchers have questioned the scientific and ethical basis for the use of body mass index thresholds in fertility treatment (Koning et al, 2017; Tremellen et al, 2017), citing evidence that other factors may have a greater effect on the chance of success (Sneed et al, 2008; Koning et al, 2017).

Beyond body mass index, a number of other lifestyle factors are thought to potentially impact in vitro fertilisation outcomes, including smoking, alcohol consumption, caffeine, dietary patterns and exercise (Hornstein, 2016). Access criteria among most NHS policies for assisted conception stipulate the following lifestyle factors must be met to access NHS-funded in vitro fertilisation (NHS, 2022a, b; 2023):

- Female body mass index:  $19\text{--}30\text{kg}/\text{m}^2$  before treatment can commence
- Both partners must be non-smoking and not using any product containing nicotine to access any fertility treatment and must continue to be non-smoking throughout treatment
- Couples should give assurances that their alcohol intake is within Department of Health and Social Care (2021) guidelines and that they are not using recreational drugs. Any evidence to the contrary will result in termination of treatment.

Although not included in UK access criteria, guidance on excess caffeine consumption is included in some policy documents for in vitro fertilisation (NHS, 2022a; 2023). In most criteria, factors such as physical activity and dietary patterns are seldom mentioned, and only referred to for specific populations (eg women with hypothalamic pituitary failure, advising them to moderate their exercise levels if currently undertaking high levels of exercise) (NHS, 2023). This suggests that while some criteria may be evidence based, policy documents may not be considering the wide range of factors that could reduce the probability of live birth following in vitro fertilisation (Sneed et al, 2008; Hornstein, 2016; Zhou et al, 2020; Rao et al, 2022; Sanderman et al, 2022).

This article aims to briefly review the current evidence on how alcohol, recreational drugs, smoking, caffeine, dietary patterns and physical activity may impact in vitro fertilisation outcomes. In addition to a focus on body mass index, it will consider whether a more holistic approach to assessing lifestyle may be warranted.

### Alcohol consumption

The impact of alcohol consumption on in vitro fertilisation outcomes has been assessed in several studies (Firms et al, 2015; Chandravati and Tripathi, 2021; Rao et al, 2022). Consensus among these studies suggests that maternal consumption of alcohol is negatively associated with outcomes related to successful pregnancy following in vitro fertilisation treatment (Chandravati and Tripathi, 2021; Rao et al, 2022).

A systematic review found a possible association with high alcohol levels and decreased success rates in in vitro fertilisation treatment (Rao et al, 2022). It highlighted that when women consumed more than 84g of alcohol per week, their chance of achieving pregnancy after treatment was reduced (compared to abstainers) (Rao et al, 2022). Consistent with previous evidence, the findings also showed that maternal alcohol consumption was negatively (but not significantly) associated with live birth rates. Furthermore, paternal alcohol consumption may also be negatively associated with their female partner's live birth after in vitro fertilisation. These findings concur with research that highlighted the importance of alcohol consumption as a key moderating factor for live birth following in vitro fertilisation (Ozbakir and Tulay, 2021).

To summarise the current evidence base, data show that reducing or abstaining from alcohol consumption prior to fertility treatment may improve in vitro fertilisation and pregnancy outcomes (Ozbakir and Tulay, 2021; Rao et al, 2022). This is consistent with the Royal College of Obstetricians and Gynecologists' (2015) recommendations, and the National Institute for Health

and Care Excellence (NICE, 2008), who highlighted the need to avoid drinking alcohol during pregnancy, particularly in the first 12 weeks. This evidence provides a rationale for NHS guidelines to consider alcohol as an important moderating factor when deciding whether to provide in vitro fertilisation treatment.

### Illicit drug use

Over the past two decades, several studies have evaluated the impact of illicit drug use on in vitro fertilisation and pregnancy outcomes (Klonoff-Cohen et al, 2006; Nassan et al, 2019; Har-Gil et al, 2021). However, there are some limitations regarding investigation of illicit drug use on reproductive function, because of the ethical concerns of administration and patient under-reporting (Anderson et al, 2010). That said, there is a consensus in the literature that illicit drug use (eg marijuana, cocaine, heroin, methamphetamines) during pregnancy should be avoided because of increased risk of adverse pregnancy outcomes (Cressman et al, 2014; Wright et al, 2015; Forray, 2016).

Marijuana has been identified as a commonly used illicit substance during pregnancy (Foeller and Lyell, 2017). Marijuana use during pregnancy is a concern, given that active chemicals of the drug readily cross the placenta, affecting the fetal brain (Thompson et al, 2019). Furthermore, marijuana use can impact fertility, pregnancy and fetal development by altering reproductive signalling and hormones (Battista et al, 2008). Exposure to the drug during pregnancy has been associated with significantly lower birth weight, prematurity, small for gestational age and congenital abnormalities compared non-users (Sherwood et al, 1999; Park et al, 2004; Baía and Domingues, 2022). Additionally, marijuana use during the first and second trimester has been linked to admission to neonatal intensive care, and negative impacts on fetal and adolescent brain growth (Hayatbakhsh et al, 2012; Metz and Borgelt, 2018). For women seeking in vitro fertilisation, marijuana use is likely to reduce the chance of success, given that regular use increases the risk of primary infertility when compared with non-users (Mueller et al, 1990). In addition, studies show users of marijuana have significantly less embryo transfer and fewer oocytes retrieved, which negatively impacts the chances of in vitro fertilisation success (Klonoff-Cohen et al, 2006).

Cocaine, heroin and methamphetamine use have also been associated with negative pregnancy and fertility outcomes, including infertility, placental abruption, low birth weight, preterm delivery and neonatal mortality (Addis et al, 2001; Gouin et al, 2011; Brecht and Herbeck, 2014; Cressman et al, 2014; Forray, 2016; Foeller and Lyell, 2017). However, the extent of these associations is largely unknown because of a dearth of high-quality evidence (Forray, 2016). Some research suggests that the

risk of infertility is substantially increased when women regularly use cocaine (from tubal abnormality) (Metz and Borgelt, 2018). Maternal cocaine abuse has also been associated with premature rupture of the female membrane, which can increase the risk of infant death (Addis et al, 2001; Gouin et al, 2011; Mbah et al, 2012). Similarly, methamphetamine abuse during pregnancy has been associated with premature rupture, preterm delivery and lower birth weight (Angelo et al, 2008). Reductions in birth weight have also been associated with maternal heroin use (Hulse et al, 1998). There is a consensus in the literature that advocates for a complete abstinence of these drugs prior to conception and during pregnancy (Richardson et al, 1993; Addis et al, 2001; Forray, 2016).

With the likelihood that illicit drug use negatively impacts the success of in vitro fertilisation and increases the risk of primary infertility, there is a modest evidence base to consider drug use to be an important moderating factor when making a clinical decision relating to assisted conception. That said, further high-quality research is needed to strengthen the current evidence for the benefit of practice and policy.

### Diet intake and eating behaviour

Dietary intake may impact in vitro fertilisation success rates by influencing various aspects of female fertility (Hornstein, 2016; Sanderman et al, 2022). Studies have identified several potential pathways of effect, including changes in hormone levels, ovarian insufficiency, diminished ovarian reserve and embryonic development (Sanderman et al, 2022). Evidence has suggested that two dietary factors, excess fat and dairy intake, are associated with longer time to pregnancy and an increased risk of reproductive disorders (ie anovulatory infertility, endometriosis and uterine leiomyomata) (Wise et al, 2018; Willis et al, 2020; Sanderman et al, 2022). Specifically, findings showed that trans fatty acid intake is associated with reduced conception rate (Wise et al, 2017; 2018). Despite these findings, further research is needed to explore the associations between female dietary factors, infertility and pregnancy outcomes, as recent findings have produced largely equivocal results (Sanderman et al, 2022).

Studies have shown that a Mediterranean diet, which is rich in vegetables, fruits, whole grains, fish and unsaturated fats, may improve in vitro fertilisation outcomes for women under 35 years old who are not overweight or obese (Vujkovic et al, 2010; Karayiannis et al, 2017). This diet may reduce inflammation, and improve hormonal balance and egg quality (Vujkovic et al, 2010; Karayiannis et al, 2017). However, some studies have reported inconsistent or null associations between specific dietary patterns and in vitro fertilisation outcomes (eg Mediterranean diet inclusive of alcohol consumption)

(Braga et al, 2015; Gaskins et al, 2018; 2019). Differences in study design, population characteristics, dietary assessment methods, in vitro fertilisation protocols and outcome definitions may explain these discrepancies (Gaskins et al, 2019).

A systematic review by Muffone et al (2022) examined 11 cohort studies and found a positive association between adherence to a Mediterranean diet and enhanced fertility outcomes (such as increased live births, pregnancy rates, and improved sperm concentration and count). However, the strength of evidence was such that implications cannot be made to practice recommending high adherence to a Mediterranean diet as a clinical intervention for improving fertility outcomes. A further systematic review by Kellow et al (2022) suggested that adherence to a Mediterranean diet was linked to increases in live birth rate. Similarly, Sanderman et al (2022) found that higher adherence to the Mediterranean diet was linked to pregnancy and live birth following in vitro fertilisation treatment. With this evidence, there is a rationale to suggest that a Mediterranean diet (focused on reduced trans fatty acid intake) could be deemed an important factor for clinicians to consider when providing guidance on in vitro fertilisation treatment.

### Caffeine

While the evidence on caffeine's impact on in vitro fertilisation fertility is inconsistent and limited, some studies have suggested that high caffeine intake may delay conception, reduce implantation rates and alter ovarian function, endometrial receptivity or embryo quality (Cao et al, 2016; Gaskins et al, 2018). However, other studies have found no or even a positive association between caffeine consumption and in vitro fertilisation success (Klonoff-Cohen and Natarajan, 2004; Ramlau-Hansen et al, 2007). These discrepancies are likely the result of differences in study design, population characteristics, caffeine sources, dose assessment, in vitro fertilisation protocols and outcome definitions (Gaskins et al, 2018). As a consequence, further research is needed to establish causal links between caffeine intake and in vitro fertilisation fertility.

For women undergoing in vitro fertilisation, moderate caffeine intake from natural sources, such as coffee or tea, may be safe, while high caffeine consumption may increase the risk of infertility and reduce the rate of adverse pregnancy outcomes (Rao et al, 2022). Evidence from a systematic review found no significant association between caffeine intake and in vitro fertilisation/intracytoplasmic sperm injection outcomes (Rao et al, 2022). However, a possible threshold effect at 200 mg/day was observed for clinical pregnancy rate. Additional findings also suggested that

caffeine intake from coffee or tea was not associated with in vitro fertilisation outcomes (Rao et al, 2022). Consistent with this, Lyngsø et al (2017) found that moderate caffeine consumption (<300 mg/day) did not affect fecundity, fertility, pregnancy rate or live birth rate. However, high consumption (>300 mg/day) reduced fecundity and pregnancy rate (Lyngsø et al, 2017). From this evidence, there may be a rationale to suggest in NHS assisted conception policies that women undergoing in vitro fertilisation limit their caffeine intake to below 200 mg per day (Lyngsø et al, 2017). Access criteria for NHS provided in vitro fertilisation may not yet include caffeine because of the limited strength and quality of evidence.

### Physical activity

Exercise has been shown to have numerous positive effects on both physical and mental health (Mikkelsen et al, 2017; Miko et al, 2020; Patten et al, 2021). It can help reduce stress (Hamer et al, 2006; Churchill et al, 2022), increase life expectancy (Rueggsegger and Booth, 2018), prevent chronic conditions (Warburton and Bredin, 2017) and improve general health (Wang and Ashokan, 2021). In relation to pregnancy, adults receiving physical activity interventions may increase the likelihood of conception and live birth compared to usual care (Mena et al, 2019). A systematic review corroborated these findings, indicating that physical activity can help lower the risk of infertility in healthy individuals (Xie et al, 2022). Moreover, high- and moderate-intensity exercise may be more effective in reducing the risk of infertility than low-intensity exercise (Xie et al, 2022). The World Health Organization recommends that physical activity is continued during pregnancy and postpartum (Bull et al, 2020). Furthermore, wherever possible during pregnancy, sedentary time should be replaced with any intensity of physical activity (Bull et al, 2020).

The body of research into the effects of physical activity on in vitro fertilisation treatment has been growing steadily (Rao et al, 2018). There is a consensus among studies that suggests that women who are physically active prior to undergoing in vitro fertilisation have a higher chance of clinical pregnancy compared to their non-active counterparts (Rao et al, 2018; Mena et al, 2019). Furthermore, exercise may also increase the chance of live birth (Rao et al, 2018). This is supported by more recent studies in this field, which have come to similar conclusions (Söritsa et al, 2020). However, the effects of physical activity during treatment are less certain (Söritsa et al, 2020; Läänelaid et al, 2021). From this evidence, NHS assisted conception policies should consider the inclusion of physical activity, given that it can increase the success rates of in vitro fertilisation and live birth.

### Smoking

Smoking is a harmful habit that has serious consequences for the general health of individuals (Adams, 2022). It has been linked to a variety of diseases, such as cancer (Newcomb and Carbone, 1992; Weber et al, 2021) and heart disease (Chen and Boreham, 2002; Kondo et al, 2019), and is a major risk factor for infertility (Penzias et al, 2018; Hernáez et al, 2022). In relation to pregnancy outcomes, smoking has been associated with an elevated probability of miscarriage, with an estimated relative risk increasing by 1% for every cigarette smoked daily (Pineles et al, 2014). Even when exposed to secondhand smoke, the impact can result in a substantially increased risk of miscarriage, which has an impact on guidance for couples (Pineles et al, 2014). Smoking has also been linked to earlier onset of menopause and infertility (Oboni et al, 2016; Zhu et al, 2018).

Studies have demonstrated that smoking may affect in vitro fertilisation treatment (Budani and Tiboni, 2017), as it has been associated with impaired ovarian response, fertilisation rate, implantation rates and the probability of achieving pregnancy (Budani and Tiboni, 2017). In more broad studies of the effect of smoking on assistive reproductive interventions, it has been shown to be associated with cycle cancellation with no embryo transfer, and cancellations before fresh oocyte retrieval or frozen embryo transfer (Rockhill et al, 2019), as well as affecting the mother's potential to conceive (Klonoff-Cohen et al, 2001). Smoking can also have a negative effect on a male's sperm quality (Sharma et al, 2016), where it can negatively affect sperm count, motility and morphology (Sharma et al, 2016). Modest evidence suggests that smoking habits not only during conception but also historically may negatively impact the success of in vitro fertilisation (even when smoking cessation has occurred) (Klonoff-Cohen et al, 2001).

Smoking during pregnancy can also have a negative effect on development (Abraham et al, 2017), and has been associated with decreased second and third trimester head size, femur length and estimated fetal weight (Abraham et al, 2017). It can also lead to increased odds of cleft lip and/or palate (Fell et al, 2022), cardiovascular/heart defects, musculoskeletal defects, limb reduction defects, missing/extra digits, clubfoot, craniosynostosis, gastrointestinal defects, gastroschisis, anal atresia, hernia and undescended testes (Hackshaw et al, 2011). Therefore, it is important to include smoking as a criteria for assisted conception access, as smoking history, current habits and potential future habits could likely impact success.

### Discussion

In recent years, NHS (2023) services have placed a strong emphasis on criteria that mandate women have



a body mass index  $<30\text{kg/m}^2$  to be eligible for in vitro fertilisation. The criteria also stipulate that a woman be non-smoking, have an alcohol intake within national guidelines and do not use illicit drugs. However, these guidelines place little emphasis on factors such as dietary habits, activity levels and caffeine intake, which arguably (together), may play an equal or greater role in improving the success of in vitro fertilisation and pregnancy outcomes (NHS 2022a, b; 2023).

Although heightened body mass index has been identified as a risk factor to fertility and newborn health, alcohol consumption, dietary intake and physical activity may be equally as important when trying to improve in vitro fertilisation outcomes (Klonoff-Cohen et al, 2001; Rittenberg et al, 2011; Gormack et al, 2015; Hornstein, 2016; Sermondade et al, 2019, Läänelaid et al, 2021). The evidence presented in this article provides a rationale for NHS services for assisted conception to adopt more robust criteria on dietary intake, alcohol consumption and physical activity. One method to achieve this could be the introduction of screening tools into assisted conception services which could support clinicians to identify patient dietary intake (including alcohol consumption) and physical activity levels (Santini et al, 2017; Deepak Kumar et al, 2023). The screening tool data could be used to review patient eligibility for in vitro fertilisation and identify any future intervention needs, with the intention to improve in vitro fertilisation outcomes.

Holistic approaches have been reported to improve in vitro fertilisation success (Chan et al, 2005; Kermack et al, 2014; Deepak Kumar et al, 2023). One protocol shown to be effective for adults undergoing assisted conception, is a holistic approach called FAST (fertility assessment and advice targeting lifestyle choices and behaviours) (Homan et al, 2012). This approach uses approximately five questionnaires to screen for dietary intake, activity levels, psychological distress, general health and drug use (including alcohol consumption) (Homan et al, 2012). It assesses all factors and develops individual lifestyle practice interventions, which often include motivational interviewing and telephone follow up, to support healthy lifestyle change, increasing the success of in vitro fertilisation (Homan et al, 2012).

The FAST approach is inclusive of weight management and weight reduction as a component, but helps to reduce weight stigma by shifting the focus towards a holistic approach to assisted conception (Hill et al, 2020). With a similar approach, NHS trusts could begin to develop guidelines representing a wider range of factors for improving in vitro fertilisation and pregnancy outcomes (Homan et al, 2012). New guidelines considering a holistic approach would move away from a narrow focus on a small number of factors, towards an

approach that reflects a more comprehensive scope of the current evidence.

## Conclusions

Although several lifestyle factors have been extensively explored in relation to in vitro fertilisation, some require further investigation. This article highlights that the evidence related to caffeine and illicit drug use (as risk factors to fertility and in vitro fertilisation success) is limited because of a dearth of high-quality research. Consequently, further research is needed to strengthen associations between caffeine, illicit drug use and in vitro fertilisation outcomes (and pregnancy outcomes). Policy makers should be cautious to mandate criteria related to these factors, particularly caffeine intake (for patients seeking access to NHS provided in vitro fertilisation), given the level of uncertainty surrounding the quality and strength of evidence. **BJM**

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## Key points

- High levels of alcohol consumption may decrease success rates for in vitro fertilisation treatment.
- There is no evidence of the effect of caffeine intake (>200mg per day) on in vitro fertilisation outcomes.
- Physically active women undergoing in vitro fertilisation have a higher chance of pregnancy and live birth compared to their non-active counterparts.
- Smoking is associated with fertilisation rate, and the reduced probability of achieving pregnancy.
- These factors may be at least as important to consider as body mass index for women looking to undergo in vitro fertilisation.

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## CPD reflective questions

- What are the strengths and limitations of the evidence to support the influence of various lifestyle factors on in vitro fertilisation and pregnancy outcomes?
- What are the limitations of body mass index as an eligibility threshold for in vitro fertilisation treatment?
- What other factors might be important to consider when developing guidance on assisted conception?

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