

## **TITLE**

Relationships between women's and men's modifiable preconception risks and health behaviors and maternal and offspring health outcomes: an umbrella review

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**ABSTRACT**

Parental health before conception effects maternal and offspring health outcomes.

Preconception care provides healthcare to prospective parents addressing modifiable preconception risks and health behaviors. This umbrella review aimed to consolidate evidence on women's and men's modifiable preconception risks or health behaviors associated with maternal and offspring health outcomes. MEDLINE, EMBASE, Maternity and Infant Care, CINAHL, and PsycINFO were searched from 4 March 2010 to 4 March 2020. Eligible studies were systematic reviews or meta-analyses of observational studies examining associations between modifiable preconception risks or health behaviors and maternal and offspring health outcomes. Screening, data extraction and methodological quality assessment (AMSTAR 2) occurred independently by two reviewers. Degree of overlap was examined. Findings were summarized for evidence synthesis. Twenty-seven systematic reviews were included. Modifiable preconception risks and health behaviors were identified across categories: body composition (e.g., overweight, obesity), lifestyle behaviors (e.g., caffeine, smoking), nutrition (e.g., micronutrients), environmental exposures (e.g., radiation), and birth spacing (e.g., short interpregnancy intervals). Outcomes associated with exposures affected embryo (e.g., embryonic growth), maternal (e.g., gestational diabetes mellitus), fetal/neonate (e.g., preterm birth) and child (e.g., neurocognitive disorders) health. For real world practice and policy relevance, evidence-based indicators for preconception care should include body composition, lifestyle, nutrition, environmental, and birth spacing.

**KEYWORDS**

Preconception care; risk factors; health behavior; maternal health; pregnancy complications

## **INTRODUCTION**

The preconception health environment of prospective mothers and fathers has effects on maternal and offspring health outcomes.<sup>1, 2</sup> The developmental origins of health and disease<sup>3</sup> model has fostered research efforts aimed at the prevention of disease by modifying risk exposures in the preconception period.<sup>2, 4-7</sup> Consequently, preconception care<sup>8</sup> provided before women's first pregnancy (i.e., the preconception period) or between women's subsequent pregnancies (i.e., the interpregnancy period),<sup>9</sup> aims to address modifiable preconception risks and health behaviors - whereby exposure or risk can be prevented or reduced through behaviour change or an intervention<sup>5</sup>- among prospective parents to improve maternal and offspring health.<sup>8</sup>

The substantive evidence describing preconception risks and health behaviors needs consolidation so that clear preconception care directives can be developed and translated into real-world applications. To date, Cochrane reviews have described routine pre-pregnancy health promotion for improving health outcomes,<sup>10</sup> preconception risks and interventions<sup>11</sup> and the efficacy and safety of periconception folic acid for preventing birth defects.<sup>12</sup> Other systematic and scoping reviews have outlined the effects of preconception interventions on improving reproductive health and women's pregnancy outcomes delivered in primary care<sup>13</sup> and public health and community settings.<sup>14, 15</sup> An additional review has examined preconception health interventions, knowledge, attitudes, behaviors and intentions.<sup>16</sup> The largest body of research from these reviews focuses on folic acid supplementation to reduce the incidence of neural tube defects (NTDs).

Research is needed that addresses the broad determinants of preconception health<sup>14</sup> inclusive of all individuals of reproductive age (women and their partners).<sup>14-16</sup> From a public health policy and practice viewpoint, understanding modifiable preconception risks and health behaviors is crucial to promoting health across the life course through preconception care. However, to address these risks and behaviors requires individuals (reproductive age women and their partners) and health professionals (e.g., general practitioners, obstetricians/gynaecologists and paediatricians, nurses, midwives, public health workers, health educators, and other health professionals etc.) that are aware of preconception modifiable risks and health behaviors throughout the reproductive life course.<sup>17-23</sup> As such, this review provides a summary of literature published in systematic reviews examining women's and men's preconception risks and health behaviors, and their association with maternal and offspring health outcomes.

## **METHODS**

### **Search strategy**

The protocol was developed in accordance with the PRISMA statement<sup>24</sup> and registered in PROSPERO on 28 April 2020 (CRD42020171244). Keyword and MeSH terms were employed into MEDLINE, EMBASE, Maternity and Infant Care, CINAHL, and PsycINFO on the 4th of March 2020. The full search strategy for each database can be downloaded from PROSPERO. Table 1 provides an example of the search strategy as employed in MEDLINE (OVID) database.

### *Table 1. Keywords and MeSH terms for MEDLINE (OVID)*

Search limits included title and abstract, studies in humans, articles published in the last 10 years, with no limits to language. Non-English articles were translated to the English language using Google Translate.<sup>25</sup> Abstracts were downloaded into EndNote

X9<sup>26</sup> from each database and screened for duplicates before being imported into Covidence.<sup>27</sup>

#### Selection criteria

Eligible studies were systematic reviews or meta-analyses of observational studies (i.e., cross-sectional, cohort—retrospective/prospective, case-control); that examined the association of a modifiable risk or health behavior (such as, but not limited to, dietary/nutritional, lifestyle or environmental) with an embryo, maternal, fetal/neonate or child health outcome; and sampled individuals identified as being in the preconception period (i.e., exposure had occurred before conception). Articles (or results reported in articles) were excluded if the preconception period was not the primary topic focus; the primary outcome was not related to a maternal or offspring health outcome; not on humans (i.e., animal studies); intervention studies (i.e., trials) or were other types of reviews such as narrative reviews, commentary, or opinion articles.

Title and abstract and full text screening occurred independently by two reviewers before inclusion for review. Disagreements were discussed until consensus was reached. If unresolved, a third reviewer was invited to adjudicate. The reason for article exclusion were documented. A PRISMA flow diagram was generated.

#### Methodological quality

Two review authors independently assessed the quality of the included studies using AMSTAR 2.<sup>28</sup> Disagreements were discussed until consensus was reached.

#### Data extraction

Data items were extracted independently by two reviewers. Disagreements were discussed between reviewers until consensus was reached.

#### Overlap

The degree of overlap of the included primary studies was examined from all reviews in our review by employing the method described by Pieper *et al.*<sup>29</sup> The Corrected Cover Area was calculated as a measure of overlap and described as a value indicating the proportion and percentage of overlap.<sup>29</sup>

#### Data synthesis

Characteristics and findings from included systematic review and meta-analyses were presented in tables, summarizing for evidence synthesis the population, timeframe, exposure, main outcomes measured and results as presented in the articles.

## **RESULTS**

Database searches yielded 5101 articles. After duplicate removal and title and abstract screening, 62 full text articles were assessed against the eligibility criteria. Thirty-five articles<sup>16, 30-63</sup> were excluded with reasons from the review. Reasons for exclusion from the review included: not a systematic review (n=16),<sup>16, 30-44</sup> exposure not defined or reported as occurring during the preconception timeframe (n=11),<sup>45-53, 55, 64</sup> not eligible exposures (e.g., not modifiable) (n=3),<sup>37, 57, 63</sup> ineligible study design (n=2),<sup>58, 59</sup> conference abstract (n=1),<sup>60</sup> irrelevant outcomes (n=1),<sup>61</sup> and not the relevant study population (n=1).<sup>62</sup> A total of 27 systematic reviews were included (Figure 1), of these 19 presented meta-analysis of at least one outcome and exposure of interest<sup>64-82</sup> and the remaining eight presented a systematic review without meta-analysis.<sup>83-90</sup>

### Degree of overlap

The included articles cited 655 primary publications in 738 unique instances across all reviews representing a Corrected Cover Area (CCA) of 0.5% ( $CCA = 738 - 655 / (655 \times 27) - 655 = 0.005$ ) indicating only a slight overlap. We further examined 10 reviews containing more than five articles cited more than once across all included reviews<sup>65, 68, 70, 73-75, 77, 83, 86, 88</sup> and their exposure(s) and outcome(s) of interest. Three reviews<sup>65, 77, 83</sup> studied preconception obesity and reported on childhood neurocognitive development. Two reviews<sup>68, 73</sup> examined preconception underweight and reported on preterm birth, small for gestational age and low birthweight, and two reviews<sup>68, 86</sup> studied preconception multivitamin supplementation (including folic acid) and reported on pre-eclampsia, congenital abnormalities, and neural tube defects. One review<sup>88</sup> studied folic acid supplementation and neural tube defects. Whereas the remainder of reviews<sup>70, 73-75</sup> had examined different exposures and outcomes. We determined the impact any occurrence of overlap would have on our review findings was negligible.

### *Figure 1. PRISMA Flow Diagram*

### Critical appraisal

The methodological quality of the included studies ranged between critically low (n=11),<sup>68, 70-74, 76, 79, 82, 85, 86</sup> low (n=10)<sup>64-66, 69, 77, 78, 80-82, 87, 90</sup> and moderate (n=6).<sup>67, 75, 83, 84, 88, 89</sup> Of the seven AMSTAR 2 critical domains: 23 studies failed to register a study protocol before commencement of the review, five studies failed in adequacy of the literature search, 24 studies failed in providing justification for excluding individual studies, 10 studies failed to describe risk of bias from individual studies being included in the review, 13 studies failed in appropriateness of meta-analytical methods (e.g., the use of unadjusted ORs or RRs). Where meta-analysis was performed; nine studies failed in consideration of risk of bias when interpreting the



results of the review; and six studies failed to adequately assess the presence and likely impact of publication bias. The individual assessment for each of the studies against the sixteen items of the AMSTAR 2 critical appraisal tool can be requested from the corresponding author.

#### Study characteristics

Table 2 and Table 3 summarize findings by population, timeframe, exposure, and main associated outcome(s) as embryo, maternal, fetal/neonate and child health outcomes. The data extraction tables describing detailed characteristics of the included studies can be requested from the corresponding author.

### **SUMMARY OF FINDINGS**

#### Body composition

##### ***Maternal***

##### *Underweight*

Preconception underweight significantly increases the odds of preterm birth

(OR:1.30[95% CI,1.13–1.49]),<sup>73</sup>(OR:1.32[95%CI,1.22,1.43]),<sup>68</sup> small for gestational age (OR:1.67[95%CI,1.49–1.87])<sup>73</sup> and (RR:1.64[95%CI,1.22-2.21]),<sup>68</sup> and low birth weight infants (OR:1.67[95%CI,1.39–2.02]).<sup>73</sup>

##### *Overweight*

Preconception overweight prolongs the time to pregnancy in comparison to normal weight women and increases the risk of miscarriage.<sup>85</sup> Overweight women, have increased odds of preeclampsia (OR:2.28[95%CI,2.04-2.55]), gestational diabetes mellitus (GDM) (OR:1.91[95% CI, 1.58, 2.32];<sup>68</sup> aOR:2.01[95%,1.75-2.26])<sup>75</sup> and an increased likelihood of a caesarean birth (OR:1.42[95%CI,1.21-1.66]).<sup>68</sup> Overweight women significantly increase their odds for large for gestational age infants (OR:1.45[95%CI,1.29–1.63]), infant admission to neonatal intensive care unit

(OR:1.29[95%CI,1.12–1.48]), stillbirth (OR:1.27 [95% CI, 1.18–1.36])<sup>73</sup> and infant macrosomia (OR:1.70[95% CI,1.55–1.87]);<sup>73</sup> aOR:1.93[95%CI,1.65,2.27]).<sup>67</sup>

*Table 2. Summary of findings of included systematic reviews with meta-analysis*

*Table 3. Summary of findings of included systematic reviews*

Dean *et al.*, found a significant association between preconception overweight and birth defects (NTDs, congenital heart defects) (OR:1.15[95%CI,1.07-1.24]).<sup>68</sup> Sanchez *et al.*, reported preconception overweight increased the odds for compromised neurodevelopmental outcomes in children (OR:1.17[95%CI,1.11-1.24]).<sup>77</sup> A higher maternal pre-pregnancy body mass index (BMI) was found to have a consistent relationship with childhood overweight.<sup>90</sup> In another systematic review by Weng *et al.*, one study found that the children of mothers' who were overweight before pregnancy were 1.37 times (95%CI,1.18-1.58) more likely to be overweight at three years of age than children of normal weight mothers.<sup>89</sup>

### *Obesity*

Obese women compared to normal weight women prolong their time to pregnancy and increase miscarriage risk.<sup>85</sup> Women with obesity were shown to have an increased likelihood of GDM (aOR:3.98[95%CI,3.42-4.53]; pooled aRR:2.24 [95%CI,1.97-2.51]),<sup>75</sup> premature births (OR:1.18[95%CI,1.07-1.30]), medically induced preterm births (OR:1.72[95%CI,1.45t-2.04])<sup>70</sup> and shoulder dystocia (RR:1.63[95%CI,1.33–1.99]).<sup>80</sup> Obese women significantly increase their odds of large for gestational age infants (OR:1.88[95%CI,1.67–2.11]), infant admission to neonatal intensive care unit (OR:1.91[95% CI,1.60–2.29]), stillbirth (OR:1.81[95%CI,1.69–1.93]) and giving birth to low birth weight infants

(OR:1.24[95%CI, 1.09–1.41]).<sup>73</sup> Conversely, obesity also increases the odds for infant macrosomia (OR:2.92[95%CI, 2.67–3.20]),<sup>73</sup> (OR:1.63[95%,1.51-1.76]).<sup>68</sup>

An adverse association was found between childhood cognitive development and gross motor function in children and mothers with preconception obesity.<sup>83</sup> In a meta-analysis by Alvarez-Bueno *et al.*, preconception obesity was more likely to have negative influences on a child's neurocognitive development (ES:0.06[95%CI,-0.09to-0.03]).<sup>65</sup> Similarly, Sanchez *et al.*, reported that preconception obesity increased odds for compromised neurodevelopmental outcomes in children (OR:1.51[95%CI,1.35-1.69]), attention deficit–hyperactivity disorder (OR:1.62[95%CI,1.23-2.14]), autism spectrum disorder (OR:1.36[95%CI,1.08-1.70]), developmental delay (OR:1.58[95%CI,1.39-1.79]), and emotional/behavioural problems (OR:1.42[95% CI,1.26-1.59]).<sup>77</sup> Zhang *et al.*, found a significant association between preconception obesity and an increased odd of cerebral palsy in children (aOR:1.51[95%CI,1.24–1.84]).<sup>64</sup> Children of mothers who were obese before pregnancy were 4.25 times (95%CI,2.86-6.32) more likely to be overweight at seven years of age compared with children of non-obese mothers.<sup>89</sup> Another study found that children of mothers' who were obese before pregnancy were 2.36 times (95%CI,2.36-8.85) more likely to be overweight between nine and 14 years of age compared with children of non-obese mothers.<sup>89</sup> The review by Steinig *et al.*, found a positive association between preconception obesity and antenatal and post-natal depression.<sup>87</sup>

#### *Interpregnancy Weight Change*

Women with interpregnancy weight gain, compared to normal weight women, increase their odds of developing GDM in a subsequent pregnancy that is

proportionate to their BMI increase (1-2 BMI units: aOR:1.51[95%CI,1.22–1.80]; 2–3 BMI units: aOR:1.81[95%CI,1.20–2.41]; >3 BMI units: aOR:2.37[95%CI,1.50–3.34]); the highest odds was reported for women with a BMI <25 kg/m<sup>2</sup> in their previous pregnancy and an interpregnancy weight gain of >3 BMI units (aOR:4.36[95%CI,2.29-6.44]).<sup>78</sup> Women with an interpregnancy weight gain of >3 BMI units increase their likelihood of hypertension (aOR:1.70[95%CI,1.50–1.91]) and preeclampsia (aOR:1.71[95%CI,1.51–1.91]) in a subsequent pregnancy.<sup>78</sup> There is increased odds of developing pregnancy-induced hypertension in women with a previous pre-pregnancy BMI <25 kg/m<sup>2</sup> if their weight increases more than 2 BMI units(2-3 BMI units, aOR:1.60[95%CI,1.04– 2.16]; >3 BMI units, aOR:2.21[95%CI,1.81–2.60]).<sup>78</sup> An interpregnancy weight gain of >3 BMI units increases the odds of giving birth to a large for gestational age neonate by 63% (aOR:1.63[95%CI,1.30–1.97]) in a subsequent pregnancy.<sup>78</sup> The likelihood is highest when the women’s BMI was <25 kg/m<sup>2</sup> in her previous pregnancy and her interpregnancy weight gain is >3 BMI units (aOR:1.80[95%CI,1.24–2.35]).<sup>78</sup> However, interpregnancy weight loss of >1 BMI unit was associated with lowering the odds of giving birth to a large for gestational age neonate in a subsequent pregnancy (aOR:1.63[95%CI,1.30–1.97]).<sup>78</sup>

***Paternal  
Body Mass Index***

One systematic review reports paternal preconception BMI,<sup>90</sup> finding an association between fathers with a higher preconception BMI and having children that are overweight.<sup>90</sup>

Lifestyle

**Maternal  
Smoking**

Women smoking in the preconception period have poorer fecundity ratios, prolonged time to pregnancy, reduced embryonic growth trajectories and increased miscarriage risk.<sup>85</sup> Compared to no smoking, preconception smoking has significantly higher odds of preterm birth (OR: 2.2[95%CI,1.29-3.75]),<sup>72</sup> and periconceptual smoking increases the likelihood of congenital heart defects three-fold (OR:2.80[95%CI,1.76-4.47]).<sup>72</sup>

**Alcohol**

Women consuming alcohol in the preconception and periconceptual period may experience lower conception rates and an increased risk of miscarriage.<sup>85</sup> In the systematic review by Oostingh *et al.*, three out of seven studies found greater than three drinks per week was associated with miscarriage.<sup>85</sup> In the meta-analysis by Lassi *et al.*, preconception alcohol consumption increased the risk of miscarriage by 30% (pooled RR:1.30[0.85-1.97]).<sup>72</sup> Periconception alcohol consumption is also associated with reduced embryonic growth trajectories.<sup>85</sup> Preconception alcohol consumption increased the odds of NTDs, with binge drinking increasing the risk by 20% more compared to one drink per day (OR:1.24[95%CI,0.92-1.68]).<sup>72</sup> Periconceptual alcohol consumption is associated with an increased risk of oesophageal atresia with or without tracheo-oesophageal fistula (RR:1.26[95%CI,1.03-1.56]) and periconceptual alcohol intake at once weekly increased the risk of congenital heart defects compared to no intake (OR:0.96[95%CI,0.91-1.01]).<sup>72</sup> The risk of low birth weight increased when an average of three drinks or more per day are consumed during the periconceptual period (RR: 1.07[95%CI,0.79-1.45]), and the risk of preterm birth is increased when an average of five drinks or more per day are consumed (RR:1.04[95%CI,0.65-

1.68]).<sup>76</sup> Compared to no alcohol intake during the periconceptional period consuming an average of two drinks or more per day increases risk of small for gestational age infant (RR:1.02[95%CI,0.82-1.27]).<sup>76</sup>

### *Caffeine*

Women consuming >501mg caffeine per day in the periconceptional period significantly increased their time to pregnancy and had a higher risk of miscarriage.<sup>85</sup> In the meta-analysis by Lassi *et al.*, periconception caffeine intake increased risk of miscarriage with >300mg/day (pooled RR:1.77[95%CI,0.83-3.78]).<sup>72</sup> In addition, reduced embryonic growth trajectories were observed in women consuming caffeine during preconception.<sup>85</sup>

### *Physical Activity*

Women undertaking vigorous physical activity in preconception have been associated with prolonging the time to pregnancy; however, moderate physical activity was shown to significantly decrease the risk of miscarriage.<sup>85</sup> Engaging in any type of physical activity compared to none during the preconception period is associated with approximately 30% reduced odds of GDM (pooled OR:0.70[95%CI,0.57–0.85]).<sup>74</sup> While engaging in physical activity levels >90 min/week or higher physical activity levels during preconception was associated with 46% and 55% reduced odds of GDM (pooled OR:0.54[95% CI, 0.34–0.87]),<sup>74</sup> (pooled OR:0.45[95%CI,0.28 - 0.75]),<sup>79</sup> respectively.

### *Illicit Drugs*

Illicit drug use in the periconceptional period increases the incidence of gastroschisis in infants (OR:1.76[95% CI,0.99-3.13]).<sup>72</sup> Preconception illicit drug use increases the likelihood of post-natal depression for the mother (OR:9.60[95%CI,1.80-51.20]).<sup>72</sup>

### ***Paternal***

#### ***Illicit drugs***

One meta-analysis measured paternal preconception illicit drug use, finding that paternal preconception heroin use significantly increases the risk of NTDs (RR:1.63[95%CI,1.23-2.16]).<sup>72</sup>

### Nutrition

#### ***Maternal***

##### ***Dietary pattern***

A stronger adherence to the Mediterranean dietary pattern during preconception was associated with significantly lower odds of attending an infertility consultation, reported in the review by Oostingh *et al.*<sup>85</sup>

##### ***Multivitamins and nutrients***

Supplementing multivitamins and folic acid during preconception was significantly associated with increased fecundity.<sup>85</sup> Lower vitamin B12 and lower and higher folic acid concentrations during periconception were associated with reduced morphological development of the embryo<sup>85</sup>; whereas higher vitamin B6 status was associated with a reduction in miscarriage risk<sup>85</sup>. Dean *et al.* reported a 27% risk reduction of preeclampsia with preconception multivitamin supplementation (Pooled OR:0.73[95%CI,0.58-0.92]).<sup>68</sup> Preconception and/or periconception multivitamin supplementation was negatively associated with low birth weight, small for gestational age infants and preterm birth in the systematic review by Ramakrishnan *et al.*<sup>86</sup>

##### ***Folic acid***

The systematic review by Viswanathan *et al.*, reported that preconception folic acid supplementation demonstrated a negative association with NTDs and a 43% risk

reduction of multiple congenital abnormalities (Pooled OR:0.57[95% CI, 0.34-0.82]).<sup>88</sup> An earlier meta-analysis reported that folic acid supplementation during preconception had a 49% decreased risk of NTDs (Pooled RR:0.51[95% CI, 0.31-0.82]).<sup>68</sup> Preconception folic acid supplementation [400-500µg daily] also has significantly lower odds for small for gestational age births (aOR:0.75[95%CI,0.61–0.92]).<sup>69</sup>

#### Environmental

##### ***Maternal Radiation***

Maternal periconceptional occupational radiation exposure increased risk of early miscarriage (RR:1.32[95%CI,1.04-1.66]).<sup>72</sup> Maternal preconception occupational exposure to ionising radiation increased risk of childhood cancers (RR:1.19[95%CI,0.92-1.54]).<sup>72</sup>

##### ***Pesticides***

In women a significantly lower pregnancy success rate was reported with periconceptional consumption of fish contaminated with organochlorine compounds compared to no consumption of organochlorines.<sup>85</sup> Maternal preconception pesticide exposure was associated with miscarriage.<sup>72</sup>

##### ***Air pollution***

Maternal preconception exposure to high levels of traffic-related particulate air pollution increases risk of early pregnancy loss as reported by Lassi *et al.*<sup>72</sup>

##### ***Chemicals and metal***

Maternal exposure to excess lead increased the odds of congenital heart defects (OR:2.59[95%CI,1.68-3.82]).<sup>72</sup> Use of wood when cooking increased the risk of NTDs



three-fold (95%CI,1.70-6.21), and women cooking or heating with wood, coal or tires in their homes increase the odds of infant anencephaly (OR:2.04[95% CI,1.29-3.23]).<sup>72</sup> Maternal preconception exposure to chemicals (e.g., paints, solvents, industrial products) increased risk of acute lymphoblastic leukemia in offspring<sup>72</sup> and exposure to dermal hydrocarbons and metal increased risk of leukemia and acute lymphoblastic leukemia.<sup>72</sup>

### ***Paternal***

#### *Radiation*

Paternal preconception occupational exposure to ionizing radiation increased risk of childhood cancers (RR:1.29(95%CI,1.02-1.63)).<sup>72</sup> Paternal non-occupational ionizing radiation exposure from X-rays was associated with increased risk of low birth weight (MD:-73.00[95%CI,-78.97,-67.03]) and increased risk of reduced intrauterine growth (MD:-53.00[95%CI,-58.21,-47.79]).<sup>72</sup> Father's exposed to abdominal X-ray during preconception was associated with an increased risk of leukemia in offspring.<sup>72</sup>

#### *Chemicals and metal*

Paternal exposure to pesticides in the year before conception increased the risks of haematological malignancies in offspring.<sup>72</sup> Paternal preconception exposure to chemicals (e.g., paints, solvents, industrial products) increased risk of acute lymphoblastic leukemia in offspring<sup>72</sup> and exposure to dermal hydrocarbons and metal increased risk of leukemia and acute lymphoblastic leukemia.<sup>72</sup> Paternal preconception exposure to excess lead increased the odds of congenital heart defects (OR:2.59[95%CI,1.68-3.82]).<sup>72</sup>

Birth spacing

### ***Maternal***

*Short interpregnancy interval*

Short interpregnancy intervals (<6 and 6-11 months) were associated with increased likelihood of maternal obesity compared with intervals of 18-23 months (aOR:1.61[95%CI,1.05-2.45], and aOR: 1.43[95%CI,1.10-1.87]).<sup>84</sup> The odds of GDM were also higher with shorter interpregnancy intervals <6 vs. 18-23 months (aOR:1.35[95%CI,1.02-1.80]);<sup>84</sup> whereas the odds of pre-eclampsia were lower with shorter interpregnancy intervals of 6-11 vs. 18-23 months (OR:0.71[95%CI,0.54-0.94]).<sup>84</sup> The likelihood of labour dystocia was lower with shorter interpregnancy intervals <12 vs. 12-43 months (aOR:0.91[95%CI,0.85-0.97]), <24 vs. 24-47 months (aOR:0.94[95%CI,0.93-0.96]), and <24 vs. ≥120 months (aOR:0.66[95%CI,0.64-0.68]).<sup>84</sup> The odds of precipitous labour were higher with shorter interpregnancy intervals <6 vs. 18-60 months (aOR:1.30[95%CI, 1.11-1.51]), 6-12 vs. 18-60 months (aOR:1.19[95% CI, 1.04-1.36]), and 12-18 vs. 18-60 months (aOR:1.25([95%CI,1.10-1.41]).<sup>84</sup> The likelihood of placental abruption was higher with shorter interpregnancy intervals <6 vs. 24-59 months (aOR:1.9[95% CI,1.3-3.0]).<sup>84</sup> Uterine rupture was more likely with short interpregnancy intervals <6 vs.18-59 months in women attempting vaginal birth after caesarean birth (aOR:3.05[95%CI,1.36-6.87]).<sup>84</sup>

## **DISCUSSION**

### **Main findings**

Modifiable preconception risks and health behaviours across multiple categories

(body composition, lifestyle, nutrition, environmental, and birth spacing) were found to be associated with numerous maternal and offspring health outcomes.

### **Strengths and Limitations**

This review – employing a thorough, rigorous search strategy and overlap assessment to minimise amplifying findings from one study - is the most comprehensive examination of research investigating preconception modifiable risks and health

behaviours to date. The review identified variable amounts of evidence for a range of exposures. Greater quantities of evidence may be due to a research focus on health priority areas, such as obesity. Whereas limited research examining environmental exposures and paternal exposures in humans may reflect a need to broaden the current gaze among preconception epidemiological research. Given this umbrella review only included systematic reviews, it does not include primary research on these topics not already reviewed. As such, there is potential that non-reviewed topic areas have been excluded. For example, research on men's preconception health has received attention over the last decade on various types of paternal exposure and offspring health outcomes,<sup>91-94</sup> however this has not yet been comprehensively summarised, although further work is underway.<sup>95</sup> Heterogeneity existed between the data (e.g., OR/RR) therefore further analyses to determine the strength of the association between an exposure and outcome, was not possible.

#### Interpretation

The vast amount of evidence outlined in this review emphasises preconception care's critical role in noncommunicable diseases prevention through modification of preconception risk exposure,<sup>2, 6, 7</sup> and providing primary prevention for adverse maternal and offspring health outcomes. The review identified a list of modifiable preconception risks and health behaviours that could be applied to improve screening for preconception risks, enabling the timely initiation of preconception counselling and education where needed.<sup>96</sup> These modifiable risk factors can be scaffolded by existing conceptual frameworks that outline the critical timing to commence preconception care.<sup>97</sup> For example, addressing body composition through adopting a healthy diet and increased physical activity should be considered as early as three years prior to conception,<sup>97</sup> whereas, cessation of smoking and alcohol consumption

should commence at least three months before conception or when intending to become pregnant.<sup>97</sup>

Particularly given the lack of consensus regarding the best way to provide preconception care in healthcare systems,<sup>96</sup> one of the challenges for preconception care is identifying opportunities for population level delivery that aims to benefit the whole population and is equitable, considering the unique needs of low socioeconomic, adolescent, LGBTQIA+, men, ethnic minority and culturally and linguistically diverse populations<sup>98</sup>. Barker *et al.* propose a preconception care framework that identifies preconception health awareness and intervention opportunities throughout the reproductive life course.<sup>21</sup> Another approach reflects differing aspects of preconception care healthcare delivery models including: screening, education and intervention in primary care, hospital, community, and community outreach settings.<sup>96</sup> The findings of this review may help to inform future planning for preconception care initiatives in the community.

The modifiable preconception risks identified in the review may be best ameliorated by both population and individual level behavioural change strategies. Behaviour change interventions such as preconception counselling and education delivered in primary care, public health and community settings are effective at reducing risks and encouraging health promoting behaviours including supplementing with folic acid and/or folic acid containing multivitamin, consumption of a healthy diet, physical activity, and reduction in use of harmful substances (caffeine, smoking, alcohol and illicit drugs).<sup>10, 11, 13, 15, 16, 99</sup> Some preconception care initiatives, programs and clinical practice guidelines have been developed;<sup>9, 100-107</sup> however, these efforts need to be wider spread.

A range of health professionals can assist with preconception care delivery such as physicians (e.g., general practitioners, obstetricians/gynaecologists and paediatricians) and other health professionals (e.g., nurses, midwives, public health workers, social workers, health educators, pharmacists, nutritionists, naturopaths and acupuncturists).<sup>108, 109</sup> One of the known barriers to implementing preconception care is health professionals' confidence in, and capacity to deliver, preconception care.<sup>22, 110</sup> Consequently, identifying and addressing barriers to providing preconception care requires close attention to health professionals' time constraints, limited resources and knowledge of preconception care.<sup>96, 110</sup> There is a need to develop preconception care resources to support health professionals in their role and policies to support preconception care implementation across a wide range of private and public health settings.<sup>23, 111</sup> For this to be achieved, the development and application of a validated preconception care health literacy instrument can be used to undertake assessment of health professionals' preconception care knowledge to determine the next steps needed for preconception care education and evaluation of preconception care delivery.<sup>112</sup>

## **CONCLUSION**

For real world practice and policy relevance, evidence-based indicators for preconception care should include body composition, lifestyle, nutrition, environmental, and birth spacing. Identifying the effects of modifiable risk factors on maternal and offspring health outcomes can help inform future public health messages, clinical guidelines, and preconception care interventions to confirm whether modifying preconception risks and exposures affects maternal and offspring

outcomes. Future research attention on the effects of preconception environmental exposures and paternal exposures is needed.

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#### **CONFLICTS OF INTERESTS**

The authors have no conflicts of interest to declare.

#### **ETHICAL STATEMENT**

Ethics approval was not required for this umbrella review.

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#### **AUTHOR CONTRIBUTIONS**

CC designed the protocol and carried out the searches, screening, quality appraisal, overlap assessment, data extraction and analysis and drafted, reviewed, and edited the manuscript. AS was second reviewer for article screening at the title and abstract stage, DS was second reviewer for article screening at the full text stage, AG was second reviewer for quality appraisal, DV was second reviewer for data extraction, and AS, DS and EM reviewed and edited the manuscript.

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*Figure 1. PRISMA Flow Diagram*

*Table 1. Keywords and MeSH terms for MEDLINE (OVID)*

((preconception OR pre-conception OR periconceptional OR peri-conceptional OR pre-pregnancy OR prepregnancy OR interconception OR preconception care).tw. OR preconception care.sh) AND (risk factors OR risk taking OR exp health behavior OR exp attitude to health OR health knowledge, attitudes, practice OR exp life style OR exp diet OR exp dietary supplements OR nutrients OR micronutrients OR illicit drugs OR prescription drugs OR exp environmental exposure).sh) AND (infertility OR exp pregnancy outcome OR exp pregnancy complications OR maternal health OR maternal death OR maternal mortality OR exp fetal development OR perinatal death OR child mortality OR exp congenital abnormalities OR exp fetal diseases OR exp infant newborn diseases OR noncommunicable diseases).sh OR (maternal outcome OR infant outcome OR child outcome OR life course).tw.)).

Table 2. Summary of findings of included systematic reviews with meta-analysis

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child		
<b>Body composition</b>	Dean <i>et al.</i> , 2014	Reproductive- aged women	Preconception	Underweight			+			
	Liu <i>et al.</i> , 2016									
	Alvarez-Bueno <i>et al.</i> , 2017			Overweight and Obesity			+		+/-	+
	Liu <i>et al.</i> , 2016									
	Najafi <i>et al.</i> , 2019			Overweight			+		+	
	Sanchez <i>et al.</i> , 2017									
	Zhang <i>et al.</i> , 2015									
	Dean <i>et al.</i> , 2014									



	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Dai <i>et al.</i> , 2018							
	Zhang <i>et al.</i> , 2019							
	Kanadys <i>et al.</i> , 2012			Obesity		+	+	+
	Liu <i>et al.</i> , 2016							
	Sanchez <i>et al.</i> , 2017							
	Teulings <i>et al.</i> , 2019	Parous reproductive aged women	Interpregnancy	$\Delta$ BMI kg/m <sup>2</sup> (weight gain: 1 and 2, 2–3 or > 3 BMI units)		+		
	Teulings <i>et al.</i> , 2019			$\Delta$ BMI kg/m <sup>2</sup> (weight gain: >3 BMI units)		+	+	

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Teulings <i>et al.</i> , 2019			$\Delta$ BMI kg/m <sup>2</sup> (weight loss: >1 BMI unit)			+	
	Teulings <i>et al.</i> , 2019			$\Delta$ BMI kg/m <sup>2</sup> (weight gain:>3 BMI units, normal BMI at index pregnancy)		+	+	
	Teulings <i>et al.</i> , 2019			$\Delta$ BMI kg/m <sup>2</sup> (weight gain: 2–3, >3 BMI units; normal BMI at index pregnancy)		+		
<b>Lifestyle</b>	Karalexi <i>et al.</i> , 2017	Male partners	Preconception	Alcohol intake				-
	Lassi <i>et al.</i> , 2014	Reproductive-aged women	Periconception	Caffeine intake	+			

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Lassi <i>et al.</i> , 2014		Preconception	Alcohol intake	+		+	
	Patra <i>et al.</i> , 2011			Alcohol consumption (average of between 2 and 4 drinks or more per day)			+	
	Lassi <i>et al.</i> , 2014			Smoking			+	-
	Lassi <i>et al.</i> , 2014	Male partners		Illicit drug use (heroin)			+	
	Lassi <i>et al.</i> , 2014	Reproductive- aged women	Periconception	Illicit drug use			-	
	Lassi <i>et al.</i> , 2014			Illicit drug use			+	

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Lassi <i>et al.</i> , 2014		Preconception	Illicit drug use		+		
	Mijatovic- Vukas <i>et al.</i> , 2018			Physical activity (any type and >90 min/wk in leisure time physical activity)		+		
	Tobias <i>et al.</i> , 2011			Physical activity		+		
Nutrition	Crider <i>et al.</i> , 2013	Reproductive- aged women	Preconception	Folic Acid Supplementation [range 400-700 µg daily]				-
	Periconception							
	Hodgetts <i>et al.</i> , 2015		Preconception	Folic Acid Supplementation [400-500 µg daily]			+	

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
<b>Environment</b>	Dean <i>et al.</i> , 2014			Multivitamin supplementation		+	+	
	Lassi <i>et al.</i> , 2014			Occupational radiation	+			
	Lassi <i>et al.</i> , 2014	Reproductive- aged women male partners		Occupational radiation				+
	Lassi <i>et al.</i> , 2014	Male partners		Non-occupational radiation			+	+
	Lassi <i>et al.</i> , 2014	Reproductive- aged women		Pesticides	+			
	Lassi <i>et al.</i> , 2014	Male partners		Pesticides				+

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Lassi <i>et al.</i> , 2014	Reproductive- aged women male partners		Chemicals (paints, solvents, industrial products etc.)				+
	Lassi <i>et al.</i> , 2014			Dermal hydrocarbons and metal				+
	Lassi <i>et al.</i> , 2014			Lead			+	
	Lassi <i>et al.</i> , 2014	Reproductive- aged women	Periconception	Cooking with wood, coal and/or tires			+	
	Lassi <i>et al.</i> , 2014		Preconception	Particulate air pollution	+			
	Zhang <i>et al.</i> , 2020		Ambient Air pollution and Ozone (O <sub>3</sub> )		+			

	<b>Reference</b>	<b>Population</b>	<b>Timeframe</b>	<b>Exposure</b>	<b>Embryo</b>	<b>Maternal</b>	<b>Fetal/neonate</b>	<b>Child</b>
<p>The analysis includes only observational study findings from the review.</p> <p>Main associated health outcome: embryo (e.g., reduced fecundity, miscarriage, prolonged time to pregnancy, reduced embryonic growth trajectories), maternal (e.g., antenatal/post-natal depression, maternal obesity, pre-eclampsia, gestational diabetes mellitus, caesarean, pregnancy induced hypertension, shoulder dystocia, labour dystocia, precipitous labour, placental abruption, uterine rupture), fetal/neonate (e.g., congenital heart defects, neural tube defects, congenital abnormalities, anencephaly, large for gestational age, macrosomia, intensive care neonatal admission, stillbirth, low birthweight, preterm birth, small for gestational age, gastroschisis, reduced intrauterine growth, cryptorchidism, oesophageal atresia), child (e.g., reduced neurocognitive development, attention deficit hyperactivity disorder, autism spectrum disorder, developmental delay, emotional/behavioural problems, cerebral palsy, asthma, leukemia, acute lymphoblastic leukemia, childhood cancers, childhood overweight).</p> <p>+ = association found - = no association found</p>								

Table 3. Summary of findings of included systematic reviews

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child	
<b>Body Composition</b>	Adane <i>et al.</i> , 2016	Reproductive-aged women	Preconception	Obesity				+	
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Body Mass Index (BMI)	+				
	Steinig <i>et al.</i> , 2017	Reproductive-aged women		Obesity [BMI >30 kg/m <sup>2</sup> ]		+			
	Weng <i>et al.</i> , 2012	Children aged 2 years to 16 years		Maternal Overweight					+
	WooBaidal <i>et al.</i> , 2016	Children aged 6 months to 18 years		Maternal pre- pregnancy BMI					+
	WooBaidal <i>et al.</i> , 2016	Children aged 6 months to 18 years		Paternal BMI					+



	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
<b>Nutrition</b>	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Diet (Mediterranean dietary pattern)	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Folic acid and multivitamin supplement	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women	Periconception	Vitamin B6 levels	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Folic acid levels	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Vitamin B12 levels	+			
	Ramakrishnan <i>et al.</i> , 2012	Reproductive-aged women	Preconception	Multivitamin			+	

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Ramakrishnan <i>et al.</i> , 2012	Reproductive-aged women		Multivitamin		+		
	Viswanathan <i>et al.</i> , 2017	Reproductive-aged women	Preconception	Folic acid supplementation			+	
Lifestyle	Oostingh <i>et al.</i> , 2019	Reproductive-aged women	Periconception	Smoking	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Alcohol	+			
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women		Caffeine				
	Oostingh <i>et al.</i> , 2019	Reproductive-aged women	Preconception Periconception	Physical Activity (Moderate)	+			

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	WooBaidal <i>et al.</i> , 2016	Children aged 6 months to 18 years	Preconception	Paternal smoking				-
Birth Spacing	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women	Interpregnancy (<24 months)	Short interpregnancy interval (<6 and 6-11 months)		+		
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (<6 vs. 18-23 mo)		+		
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (6-11 vs. 18-23 mo)		+		

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (<12 vs. 12-43 mo and <24 vs. 24-47 mo and <24 vs. ≥120 mo)		+		
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (<6 vs. 18-60 mo and 6- 12 vs. 18-60 mo and 12-18 vs. 18- 60 mo)		+		

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (<6 vs. 24-59 mo)		+		
	Hutcheon <i>et al.</i> , 2019	Parous reproductive-aged women		Short interpregnancy interval (<6 vs. 18-59 mo) in women attempting vaginal birth after caesarean		+		

	Reference	Population	Timeframe	Exposure	Embryo	Maternal	Fetal/neonate	Child
<b>Environment</b>	Oostingh <i>et al.</i> , 2019	Reproductive-aged women	Preconception	Diet (fish contaminated with organochlorine compounds)	+			
<p>The analysis includes only observational study findings from the review.</p> <p>Main associated health outcome: embryo (e.g., reduced fecundity, miscarriage, prolonged time to pregnancy, reduced embryonic growth trajectories), maternal (e.g., antenatal/post-natal depression, maternal obesity, pre-eclampsia, gestational diabetes mellitus, caesarean, pregnancy induced hypertension, shoulder dystocia, labour dystocia, precipitous labour, placental abruption, uterine rupture), fetal/neonate (e.g., congenital heart defects, neural tube defects, congenital abnormalities, anencephaly, large for gestational age, macrosomia, intensive care neonatal admission, stillbirth, low birthweight, preterm birth, small for gestational age, gastroschisis, reduced intrauterine growth, cryptorchidism, oesophageal atresia), child (e.g., reduced neurocognitive development, attention deficit hyperactivity disorder, autism spectrum disorder, developmental delay, emotional/behavioural problems, cerebral palsy, asthma, leukemia, acute lymphoblastic leukemia, childhood cancers, childhood overweight).</p> <p>+ = association found - = no association found</p>								