The impact of maternal lifestyle factors on periconception outcomes: a systematic review of observational studies

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Abstract

Main risk factors for important reproductive health issues such as subfertility and perinatal mortality largely originate in the periconception period. To evaluate associations between modifiable maternal lifestyle factors and periconception outcomes, we conducted a systematic search for relevant studies published from 1990 to February 2017 on Embase, Medline, PubMed, Web of Science, Cochrane database, PubMed, and Google Scholar. The initial search identified 6166 articles out of which 49 studies were eligible for inclusion.

Fecundity (the capacity to have a live birth) showed significant inverse associations with smoking, alcohol use and poor diet. Studies regarding time to pregnancy showed a decline in fecundability ratios (the monthly conception rate among exposed relative to unexposed couples) with increasing body mass index (BMI). Furthermore, risk of first-trimester miscarriage was found to be increased in smokers, when consuming alcohol and caffeine, and with increasing BMI. Vitamin supplement use showed a decrease in this risk.

This review demonstrates that maternal modifiable lifestyle factors have impact on periconception outcomes. If couples planning a pregnancy are more aware and supported to adopt healthy lifestyles during the periconceptional ‘window of opportunity’, short-term reproductive health as well as health in later life and even of future generations can be further improved.

Key Message

In this systematic review of observational studies, modifiable maternal lifestyle factors were found to influence several periconception outcomes. This data further support the importance of adopting healthy lifestyles of couples planning a pregnancy to improve reproductive health.

Keywords

Behavior, folic acid, body mass index, time to pregnancy, fecundity, miscarriage

Introduction

Ravelli *et al.* (1976) were one of the first to show increased rates of obesity as a composite determinant of poor lifestyles, in individuals who had been exposed to famine in utero. The link between early-life environment and adult disease was subsequently investigated in women exposed to famine in the Dutch hunger winter during the last winter of the Second World War, showing that offspring exposed to starvation in utero indeed had an increased risk of metabolic and cardiovascular diseases in adulthood (Stein 1975, Painter *et al.* 2005). In the 1980s, this concept was developed by David Barker, who reported for the first time a negative correlation between low birth weight and the rate of death from ischemic heart disease (Barker and Osmond 1986, Barker *et al.* 1989). He also hypothesized that low birth weight in offspring, as a proxy for poor prenatal maternal nutrition, not only increases the risk of coronary heart disease in adulthood, but also of other non-communicable diseases (NCDs), such as obesity and certain cancers (Barker and Osmond 1986, Barker *et al.* 1989, Barker *et al.* 1993). To explain these findings, it was suggested that, due to plasticity, fetuses can adapt to the environment they expect to enter into once outside the womb. This has been the basis for the hypothesis of the Developmental Origins of Health and Disease (DOHaD) (Barker 2004).

The DOHaD paradigm focusses mainly on exposures during pregnancy and outcomes at birth and in later life. However, many adverse pregnancy outcomes, such as subfertility, congenital malformations, low birth weight and preterm birth, originate in the periconception period, a critical window which has been neglected in both research and patient care. Therefore, based on molecular biological processes and epigenetics, we have defined the periconception period as a time span of 14 weeks before to up to 10 weeks after conception (Steegers-Theunissen *et al.* 2013). During this critical period, fertilization, implantation, and development and growth of the embryo and placenta take place (Macklon *et al.* 2002, Steegers-Theunissen 2010). This window is therefore pivotal to human reproduction in general and pregnancy outcome in particular.

The periconception environment is determined by maternal pre-existing medical conditions and modifiable lifestyles, including smoking, diet and body mass index (BMI) (Steegers-Theunissen and Steegers 2015). The prevalence of poor lifestyle behaviors in the reproductive population is comparable to the prevalence in the general population (Hammiche *et al.* 2011). There is growing evidence about the impact of lifestyle factors on fertility in women of reproductive age (Bunting *et al.* 2013, Temel *et al.* 2014). Being obese or overweight before conception is thought to exert a negative influence on female fertility due to dysregulation of the hypothalamic-pituitary-ovarian axis leading to ovulatory dysfunction (Broughton and Moley 2017). Excessive gestational weight gain and obesity during pregnancy are key predictors of childhood obesity and of metabolic complications in adulthood (Gaskins *et al.* 2014a). Children of women who are overweight or obese from the beginning of pregnancy are also at increased risk of cognitive deficits, externalizing problems (particularly attention-deficit/hyperactivity disorder), and internalizing psychopathology in childhood and adolescence (Van Lieshout 2013). Besides BMI, smoking is another common lifestyle factor affecting both fecundity (Crawford *et al.* 2017) and embryonic growth during the first six months of life (de Brito *et al.* 2017). These data suggest an extension of the window of opportunity for prevention and intervention in to the earliest moments of life.

Before the advent of high-resolution ultrasound, and in particular of three-dimensional ultrasound, *in vivo* data on embryonic and placental development during the first trimester of pregnancy was limited. These non-invasive technique have now provided large databases on normal and abnormal feto-placental development, thus enabling a better understanding of the pathophysiology of the early embryonic development and its possible impact during pregnancy and after birth (Rousian *et al.* 2010, Rousian *et al.* 2011, van Uitert *et al.* 2013a). This has also stimulated periconceptional prospective research on the influence of maternal lifestyle factors on the risk of first trimester abnormal outcomes, mainly miscarriage, congenital malformations and embryonic growth (van Uitert *et al.* 2013b, Koning *et al.* 2016, Koning *et al.* 2017).

The awareness of the importance of the periconception period is rising, resulting in more published research on this topic. The aim of this review was to provide a systematic and detailed analysis of the literature on maternal lifestyle factors during the periconception period and their impact on fecundity and time to pregnancy, as preconception outcomes, and on miscarriage and embryonic growth as first-trimester pregnancy outcomes.

Materials and Methods

Systematic review information sources and search strategy

The literature review was conducted using the 'Meta-analysis of Observational Studies in Epidemiology (MOOSE)' guidelines (Stroup *et al.* 2000). Searches were carried out using the electronic databases Embase, Medline, PubMed, Web of Science, Google Scholar and Cochrane databases. The search protocol was designed a priori and registered with the PROSPERO registry (PROSPERO 2016: CRD42016046123). The search strategy consisted of MeSH terms and keywords for lifestyle exposures of interest, including diet, smoking, alcohol, folic acid / vitamin supplement use, physical activity, and obesity ***(Supplemental Table 1)***. These were combined using the Boolean operator 'or'.

Systematic review eligibility criteria and used definitions

The periconception outcomes, as defined in the International glossary on infertility and fertility care, 2017 (Zegers-Hochschild *et al.* 2017), were:

- Fertility: the capacity to establish a clinical pregnancy.
- Fecundity: the capacity to have a live birth.
- Fecundability: The probability of a pregnancy, during a single menstrual cycle in a woman with adequate exposure to sperm and no contraception, culminating in live birth. Frequently measured as the monthly probability.

- Fecundability ratio: the monthly conception rate among exposed relative to unexposed couples.
- Time to pregnancy (TTP): the time taken to establish a pregnancy, measured in months or in numbers of menstrual cycles.
- Miscarriage: spontaneous loss of a clinical pregnancy before 22 completed weeks of gestational age. In this review however, only first-trimester miscarriages (until the 12^{th} week of gestation) were taken into account.
- Embryonic growth: the process by which the embryo forms and develops. In this review only growth, measured by crown-rump length (CRL) was taken into account. For embryo development the Carnegie stages were used.
- Yolk sac: a membranous sac attached to the embryo, formed by cells of the hypoblast adjacent to the embryonic disk. In this review the size of the yolk sac was taken into account.

We found that the terms fertility, fecundity and fecundability were used interchangeably in the literature. We therefore included all terms in the literature search and excluded papers that only provided data on birth outcomes. We did not expect to find literature on congenital malformations and placental size in the first trimester, therefore we did not include those keywords in the literature search. The results of all the periconception outcome searches were combined with 'or'. The results of the separate lifestyle factors and periconception outcome searches were then combined with 'and'.

Inclusion and exclusion criteria

Observational studies of any design that investigated the relationship between maternal lifestyle factors and any of the periconception outcomes of interest were eligible for inclusion in the review. The periconception period was defined as the 14 weeks before and 10 weeks after conception (Steegers-Theunissen *et al.* 2013). Articles published between 1990 and February 2017 were included and our search was limited to articles published in English. We excluded animal studies and those focused on IVF/ICSI-treatment, male lifestyle factors, semen parameters, congenital anomalies or teratogenicity. Articles that only reported outcomes in the second or third trimester or later life, editorials and review articles were also excluded.

Full text review and data extraction

Title, abstracts and full-text articles were independently assessed for content, data extraction and analysis. References of included studies were also reviewed. ECO reviewed the titles and abstracts and selected papers for full-text review. Full-text review and data extraction was completed by ECO, JH and BG, with all papers reviewed by at least two people. Data were inputted into a template designed specifically for this review. Differences were resolved by discussion between these three authors. Data extracted included the location, year of publication, study design, setting, study population, sample size, exposures of interest, outcome data, exclusion criteria, statistical analysis, potential confounders, results, and conclusion.

Quality of study and risk of bias

The ErasmusAGE quality score for systematic reviews was used to assess the quality of studies included in our review (see ***Supplemental Table 2***). This tool is based on previously published scoring systems (National Collaborating Centre 2008, Carter *et al.* 2010) and is composed of five items covering study design, study size, method of measuring exposure and outcome, and analysis. The parameters for these items can be adapted, based on literature and discussion with experts, as relevant for each review. The parameters chosen for our review are shown in ***Supplemental Table 2***. Each item was allocated zero, one or two points giving a total score between zero and ten, with ten representing the highest quality.

Results

Results of search and description of studies

Figure 1 summarizes the process of literature identification and selection of studies. The initial search identified 10,696 records of which 4,530 were duplicates. Of the remaining 6,166 records, a total of 6,012 publications were excluded because they did not fulfil the selection criteria. The full text of 154 papers were read, 105 papers were excluded leaving 49 articles for analysis.

The characteristics of the included studies are shown in ***Table 1***. Thirty-five studies were identified as prospective, and six as retrospective cohort studies, and three and five studies as prospective and retrospective case-control studies, respectively. The search term yolk sac size yielded no results, therefore this parameter is not included in the review.

Fecundity

Nine studies reported associations between maternal lifestyle factors and fecundity (Laurent *et al.* 1992, Caan and C. P. Quesenberry 1998, Hakim *et al.* 1998, Jensen *et al.* 1998, Axmon *et al.* 2000, Toledo *et al.* 2011, Radin *et al.* 2014, Lopez-del Burgo *et al.* 2015, Cueto *et al.* 2016) *(Table 2).* The impact of smoking was evaluated in three studies, all showing poorer fecundability ratios with higher levels of smoking (Laurent *et al.* 1992, Axmon *et al.* 2000, Radin *et al.* 2014). The association between alcohol and fecundity was evaluated in three studies (Hakim *et al.* 1998, Jensen *et al.* 1998, Lopez-del Burgo *et al.* 2015) and showed lower conception rates with the consumption of alcohol. There was no significant relationship between caffeine consumption and conception rates in the two studies investigating this outcome (Caan and C. P. Quesenberry 1998, Hakim *et al.* 1998). The association of diet was evaluated in two studies (Axmon *et al.* 2000, Toledo *et al.* 2011). Toledo *et al*. (2011) found that stronger adherence to the Mediterranean dietary pattern was associated with significantly lower odds of consulting a physician because of failure to conceive. The possible negative association of consuming fish from the Baltic sea contaminated with persistent organochlorine compounds was evaluated by Axmon *et al.* (2000). This study found a significantly lower pregnancy success rate ratio in women living in the east coast of Sweden, where higher blood levels of persistent organochlorine compounds have been found, compared to women living in west coast. Folic acid and multivitamin supplement use were both found to be associated with increased fecundity (Cueto *et al.* 2016).

Time to pregnancy

The association between maternal lifestyle factors and time to pregnancy was evaluated in nineteen studies (Florack *et al.* 1994, Bolúmar *et al.* 1997, Hull *et al.* 2000, Juhl *et al.* 2001, Juhl *et al.* 2003, Arakawa *et al.* 2006, Axmon *et al.* 2006, Law *et al.* 2007, Ramlau-Hansen *et al.* 2007, Wise *et al.* 2010, Hatch *et al.* 2012, Mutsaerts *et al.* 2012, Wise *et al.* 2012, Wise *et al.* 2013, McKinnon *et al.* 2016, Mikkelsen *et al.* 2016, Sapra *et al.* 2016, Somigliana *et al.* 2016, Wesselink *et al.* 2016) *(Table 3)*. Six studies evaluated the impact of smoking on time to pregnancy (Florack *et al.* 1994, Hull *et al.* 2000, Axmon *et al.* 2006, Law *et al.* 2007, Mutsaerts *et al.* 2012, Sapra *et al.* 2016), all showing a prolonged time to pregnancy among smokers.

The possible association of alcohol consumption and time to pregnancy was also reported in six studies (Florack *et al.* 1994, Juhl *et al.* 2001, Juhl *et al.* 2003, Axmon *et al.* 2006, Mutsaerts *et al.* 2012, Mikkelsen *et al.* 2016), but showed inconsistent results. Mutsaerts *et al.* (2012) and Axmon *et al.* (2006) reported that women consuming >7 units of alcohol per week have a significantly longer time to pregnancy compared to women consuming less units per week whereas Juhl *et al*. (2001, 2003), reported a slightly shorter time to pregnancy for women consuming alcohol weekly compared to drinking no alcohol.

The association of consumption of caffeine and time to pregnancy was addressed in four studies (Florack *et al.* 1994, Bolúmar *et al.* 1997, Hatch *et al.* 2012, Wesselink *et al.* 2016). Significant increases in time to pregnancy were found for those women drinking $\geq$501 mg caffeine per day (Bolúmar *et al.* 1997). By contrast, Florack *et al.* (1994) showed a significant decrease when drinking 3-7 cups of caffeine drinks per day compared to drinking <3 cups.

The association of diet and vitamin supplement use was evaluated in four studies; however, none of the results were statistically significant (Arakawa *et al.* 2006, Axmon *et al.* 2006, Mutsaerts *et al.* 2012, Somigliana *et al.* 2016). Overall, there was a suggestion of shorter time to pregnancy when using vitamin supplements. By contrast, vitamin D deficiency does not seem to prolong the time to pregnancy.

Six studies reported on the association of BMI and time to pregnancy, showing consistently prolonged time to pregnancy in overweight or obese women (Law *et al.* 2007, Ramlau-Hansen *et al.* 2007, Wise *et al.* 2010, Mutsaerts *et al.* 2012, Wise *et al.* 2013, McKinnon *et al.* 2016). The association of physical activity was evaluated in three studies (Mutsaerts *et al.* 2012, Wise *et al.* 2012, McKinnon *et al.* 2016). In one study, vigorous physical activity was found to be associated with a prolonged time to pregnancy, in all other studies no association with time to pregnancy was found.

Miscarriage

Fourteen studies evaluated the association between maternal lifestyle factors and first trimester miscarriage (Parazzini *et al.* 1991, Windham *et al.* 1997, Cnattingius *et al.* 2000, Kesmodel *et al.* 2002, Ronnenberg *et al.* 2002, Strandberg-Larsen *et al.* 2008, Feodor Nilsson *et al.* 2014, Gaskins *et al.* 2014b, Hahn *et al.* 2014, Xu *et al.* 2014, Andersen *et al.* 2015, Hahn *et al.* 2015, Gaskins *et al.* 2016, Zhou *et al.* 2016) *(Table 4)*. The impact of smoking was evaluated in three studies (Parazzini *et al.* 1991, Cnattingius *et al.* 2000, Xu *et al.* 2014) all showing a statistically significant increase in risk of miscarriage in smokers.

The seven studies reporting on the association between maternal alcohol consumption and miscarriage showed inconsistent results (Parazzini *et al.* 1991, Windham *et al.* 1997, Kesmodel *et al.* 2002, Strandberg-Larsen *et al.* 2008, Feodor Nilsson *et al.* 2014, Xu *et al.* 2014, Gaskins *et al.* 2016). The study with the highest quality reported no association between binge drinking in the first 12 weeks of pregnancy and the risk of spontaneous miscarriage (Strandberg-Larsen *et al.* 2008). This finding is supported by a hospital-based case-control study among Chinese women (Xu *et al.* 2014) and by Parazzini *et al.* (1991). In contrast, Windham *et al.* (1997) found a significant association for drinking >3 drinks per week and the risk of spontaneous miscarriage. A similar significant association was found by Kesmodel *et al.* (2002) and Feodor Nilsson *et al.* (2014).

The association between maternal caffeine consumption and miscarriage was evaluated by four studies consistently reporting inverse associations (Parazzini *et al.* 1991, Cnattingius *et al.* 2000, Feodor Nilsson *et al.* 2014, Hahn *et al.* 2015), though not all were statistically significant.

The impact of diet was evaluated in one study (Xu *et al.* 2014). The authors reported on the association of eating fresh fruit / vegetables on a daily basis compared with not eating fresh fruit / vegetables daily and the risk of miscarriage and they found no significant reduction in risk.

Four studies examined the association between folic acid and / or vitamin supplement use and miscarriage (Ronnenberg *et al.* 2002, Gaskins *et al.* 2014b, Xu *et al.* 2014, Andersen *et al.* 2015). Ronnenberg *et al.* (2002) showed a positive trend for an increase in the relative odds of spontaneous miscarriage as plasma folate concentration decreased, which was weakened after adjusting for confounders. A borderline significant increase in risk of miscarriage was seen for Vitamin B6 status (p for trend 0.06) but this also diminished after adjustment. However, comparing Vitamin B6 status between women whose pregnancies ended in a clinically recognized spontaneous miscarriage and in those with live births, showed a significantly ($p = 0.04$) lower mean pre-pregnancy plasma Vitamin B6 concentration in women with miscarriage. This finding is supported by a case-control study among Chinese women showing a significant reduction in risk for miscarriage among women using multivitamin supplements compared to those without using supplements (Xu *et al.* 2014).

The association between BMI, physical activity and miscarriage was evaluated in five studies (Parazzini *et al.* 1991, Feodor Nilsson *et al.* 2014, Hahn *et al.* 2014, Xu *et al.* 2014, Zhou *et al.* 2016). Higher BMI was shown to increase the risk of miscarriage, whereas moderate physical activity decreased the risk of miscarriage.

Embryonic growth

The association between maternal lifestyle factors and embryonic growth was reported in seven studies (Bakker *et al.* 2010, Mook-Kanamori *et al.* 2010, Prabhu *et al.* 2010, Bouwland-Both *et al.* 2013, van Uitert *et al.* 2013b, Van Uitert *et al.* 2014, Parisi *et al.* 2017) *(Table 5)*. Van Uitert *et al.* (2013b) showed that periconception smoking and periconception alcohol use were independently associated with reduced embryonic growth trajectories, measured by CRL. No associations were observed with BMI and timing of folic acid supplement use. Bakker *et al.* (2010) evaluated the impact of caffeine; intake of >6 cups per day was associated with a decline in CRL.

Evaluation of maternal red blood cell (RBC) folate levels in the first-trimester as a measure of nutrition and supplement use showed an optimum use curve, in which both lower and very high levels are associated with reduced embryonic growth (Van Uitert *et al.* 2014). Another study showed that smoking in combination with lack of use of folic acid supplements was associated with reduced embryonic size (Mook-Kanamori *et al.* 2010). This association between smoking and embryonic size was not found by Prabhu *et al*. (2010). Increasing adherence to an energy-rich dietary pattern is significantly associated with an increased CRL, as reported by Bouwland-Both *et al.* (2013).

Association between embryonic morphological development according to the Carnegie stages and maternal biomarkers of the one carbon metabolism was evaluated in the study by Parisi *et al.* (2017). Low vitamin B12 concentrations (-2SD, corresponding to 73.4 pmol/l) were associated with a 1.4-day delay in morphological development compared with high concentrations (+2SD, corresponding to 563.1 pmol/l) and high total homocysteine concentrations (+2SD, corresponding to 10.4 μmol/l) were associated with a 1.6-day delay in morphological development compared with low concentrations (-2SD, corresponding to 3.0 μmol/l).

Discussion

The results of our systematic review highlight the impact of maternal modifiable lifestyle factors including smoking, alcohol, caffeine, BMI, physical activity, diet and vitamin supplement use on fecundity and first trimester pregnancy outcomes.

Smoking

Cigarette smoke contains about 4,000 compounds belonging to a variety of chemical classes known to be toxic, including polycyclic aromatic hydrocarbons (PCH), nitrosamines, heavy metals, alkaloids, aromatic amines and so forth (Dechanet *et al.* 2011). The exact mechanism remains unclear but there is strong evidence that these constituents may affect the follicular microenvironment and alter hormone levels in the luteal phase (Homan *et al.* 2007). These alterations in hormone levels shorten the luteal phase, which results in a shorter time period of being able to become pregnant. Besides, decreased ovarian function and reduced ovarian reserve may also be possible consequences of smoking, as shown by lower Anti-Müllerian hormone (AMH) levels in smokers compared to non-smokers (Freour *et al.* 2008). Studies included in this review confirm these hypotheses by showing statistically significant negative associations of smoking especially with fecundity parameters (Laurent *et al.* 1992, Axmon *et al.* 2000, Radin *et al.* 2014), although a significantly prolonged time to pregnancy was found in only two out of six studies included in our review (Hull *et al.* 2000, Sapra *et al.* 2016).

Different compounds of cigarette smoke also impair endometrial maturation, implantation and early placentation (Dechanet *et al.* 2011). Nicotine is suspected to have an adverse effect on the decidualization process and cadmium, for example, is known to impair endometrial maturation. Moreover, several studies have indicated the negative influence of benzo(a)pyrene on angiogenesis by inhibiting endothelial cell proliferation (Dechanet *et al.* 2011). These mechanisms could explain the significant increase in the risk of first trimester miscarriage found in two large studies

(Cnattingius *et al.* 2000, Xu *et al.* 2014). These associations are dependent on the number of cigarettes smoked per day (Xu *et al.* 2014).

Alcohol

Although the evidence of associations between alcohol and reproductive performances are inconclusive, antenatal alcohol consumption is a known teratogen and several studies have reported an association with higher rates of early pregnancy failure and decreased fecundity (Homan *et al.* 2007, Lassi *et al.* 2014) as supported by two studies included in our review (Hakim *et al.* 1998, Jensen *et al.* 1998). One of the biological explanations for these periconception complications is that hormonal fluctuations, including alcohol-induced increase of aromatization of testosterone leading to increase in estrogen levels, reduces follicle stimulating hormone and suppresses both folliculogenesis and ovulation. Furthermore, alcohol may have a direct association on the maturation of the ovum, ovulation, blastocyst development and implantation (Gill 2000, Eggert *et al.* 2004). As a result of these maturations, time to pregnancy may be prolonged in women who consume alcohol. In two studies included in this review, time to pregnancy was found to be increased in women who consume alcohol (Florack *et al.* 1994, Mutsaerts *et al.* 2012). In contrast, two other studies showed a significantly shorter time to pregnancy (Juhl *et al.* 2001, Juhl *et al.* 2003). This contradiction may be due to differences in the populations studied, residual confounding, or the type of alcohol consumed. For example, Juhl *et al.* (2003) found a shorter time to pregnancy among wine drinkers than non-wine drinkers.

Alcohol readily crosses the placenta, which can result in irreversible damage to the placenta and organs of the developing embryo (Popova *et al.* 2017b). Besides adverse pregnancy outcomes such as stillbirth, preterm birth, intrauterine growth restriction and Fetal Alcohol Syndrome (FAS) Disorders, the risk of miscarriage in the first trimester is also increased. Three out of five reviewed studies indeed showed a significantly increased risk of miscarriage with higher levels of alcohol consumption (Windham *et al.* 1997, Kesmodel *et al.* 2002, Feodor Nilsson *et al.* 2014). One other study showed a significant association between a reduced embryonic growth and exposure to alcohol (van Uitert *et al.* 2013b). While many studies have demonstrated an association between alcohol and perinatal outcomes, the exact dose-response relationship and the differential effects of different types of alcohol, remain unknown and urgently require further research because of the large number of social alcohol consumers in the reproductive population.

Caffeine

It has been hypothesized that caffeine could affect female reproduction by increasing estrogen production and thereby affecting ovulation (Barbieri 2001) and corpus luteal function (Homan *et al.* 2007), resulting in an increase of the time to pregnancy (Sharma *et al.* 2013). Caffeine is known to pass the placental barrier and may lead to vasoconstriction of the uteroplacental circulation affecting embryonic and placental growth and development (Chen *et al.* 2016). Furthermore, during pregnancy the rate of caffeine metabolism decreases and the half-life doubles, leading to higher exposure of the embryo (Chen *et al.* 2016).

A possible explanation for the heterogeneous results of the time to pregnancy in studies included in the present review (Florack *et al.* 1994, Bolúmar *et al.* 1997, Hatch *et al.* 2012) may be that studies did not always control for residual confounding such as smoking, which, is known to be highly correlated with caffeine consumption. Moreover, the rate at which caffeine is cleared from the body, which varies between individuals and is affected by environmental factors such as smoking and diet (Peck *et al.* 2010), may influence the biologic dose and exposure interval. Although these hypothesized mechanisms may explain the association found between caffeine consumption and the increased risk of miscarriage (Cnattingius *et al.* 2000, Feodor Nilsson *et al.* 2014, Hahn *et al.* 2015), reverse causation must be taken into account. It is known that pregnancy symptoms such as nausea and vomiting, which may cause women to consume less caffeine, are more common in healthy pregnancies that result in live births than when a pregnancy ends in a miscarriage (Florack *et al.* 1994, Bolúmar *et al.* 1997, Peck *et al.* 2010, Hatch *et al.* 2012).

Diet

Diet is known to affect female fecundity (Homan *et al.* 2007, Sharma *et al.* 2013). In women of reproductive age, the adherence to the Mediterranean diet (characterized by high consumption of vegetables, fish, fruits, poultry, low-fat dairy products, and olive oil (Toledo *et al.* 2011)) reduces the risk of weight gain and insulin resistance (Vujkovic *et al.* 2010) and increases pregnancy rates by 40% in couples undergoing IVF/ICSI (Fontana and Della Torre 2016). Olive oil is an important source of linoleic acid, which is known to improve the reproductive process (Fontana and Della Torre 2016). The energy-rich dietary pattern described by Bouwland-Both *et al.* (2013) is significantly associated with embryonic growth, as measured by CRL. Its high methionine content could explain this association, as this is an essential substrate for the one-carbon pathway. Folate, which is a substrate, and other vitamins, such as B6 and B12 which are co-factors for this pathway, could also play a role in biological processes implicated in growth and programming, especially in the periconception period (Steegers-Theunissen *et al.* 2013). Furthermore, these vitamins are also associated with increased progesterone levels in luteal phase, improved menstrual cycle regularity and normalization of cycle length, which have all been associated with fecundity (Cueto *et al.* 2016). These findings could explain the positive association of concentration of vitamin B12 on embryonic development (Parisi *et al.* 2017) and on fecundity (Cueto *et al.* 2016).

The expected positive association of multivitamin supplement use and a reduced time to pregnancy was not seen in two studies (Axmon *et al.* 2006, Mutsaerts *et al.* 2012). A possible explanation is the low response rate in one study (Axmon *et al.* 2006) and the fact that the other study was designed for detection of risk factors for child obesity instead of fertility measures (Mutsaerts *et al.* 2012). Lower miscarriage rates were found with folic acid and/or multivitamin supplement use in all four studies included in this review (Ronnenberg *et al.* 2002, Gaskins *et al.* 2014b, Xu *et al.* 2014, Andersen *et al.* 2015). Vitamin D is also an important contributor to explain some of the underlying mechanism, as it regulates the synthesis of several hormones including estradiol, progesterone, and human chorionic gonadotrophin by the villous tissue. These hormones are all essential in maintaining the regulation of utero-placental blood flow, the simulation of neovascularization, and maternal immunotolerance to the embryonic allograft (Mousa *et al.* 2016).

BMI and physical activity

The detrimental effect of being overweight or obese on the time to pregnancy was observed in five out of six studies included in this review (Law *et al.* 2007, Ramlau-Hansen *et al.* 2007, Wise *et al.* 2010, Mutsaerts *et al.* 2012, Wise *et al.* 2013, McKinnon *et al.* 2016). This is in agreement with a dysregulation of the hypothalamic-pituitary-ovarian axis resulting in abnormalities in secretion of gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone leading to anovulation or decreased oocyte quality and decreased endometrial receptivity in obese women (Barbieri 2001, Talmor and Dunphy 2015). Associated hyperinsulinemia is also known to disturb the hypothalamic pituitary gonadal axis. The increased levels of insulin and leptin lead to insulin and leptin resistance which, in the end impairs ovarian function and fertility success rate (Fontana and Della Torre 2016). Besides the detrimental effects on fecundity, obesity is also known to increase the risk of miscarriage. It is thought that insulin resistance may be involved in several mechanisms such as diminished endometrial production of adhesion factors and a lower serum level of immunosuppressive proteins (Veleva *et al.* 2008). In this review, we found heterogeneous results for miscarriage in the four included studies (Parazzini *et al.* 1991, Hahn *et al.* 2014, Xu *et al.* 2014, Zhou *et al.* 2016). This can partly be explained by the fact that it is not always clear whether pre-pregnancy or present BMI was used. Furthermore, only one paper obtained direct measurements of weight and height instead of obtaining this information through self-reported questionnaires (Zhou *et al.* 2016).

A healthy amount of physical activity can be beneficial by leading to relaxation and reducing stress. Vigorous physical activity however, is known to be potentially harmful by exceeding the energy demand over dietary energy intake, thereby resulting in a negative energy balance which results in hypothalamic dysfunction eventually leading to menstrual abnormalities (Sharma *et al.*

2013). Subsequently, a prolonged time to pregnancy may occur. In this review we found inconclusive associations in studies reporting the association of physical exercise and time to pregnancy (Mutsaerts *et al.* 2012, Wise *et al.* 2012, McKinnon *et al.* 2016). Increasing levels of physical activity is known to be associated with an increased risk of miscarriage (Hegaard *et al.* 2016). The association between physical activity and risk of miscarriage was reported by two studies in this review. One study reported a decreased risk of miscarriage when performing regular exercise (Xu *et al.* 2014), whereas the other (Feodor Nilsson *et al.* 2014) showed a significant increase in the risk of miscarriage with ascending amounts of exercise in minutes per week. This may be due to the fact that the assessment of exercise and the types and intensity differed between the included studies. Furthermore, not every study has data on factors that may affect the level of exercise, for example, nausea in first trimester.

Strengths and limitations

The present work is the first to systematically review the currently available evidence on the impact of maternal lifestyle factors on periconception outcomes. Although paternal lifestyle factors are known to influence semen quality and quantity and thereby play an important role in the aetiology of periconception outcomes (Hammiche *et al.* 2012, Oostingh *et al.* 2017), literature on this matter is still scarce. Therefore, we chose to only include literature assessing maternal lifestyle factors.

Previous reviews have focused mainly on outcomes in the second or third trimester, birth outcomes or outcomes in childhood or adult life, thereby ignoring the importance of fecundity, miscarriages and adverse embryonic and placental growth in first trimester. In most of the human studies, data were obtained at birth or after the end of the first trimester of pregnancy, thereby missing the periconception period where most poor perinatal outcomes originate (Macklon *et al.* 2002, Steegers-Theunissen 2010). Other strengths of our study are that 35 out of 49 studies included in our review were large, with more than 1000 participants, increasing the power of the studies. Most studies focusing on the impact of periconceptional maternal lifestyle factors have only been performed in the subfertile population (Chavarro *et al.* 2007, Vujkovic *et al.* 2009, Vujkovic *et al.* 2010), whereas in this review studies in the IVF/ICSI-population were excluded making the results more applicable for the general population. Finally, most of the included studies were prospective studies, which reduced the chances of selection bias, recall bias and reverse causation. Nonetheless, prospective studies may be affected by selection bias because they are usually limited to couples planning a pregnancy and thus excluding the large group of couples with an unplanned pregnancy. The chance of inclusion bias, however, was reduced by including studies of countries from all around the world. The retrospective studies may be at higher risk of selection bias because most of these studies were limited to women who became pregnant, thus excluding less fertile or sterile women. Moreover, It is also known that highly educated people are more often wiling to complete questionnaires (Thiel 2014), giving rise to selection bias.

Despite our extensive literature search, the amount of evidence and its quality was relatively low. From the current literature, no definite conclusions on causal relations can be drawn. There is lack of uniformity in the application of terminology in this field with terms such as fertility, fecundity, fecundability often being used interchangeably and with variations in the definition of time to pregnancy. Observational studies on the impact of alcohol usage, caffeine and smoking are often based on self-reported information giving rise to recall and social desirability bias and are not always supported by biological data, such as cotinine levels for the cigarette exposure. There was also a possible bias of under-reporting negative issues such as smoking and alcohol use in couples trying to conceive, which should be taken into account. Finally, there was inconsistency in how exposures and outcomes were reported. For example, alcohol use was variously coded as grams of alcohol per day, drinks per week, units per week, number of days per week alcohol was consumed or frequency of binge drinking. The same is true for caffeine and smoking. Misclassification of gestational age can occur when using the first day of the last menstrual period due to variation in cycle length. Even when studies only included women with regular cycles of approximately 28 days, misclassification might still be an issue of concern since the postconceptional age is dependent on the timing of ovulation and implementation. Furthermore, miscarriage was often not divided into first- or second-trimester, instead, the whole period until a gestational age of 20 weeks is included. Within this context, we were unable to perform a meta-analysis.

Conclusion

This review shows that several modifiable maternal lifestyle factors are associated with fecundity and other periconception outcomes such as miscarriage, time to pregnancy and embryonic growth. Several studies have indicated that poor lifestyle factors are very common among women of childbearing age and thus remain of major concern (Inskip *et al.* 2009). The prevalence of smoking by women in reproductive age for example, is the same as for society in general (Oskarsdottir *et al.* 2017), even though it is well known that exposure in utero impairs pregnancy outcome and health in childhood and later life (Been *et al.* 2014). The same applies to the use of alcohol. Several studies have indicated that, despite public health efforts to increase awareness of the risks associated with drinking during pregnancy, worldwide approximately 10% of pregnancies are alcohol-exposed, and in the European region this is up to 25% (Popova *et al.* 2017a). This review makes clear that future research is needed to understand the associations between maternal lifestyle factors and periconception outcomes, and should in particular focus on unifying measurements of lifestyle factors and outcomes, thereby enabling researchers to collect data for a robust meta-analysis to calculate risk ratios. Furthermore, causal pathways should be investigated in more detail. Moreover, the data collected in this review suggest that the target window for the investigation of the DOHaD paradigm should be expanded to include the periconception period and support the concept of preconception care accessible to every woman and couple planning a pregnancy.

Overall, the data in the current review indicate that there is urgent need to implement more effective periconception preventative and surveillance strategies. We hope that our data will stimulate a general interest in developing and funding well-designed prospective periconception intervention studies, rather than observational studies, and contribute to a more general awareness in couples planning a pregnancy and the health care professionals supporting them to adopt healthy lifestyles during this critical window of opportunity. They should also be made aware that these adaptations would also reduce subfertility, perinatal mortality and morbidity and subsequent diseases in later life and next generations.

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Authors' roles

RST and EJ conceived and designed the study. EO performed an initial screening on title and abstract of all articles to exclude citations deemed irrelevant. EO, JH and BG independently evaluated all articles and abstracted data. EO, JH, MK, EJ, RST drafted the first version of the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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Conflict of interest

BG is an employee of 'SPD GmBH'. None of the other authors have any conflict of interest related to the discussed topic.

Table 1. *Main characteristics of 49 included studies*

Author	Year	Country	Study population	Study design	Sample size	Exposure(s)	Outcome(s)	Quality score
Andersen *et al.*	2015	Denmark	Odense child cohort, pregnant women January 2010 - December 2012.	Prospective cohort study	1683	Vitamin use	Miscarriage	5
Arakawa *et al.*	2006	Japan	Women delivering from January 2002 - march 2004 in two Japanese hospitals	Prospective cohort study	180	Diet	TTP	4
Axmon *et al.*	2000	Sweden	Fishermen's wives from Swedish east and west coast, born from 1945.	Retrospective cohort study	1335	Smoking, Diet	Fertility, TTP	5
Axmon *et al.*	2006	Sweden	random sample of women from the general Swedish-population, born from 1960 onwards.	Retrospective cohort study	1557	Smoking, alcohol, vitamin use, drug use	TTP	5
Bakker *et al.*	2010	The Netherlands	The Generation R study; Dutch women who were resident in the study area and who delivered between April 2002 and January 2006	Prospective cohort study	1310	Caffeine	Embryonic growth	6
Bolúmar *et al.*	1997	Spain	Random sample of women 25-44 years, five European countries (Denmark, Germany, Italy, Poland and Spain).	Retrospective cohort study	3092	Caffeine	TTP	5
Bouwland-Both *et al.*	2013	The Netherlands	The Generation R study; Dutch women who were resident in the study area and who delivered between April 2002 and January 2006	Prospective cohort study	847	Diet	Embryonic growth	5
Caan *et al.*	1998	USA	Volunteer members of the Kaiser Permanente Medical Program who were trying to conceive (for max 3 months before entering the study).	Prospective cohort study	187	Caffeine	Fecundity	4
Cnattingius *et al.*	2000	Sweden	Between 1996-1998, Uppsala Sweden, women with spontaneous abortion who presented at the department at 6-12 weeks and had a positive pregnancy test	Retrospective case-control study	1448	Smoking, caffeine	Miscarriage	6
Cueto *et al.*	2015	Denmark	The Danish pregnancy planning study (Snart Gravid)	Prospective cohort study	3895	Folic acid, vitamin use	Fecundity	5
Feodor Nilsson *et al.*	2014	Denmark	Danish national birth cohort. All pregnancies with info on risk factors for miscarriage.	Retrospective cohort study	88373	Alcohol, caffeine, physical activity	Miscarriage	6

Florack *et al.*	1994	The Netherlands	Between June 1987- Jan 1989, female workers 18-39 years, working in non-medical functions at Dutch Hospitals, planning pregnancy	Prospective cohort study	259	Smoking, alcohol, caffeine	TTP	5
Gaskins *et al.*	2014	USA	Female nurses 24-44 years in the Nurses' Health Study II. With no history of pregnancy loss in 1991 and reported at least one pregnancy during 1992-2009	Prospective cohort study	11072	Folic acid	Miscarriage	6
Gaskins *et al.*	2016	USA	Female nurses 24-44 years in the Nurses' Health Study II. With no history of pregnancy loss in 1991 and reported at least one pregnancy during 1992-2009	Prospective cohort study	27580	Alcohol	Miscarriage	5
Hahn *et al.*	2015	Denmark	Snart-Gravid study; Danish women 18-40 years, resident of Denmark, stable relation with male partner, not using fertility treatment, trying to become pregnant.	Prospective cohort study	5132	Caffeine	Miscarriage	6
Hahn *et al.*	2014	Denmark	Snart-Gravid study; Danish women 18-40 years, resident of Denmark, stable relation with male partner, not using fertility treatment, trying to become pregnant.	Prospective cohort study	5132	BMI	Miscarriage	6
Hakim *et al.*	1998	USA	women reproductive age, no contraceptive use, not sterilized.	Prospective cohort study	98	Alcohol, Caffeine	Fecundity	5
Hatch *et al.*	2012	Denmark	Danish, 18-40 years, male partner, trying to conceive <12 months	Prospective cohort study	3628	Caffeine	TTP	5
Hull *et al.*	2000	United Kingdom	Couples residence in the defined geographic area administered by the Avon Health Authority and if the expected date of birth was between April 1991 - December 1992	Prospective cohort study	12106	Smoking	TTP	6
Jensen *et al.*	1998	Denmark	Danish couples, 20-35 years, no children, trying to conceive for the first time	Prospective cohort study	423	Alcohol	Fecundity	4
Juhl *et al.*	2003	Denmark	Pregnant women within the first 24 weeks of pregnancy recruited to the Danish National Birth Cohort in 1997-2000.	Retrospective cohort study	29844	Alcohol	TTP	5
Juhl *et al.*	2001	Denmark	Pregnant women within the first 24 weeks of pregnancy recruited to the Danish National Birth Cohort in 1997-2000.	Retrospective cohort study	29844	Alcohol	TTP	5
Kesmodel *et al.*	2002	Denmark	women attending routine antenatal care at Aarhus University Hospital Denmark from 1989-1996	Prospective cohort study	18226	Alcohol	Miscarriage	5

Laurent *et al.*	1992	USA	20- 54 years old women who were randomly selected to serve as the control group of the Cancer and Steroid Hormone Study coordinated by the Reproductive Health Division of the Center for Chronic Disease Prevention and Health Promotion, Centers for Disease rol, USA	Prospective cohort study	2714	Smoking	Fertility	5
Law *et al.*	2007	USA	Pregnant women enrolled in the Collaborative Perinatal Project at 12 study centers across the United States	Prospective cohort study	7327	Smoking, BMI	TTP	5
Lopez-del Burgo *et al.*	2015	Spain	university graduates from Spain	Prospective case-control study	1372	Alcohol	Fertility	7
McKinnon *et al.*	2016	USA en Canada	women 21-45 years, not using contraception, no fertility treatment, stable relation man, planning a pregnancy, not pregnant. PRESTO study.	Prospective cohort study	1274	BMI, physical activity	TTP	6
Mikkelsen *et al.*	2016	Denmark	women 18-40 years, stable relationship male, trying to conceive, no fertility treatment. Snart Gravid.	Prospective cohort study	4210	Alcohol	TTP	6
Mook-Kanamori *et al.*	2010	The Netherlands	Generation R study, mothers enrolled 2001-20015	Prospective cohort study	1631	Smoking, alcohol, folic acid, BMI	Embryonic growth	8
Mutsaerts *et al.*	2011	The Netherlands	Pregnant women in Drenthe with the expected date of delivery between April 2006 and April 2007	Prospective cohort study	1924	Smoking, alcohol, vitamin use, BMI, physical activity	TTP	5
Parazzini *et al.*	1991	Italy	Jan 1987-1988, cases: women ≥2 unexplained miscarriages in first 3 months of gestation, without full-term pregnancies. Controls: women admitted for normal delivery.	Retrospective case-control study	270	smoking, alcohol, caffeine, BMI	Miscarriage	5
Parisi *et al.*	2017	The Netherlands	Predict study. 2010-2014 women with singleton pregnancies.	Prospective cohort study	234	Vitamin use	Embryonic growth	5
Prabhu *et al.*	2010	United Kingdom	Mothers attending a first trimester dating ultrasound scan	Prospective cohort study	903	Smoking	Embryonic growth	7

Radin *et al.*	2014	Denmark	female pregnancy planners aged 18–40 years	Prospective cohort study	3298	Smoking	Fecundity	3
Ramlau-Hansen *et al.*	2007	Denmark	Couples from Danish National Birth with pregnancy(ies) between 1996 -2002	Retrospective case-control study	47835	BMI	TTP	4
Ronnenberg *et al.*	2002	China	Female textile workers in Anqing, China	Prospective case-control study	458	Folic acid, vitamin use	Miscarriage	5
Sapra *et al.*	2016	USA	LIFE study 2005-2009. Couples discontinuing contraception for becoming pregnant or were off contraception for max 2 months. 18-40 years, cycle length 21-42 days, not received injectable contraception in the past year.	Prospective cohort study	501	Smoking	TTP	6
Somigliana *et al.*	2016	Italy	Pregnant women undergoing first trimester screening for aneuploidies. Cases: seeking pregnancy 12-24 months. Controls: age-matched conceiving in less than 1 year	Prospective case-control study	146	Diet	TTP	5
Strandberg-Larsen *et al.*	2008	Denmark	Danish national birth cohort, women enrolled between 1996 and 2002, interview done mid-pregnancy	Prospective cohort study	89201	Alcohol	Miscarriage	7
Toledo *et al.*	2011	Spain	Nested case control study selected from a prospective cohort of university graduates.	Retrospective case-control study	2154	Diet	Fertility	5
van Uitert *et al.*	2013	The Netherlands	Rotterdam Predict study, an ongoing prospective periconception cohort study that is part of the preconception and antenatal care at the outpatient clinics of the Erasmus MC, University Medical Center Rotterdam. All women who were at least 18 years old with ongoing intrauterine singleton pregnancies of 6–8 weeks of gestation were eligible for participation and recruited in 2009 and 2010. Spontaneously conceived, plus intrauterine insemination	Prospective cohort study	87	Smoking, alcohol, folic acid, BMI	Embryonic growth	6
van Uitert *et al.*	2014	The Netherlands	singleton pregnancies recruited in 2009-2010. Predict Study. 77 patients, 440 ultrasounds	Prospective cohort study	440	Folic acid	Embryonic growth	5
Wesselink *et al.*	2016	USA en Canada	women 21-45 years, not using contraception, no fertility treatment, stable relation man, planning a pregnancy, not pregnant. PRESTO study.	Prospective cohort study	1318	Caffeine	TTP	6

Windham *et al.*	1997	USA	Women were recruited during 1990-1991 from a large pre-paid health plan (Kaiser Permanente Medical Care Program) in three geographical areas in California, they were informed of the study when they called to make their first antenatal appointment.	Prospective cohort study	5307	Alcohol	Miscarriage	5
Wise *et al.*	2010	Denmark	Women were part of the the ‘‘Snart Gravid’’ study, an internet-based prospective cohort study of women planning a pregnancy in Denmark. Recruitment began in June 2007. Eligible women were aged 18–40, residents of Denmark, in a stable relationship with a male partner, and not receiving any type of fertility treatment.	Prospective cohort study	1410	BMI	TTP	5
Wise *et al.*	2012	Denmark	Women were part of the the ‘‘Snart Gravid’’ study, an internet-based prospective cohort study of women planning a pregnancy in Denmark. Recruitment began in June 2007. Eligible women were aged 18–40, residents of Denmark, in a stable relationship with a male partner, and not receiving any type of fertility treatment.	Prospective cohort study	3027	Physical activity	TTP	7
Wise *et al.*	2013	USA	Women were part of the Black Women's Health Survey, a prospective cohort study of 59 000 African-American women aged 21 to 69 at entry in 1995. This analysis is of the 2011 follow up, where 16462 responded	Prospective cohort study	2022	BMI	TTP	5
Xu *et al.*	2014	China	Cases - hospitalized in one of 3 hospitals in Zhengzhou City for an early miscarriage (<13 weeks) from Oct 2009-Dec 2012. 620 cases randomly selected from 3,277, 1,240 age matched controls, post 13 weeks, randomly selected from the same period from 21,491 outpatients attending routine prenatal care.	Retrospective case-control study	1860	Smoking, alcohol, diet, vitamin use, BMI, physical activity	Miscarriage	6
Zhou *et al.*	2016	China	2013-2014 in Anhui China. 18-40 years, residents of Anhui, married, not using fertility treatment, trying to become pregnant during the next six months.	Prospective cohort study	2940	BMI	Miscarriage	5

Note: TTP = Time to pregnancy. BMI = Body mass index.

Table 2. *Description and summary of data for 9 studies that investigated associations between lifestyle factors and fecundity.*

Author	Study design	Sample size	Exposure	Outcome description	Outcome definition	OR (95% CI)
Axmon *et al.* 2000	Retrospective cohort study	1335	Diet	consuming contaminated fish from Baltic sea	Success rate ratio (SuRR)	0.86 (0.75 ; 0.99)
			Smoking	smoking ≥10 cigarettes / day		0.68 (0.51 ; 0.91)
Caan *et al.* 1998	Prospective cohort study	187	Caffeine	Intake of caffeine >106.8 mg / day	Relative Odds of becoming pregnant	1.09 (0.63 ; 1.89)
Cueto *et al.* 2016	Prospective cohort study	3895	Folic acid	use of folic acid supplement in general	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	1.15 (1.06 ; 1.25)
				use of folic acid exclusively		1.15 (1.00 ; 1.31)
			Vitamin use	use of multivitamin supplements exclusively		1.20 (1.08 ; 1.32)
Hakim *et al.* 1998	Prospective cohort study	98	Alcohol	consuming < 12 grams of alcohol / week	Relative Odds of conception	0.43 (0.25 ; 0.76)
				consuming 13-90 grams of alcohol / week		0.40 (0.21 ; 0.77)
			Caffeine	Intake of caffeine ≥301 mg / day		0.83 (0.34 ; 2.01)
Jensen *et al.* 1998	Prospective cohort study	423	Alcohol	consuming 1-5 units of alcohol / week	Odds of conception	0.61 (0.40 ; 0.93)
				consuming 6-10 units of alcohol / week		0.55 (0.36 ; 0.85)
				consuming 11-15 units of alcohol / week		0.34 (0.22 ; 0.52)
Laurent *et al.* 1992	Prospective cohort study	2714	Smoking	smoking ≥20 cigarettes / day	Odds of primary infertility	1.36 (1.14 ; 1.61)
Lopez-del Burgo *et al.* 2015	Prospective case-control study	8749	Alcohol	consumption of alcohol ≥ 5 times / week	Odds ratio for presenting with difficulty getting pregnant	1.04 (0.72 ; 1.51)
Radin *et al.* 2014	Prospective cohort study	3298	Smoking	current regular smoker	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.89 (0.77 ; 1.03)
				smoking for ≥10 years		0.85 (0.72 ; 1.00)
Toledo *et al.* 2011	Retrospective case-control study	2154	Diet	high adherence to Mediterrean dietary pattern	Odds ratio for presenting with difficulty getting pregnant	0.56 (0.35 ; 0.90)

Table 3. *Description and summary of data for 19 studies that investigated associations between lifestyle factors and time to pregnancy.*

Author	Study design	Sample size	Exposure	Outcome description	Outcome definition	OR (95% CI)	Other
Arakawa *et al.* 2006	Prospective cohort study	180	Diet	Geometric means of mercury concentrations in hair			2.01 µg/g vs 1.97 µg/g, p-value NS
Axmon *et al.* 2006	Retrospective cohort study	1557	Alcohol	Consumption of alcohol	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.83 (0.72 ; 0.95)	
			Smoking	smoking cigarettes daily		0.93 (0.79 ; 1.08)	
			Vitamin use	use of vitamin supplements		1.04 (0.89 ; 1.22)	
Bolúmar *et al.* 1997	Retrospective cohort study	3092	Caffeine	none vs ≥5 cups / day none ≥501 mg /day	Waiting time to first pregnancy (ref category: 6,5 months)		8.2 months, p 0.003 8.9 months, p 0.001
Florack *et al.* 1994	Prospective cohort study	259	Alcohol	>10 units of alcohol / week	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	1.2 (0.7 ; 2.3)	
			Caffeine	3-7 cups of caffeine drinks / day vs < 3 cups		1.8 (1.1 ; 3.1)	
			Smoking	>10 cigarettes / day		0.8 (0.5 ; 1.3)	
Hatch *et al.* 2012	Prospective cohort study	3628	Caffeine	≥300 mg caffeine / day	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	1.04 (0.90 ; 1.21)	
Hull *et al.* 2000	Prospective cohort study	12106	Smoking	15-19 cigarettes daily, conceive within 6 months 15-19 cigarettes daily, conceive within 12 month	Odds ratio of taking ≥12 months to conceive	1.47 (1.15 ; 1.87) 1.99 (1.48 ; 2.69)	
Juhl *et al.* 2001	Retrospective cohort study	29844	Alcohol	7.5-14 units of alcohol / week, conceive after 5 months 7.5-14 units of alcohol / week, conceive after 12 months	Odds ratio for an increasing waiting time to pregnancy	0.84 (0.76 ; 0.93) 0.86 (0.76 ; 0.98)	
Juhl *et al.* 2003	Retrospective cohort study	29844	Alcohol	>7 units of wine / week	Odds ratio for an increasing waiting time to pregnancy	0.87 (0.78 ; 0.99)	

Law *et al.* 2007	Prospective cohort study	7327	BMI	BMI ≥30.0 kg/m^2	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.72 (0.63 ; 0.83)
			Smoking	Among smokers, BMI ≤18.5 kg/m^2 BMI 25.0-29.9 kg/m^2 BMI ≥30.0 kg/m^2		0.89 (0.78 ; 1.01) 0.97 (0.85 ; 1.11) 0.83 (0.68 ; 1.02)
McKinnon *et al.* 2016	Prospective cohort study	1274	BMI	BMI 40-44 kg/m^2 BMI ≥45 kg/m^2	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.61 (0.42 ; 0.88) 0.42 (0.23 ; 0.76)
			Physical activity	≥5 hrs / week vigorous activity		1.11 (0.96 ; 1.28)
Mikkelsen *et al.* 2016	Prospective cohort study	4210	Alcohol	≥14 units of alcohol / week	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.82 (0.60 ; 1.12)
Mutsaerts *et al.* 2011	Prospective cohort study	1924	Alcohol	>7 units of alcohol / week	Ratio of the 'hazard' of becoming pregnant	0.71 (0.53 ; 0.96)
			BMI	BMI ≥30 kg/m^2		0.87 (0.76 ; 1.01)
			Physical activity	≥4 times / week		1.04 (0.92 ; 1.18)
			Smoking	≥10 cigarettes / day		0.96 (0.84 ; 1.10)
			Vitamin use	use of vitamin supplements		0.59 (0.86 ; 1.05)
Ramlau-Hansen *et al.* 2007	Retrospective case-control study	47835	BMI	BMI 25.0-29.9 kg/m^2 BMI ≥30 kg/m^2	Odds ratio of taking >12 months to conceive	1.27 (1.18 ; 1.36) 1.78 (1.63 ; 1.95)
Sapra *et al.* 2016	Prospective cohort study	501	Smoking	use of cigarettes	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.53 (0.33 ; 0.85)
Somigliana *et al.* 2016	Prospective case-control study	146	Diet	Concentration of 25(OH)D <20 ng/ml	Odds ratio of longer time to pregnancy	0.84 (0.42 ; 1.66)
Wesselink *et al.* 2016	Prospective cohort study	1318	Caffeine	≥300 mg caffeine / day	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	1.15 (0.90 ; 1.48)
Wise *et al.* 2010	Prospective cohort study	1410	BMI	BMI 25-29 kg/m2 BMI 30-34 kg/m2 BMI ≥35 kg/m^2	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.72 (0.58 ; 0.90) 0.60 (0.42 ; 0.85) 0.48 (0.31 ; 0.74)

Wise *et al. 2*012	Prospective cohort study	3027	Physical activity	≥5 hrs / week vigorous activity ≥5 hrs / week moderate activity	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.68 (0.54 ; 0.85) 1.18 (0.98 ; 1.43)
Wise *et al.* 2013	Prospective cohort study	2022	BMI	BMI ≥35 kg/m^2	Fecundability ratio; the monthly conception rate among exposed relative to unexposed	0.73 (0.61 ; 0.87)

Note: BMI = body mass index

Table 4. *Description and summary of data for 14 studies that investigated associations between lifestyle factors and first-trimester miscarriage.*

Author	Study design	Sample size	Exposure	Outcome description	Outcome definition	OR (95% CI)
Andersen *et al.* 2015	Prospective cohort study	1683	Vitamin use	Concentration of 25(OH)D of <50 vs ≥ 50 nmol/L	Hazard ratio for miscarriage	2.50 (1.10 ; 5.69)
Cnattingius *et al.* 2000	Retrospective case-control study	1448	Caffeine	Among non-smokers; 100-299 mg of caffeine / day 300-499 mg of caffeine / day ≥500 mg of caffeine / day	Odds ratios for miscarriage	1.8 (1.2 ; 2.7) 2.7 (1.7 ; 4.5) 4.1 (2.1 ; 8.1)
			Smoking	Smokers compared to non-smokers		1.5 (1.1 ; 2.1)
Feodor Nilsson *et al.* 2014	Retrospective cohort study	88373	Alcohol	>4 alcoholic drinks per week	Hazard ratio for miscarriage	2.81 (2.25 ; 3.50)
			Caffeine	drinking 0,5 - 7,5 cups of coffee / day drinking >8 cups of coffee / day		1.28 (1.14 ; 1.42) 2.23 (1.79 ; 2.78)
			Physical activity	61-120 minutes / week regular physical activity 121-180 minutes / week 181-300 minutes / week >300 minutes / week		1.83 (1.57 ; 2.13) 2.06 (1.72 ; 2.47) 2.47 (2.07 ; 2.93) 3.29 (2.71 ; 3.99)
Gaskins *et al.* 2014	Prospective cohort study	11072	Folic acid	Folate supplement use ≥1000 mcg / day, fetal loss <8 wks Folate supplement use ≥1000 mcg / day, fetal loss 8-11 wks	Relative risk of miscarriage	0.79 (0.64 ; 0.97) 0.76 (0.63 ; 0.92)
Gaskins *et al.* 2016	Retrospective cohort study	27580	Alcohol	>10 grams of alcohol / day, miscarriage < 8 weeks >10 grams of alcohol / day, miscarriage 8-11 weeks	Relative risk of miscarriage	1.09 (0.92 ; 1.30) 1.02 (0.86 ; 1.22)
Hahn *et al.* 2014	Prospective cohort study	5132	BMI	BMI ≥ 30 kg/m^2	Hazard ratio for miscarriage	1.34 (1.01 ; 1.77)
Hahn *et al.* 2015	Prospective cohort study	5132	Caffeine	>300 mg caffeine per day (preconceptionally)	Hazard ratio for miscarriage	0.93 (0.72 ; 1.22)
Kesmodel *et al.* 2002	Prospective cohort study	18226	Alcohol	>5 alcoholic drinks per week	Hazard ratio for miscarriage	3.7 (2.0 ; 6.8)

Parazzini *et al.* 1991	Retrospective case-control study	270	Alcohol	Alcohol consumption in pregnancy	Relative risk of recurrent miscarriage	0.9 (0.6 ; 1.5)
			BMI	BMI ≥ 22.5 kg/m2		1.1 (0.6 ; 2.0)
			Caffeine	Coffee consumption in pregnancy		1.4 (0.7 ; 2.6)
			Smoking	Current smoking in pregnancy increasing number of cigarettes / day		1.4 (0.8 ; 2.9) p for trend 0.04
Ronnenberg *et al.* 2002	Prospective case-control study	458	Folic acid	lowest quintiles of plasma folate concentration (≤ 6.60 nmol/L)	Odds ratios for miscarriage	1.5 (0.6 ; 3.8)
			Vitamin use	lowest quintiles of plasma Vitamin B6 concentration (≤28.9 nmol/L)		2.5 (0.8 ; 7.8)
Strandberg-Larsen *et al.* 2008	Prospective cohort study	89201	Alcohol	binge drinking in first 12 weeks of pregnancy	Hazard ratio for miscarriage	0.84 (0.62 ; 1.14)
Windham *et al.* 1997	Prospective cohort study	5307	Alcohol	>3 alcoholic drinks per week	Odds ratios for miscarriage	2.3 (1.1 ; 4.5)
Xu *et al.* 2014	Retrospective case-control study	1860	Alcohol	>4 times per week alcohol consumption	Odds ratios for miscarriage	1.04 (0.79 ; 1.27)
			BMI	Pre-pregnancy BMI ≥ 30 kg/m^2		1.05 (0.89 ; 1.25)
			Diet	eating fresh fruit / vegetables daily		0.86 (0.49 ; 1.22)
			Physical activity	>2 times per week, ≥0.5 hr		0.72 (0.51 ; 0.88)
			Smoking	smoking >20 cigarettes per day during first 12 weeks of pregnancy		1.59 (1.12 ; 3.16)
			Vitamin use	vitamin supplement use		0.75 (0.49 ; 0.91)
Zhou *et al.* 2016	Prospective cohort study	2940	BMI	Pre-pregnancy BMI <18.5 kg/m^2 Pre-pregnancy BMI 24 - 27.9 kg/m^2 Pre-pregnancy BMI ≥28 kg/m^2	Relative risk for miscarriage	2.57 (1.35 ; 4.89) 2.45 (1.26 ; 4.77) 2.84 (2.84 ; 6.57)

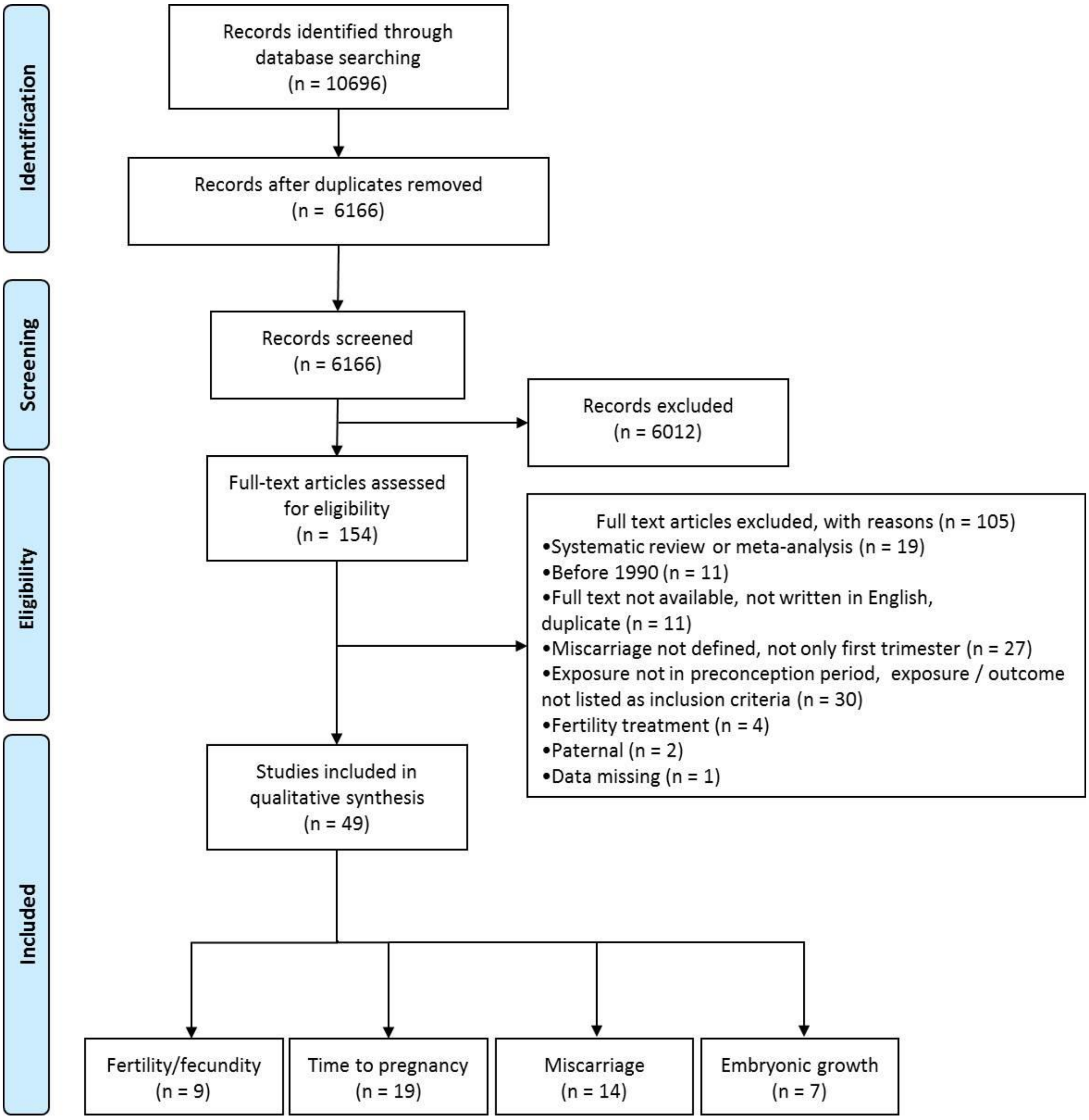
Note: BMI = body mass index

Table 5. *Description and summary of data for 7 studies that investigated associations between lifestyle factors and embryonic growth.*

Author	Study design	Sample size	Exposure	Outcome description	Outcome definition	Effect estimate (95% CI)
van Uitert *et al.* 2013	Prospective cohort study	87	Alcohol	Periconception alcohol use	CRL difference (mm)	-0.05 (-0.069 ; -0.017)
			BMI	BMI kg/m^2		0.095 (-0.11 ; 0.17)
			Folic acid	moment of initiation of folic acid; post conception		0.27 (-0.311 ; 0.49)
			Smoking	Periconception smoking ≥10 cigarettes per day		-0.46 (-0.64 ; -0.077)
van Uitert *et al.* 2014	Prospective cohort study	440	Folic acid	Quartile 1 (814-1223 nmol/L)	CRL difference (mm)	-0.49 (-0.66 ; -0.2)
				Quartile 2 (1224-1512nmol/L)		-0.45 (-0.64 ; -0.14)
				Quartile 4 (1813-2936 nmol/L)		-0.54 (-0.7 ; -0.3)
Bakker *et al.* 2010	Prospective cohort study	1310	Caffeine	>6 units of caffeine per day	CRL difference (mm)	-4.54 (-8.99 ; -0.09) p for trend <0.05
Bouwland-Both *et al.* 2013	Prospective cohort study	847	Diet	high adherence to an energy-rich dietary pattern	CRL difference (mm)	1.62 (0.52 ; 2.72) p for trend <0.05
Mook-Kanamori *et al.* 2010	Prospective cohort study	1631	Alcohol	alcohol consumption compared to no consumption	CRL difference (mm)	0.40 (-0.31 ; 1.11)
			BMI	per 1 SD (4.08 units) increase in BMI		-0.01 (-0.35 ; 0.33)
			Folic acid	No use of folic acid supplement		-1.33 (-2.41 ; -0.24)
			Smoking	smokers compared to non-smokers		-0.98 (-1.79 ; -0.16)
Parisi *et al.* 2017	Prospective cohort study	234	Vitamin use	Vitamin B12 concentration of -2 SD (73.4 pmol/L)	delay in Carnegie stage (days)	1.4 (1.3 ; 1.4)
				Total Homocysteine concentration of +2 SD (10.4 µmol/L)		1.6 (1.5 ; 1,7)
Prabhu *et al.* 2010	Prospective cohort study	903	Smoking	smokers compared to non-smokers	CRL difference (mm)	0.23 (-0.23 ; 0.70)

Note: BMI = body mass index. CRL = crown-rump length

Figure 1. *Prisma flowchart of in- and excluded studies*



Supplemental Table 1. *List of keywords*

Keyword	Category
Diet	Exposure
Smoking	Exposure
Alcohol	Exposure
Drugs	Exposure
Folic acid supplement use / Folate	Exposure
Multivitamin supplement use	Exposure
Lifestyle intervention	Exposure
Physical activity	Exposure
Body mass index (BMI) / Obesity	Exposure
Embryonic growth	Outcome
Fertility	Outcome
Fecundity / fecundability	Outcome
Time to Pregnancy	Outcome
Miscarriage	Outcome, clinical
Yolk sac	Outcome, ultrasound
Crown-rump length (CRL)	Outcome, ultrasound

Supplemental Table 2. *ErasmusAGE quality score form for systematic reviews adjusted for: The influence of maternal lifestyle factors on periconception outcomes: a systematic review of observational studies.*

Original: ErasmusAGE, 24 June 2013.

This quality score can be used to assess the quality of studies included in systematic reviews and meta-analyses and is applicable to both interventional and observational studies. The score was designed based on previously published scoring systems (Carter *et al*, 2010 and the Quality Assessment Tool for Quantitative Studies). The quality score is composed of five items, and each item is allocated 0, 1 or 2 points. This allows a total score between 0 and 10 points, where 10 represents the highest quality.

The version presented below is a general version and needs to be adapted for each review separately , e.g. concerning what study size is large or small within the study field, what exposure and outcome measurement methods are adequate, and what the key confounders are. Decisions on these detailed criteria should be based on literature, guidelines and/or discussions with experts. The criteria should be defined before the review process.

1. **Study design**
   0 for studies with cross-sectional data collection
   1 for studies with longitudinal data collection (both retrospective and prospective)
   2 for intervention studies

2. **Study size** (predefined) *
   Observational studies
   0 small population for analysis: n < 1000
   1 intermediate population for analysis: n = 1000-4999
   2 large population for analysis: n > 5000

3. **Exposure**
   Observational studies
   0 if the study used no appropriate exposure measurement method or if not reported
   1 if the study used moderate quality exposure measurement methods (self-reported)
   2 if the study used adequate exposure measurement methods (real measurement)

4. **Outcome**
   0 if the study used no appropriate outcome measurement method or if not reported
   1 if the study used an appropriate outcome measurement methods (self-reported)
   2 if the study used an appropriate outcome measurement methods (real measurement)

5. **Adjustments**
   0 if findings are not controlled for at least for all three key confounders, as mentioned below† *
   1 if findings are controlled for key confounders
   2 if an intervention is adequately randomized <u>or</u> when findings are additionally controlled for at least two

* Needs to be specified for each review, based on literature, guidelines and/or expert opinions in the field
† Either adjusted for in the statistical analyses; stratified for in the analyses; or not applicable (e.g. a study in women only does not require controlling for sex)

Vitae

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