**Narrative review of reviews of preconceptional interventions to prevent increased risk of obesity and non-communicable diseases in children**

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**Abstract**

**Background:** Evidence for the effect of preconceptional and peri-conceptional risk factors on childhood outcomes such as obesity is growing. Insights into mechanisms that influence the early nutritional environment of the fetus have also suggested that epigenetic processes during this period can increase susceptibility to obesity and other non-communicable diseases (NCDs) in later life. Thus, if issues such as maternal malnutrition (both over and under nutrition) are not addressed before pregnancy they could led to a passage of risk of NCDs to the next generation. Birthweight (both low and high birth weight) has been extensively studied as a risk factor for future obesity, although it is a crude marker of prenatal development.

**Objective:** To synthesise evidence for interventions in the preconception period to prevent obesity and other risk factors for NCDs in children.

**Methods:** A search for systematic reviews of interventions in the preconceptional period to prevent NCDs published between 2006 - 2017 was conducted on PubMed and Cochrane Database for Systematic Reviews.

**Results:** Fifteen reviews were included in the final report. There was considerable variation in the outcomes assessed between the reviews. The reviews predominantly included observational studies, leading to an overall low-quality of evidence. For the target group of this review, preconceptional women, very few studies were identified. Results from these reviews suggest that exercise and diet based interventions can significantly reduce maternal weight post-partum (Mean difference (MD) -1.93 kg [95% CI -2.96 to -0.89]). Compared to standard care, women in the intervention groups gained less weight during pregnancy (MD for gestational weight gain MD -1.66 kg [95% CI -3.12 to -0.21]). Pre-pregnancy exercise was associated with GDM risk reduction and women who received preconceptional care (PCC) had a lower mean glycosylated haemoglobin (MD -2.43 [95% CI -2.58, -2.27]) compared to women who did not receive PCC. Balanced protein energy supplementation during and before pregnancy was associated with a 32% reduction in low birthweight in the intervention compared with the control group (Relative risk 0.68 [95% CI 0.51, 0.92]), and an increase in mean birth weight (MD 73.78g [95%CI 30.42, 117.15]).

**Conclusion**: The quality of evidence from eligible reviews hinders development of global recommendations on the prevention of obesity and NCDs in children. Nevertheless, this review has highlighted that women who received preconception education and counselling for lifestyle modification, were more likely than those who did not receive any PCC to have improved pregnancy outcomes, such as improved control of GDM and significantly improved birthweight. Further, behavioural outcomes such as improved eating habits and increased physical activity were observed in women, which are likely to have longer-term beneficial effects on maternal and child health.

**Abbreviations**

Maternal, neonatal and child outcomes (MNCH)

Low birth weight (LBW)

Gestational diabetes mellitus (GDM).

Non-communicable diseases NCDs

Developmental origins of health and disease (DOHaD)

Large for gestational age (LGA)

# Background

The potential of preconception services has been identified for tackling various issues related to MNCH across the globe1. These include issues such as preterm birth, undernutrition, low birth weight (LBW) and maternal outcomes such as weight gain in pregnancy and gestational diabetes mellitus (GDM). Preconception care is defined as “a set of interventions that aim to identify and modify biomedical, behavioural, and social risks to a woman’s health or pregnancy outcome through prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact” 2. Obesity in women is of growing concern because it puts them in danger of GDM, hypertension, and increased risk for obstetric intervention along with adverse neonatal outcomes3. With the growth in literature concerning the influence of the periconceptional period on fetal growth and long-term effects on risk factors for Non-communicable diseases (NCDs)4, it is essential that preconception services also incorporate interventions to prevent this passage of risk to the next generation.

The relationship between birthweight and later obesity has been widely researched in studies related to developmental origins of health and disease (DOHaD)5, results of which suggest that being on either end of the spectrum for birthweight can predispose to obesity in later life6. Maternal over or undernutrition during pregnancy can also lead to such a ‘programming’ effect on the fetus during critical periods. This causes a further increased predisposition of the child to chronic diseases in adulthood such as type 2 diabetes mellitus, renal and coronary heart disease, hypertension and stroke. 4,5,7,8 While a higher risk of cardiovascular outcomes such as increased blood pressure and coronary heart disease has been associated with low birthweight and a high BMI in adulthood, a higher BMI is also observed following a high birthweight with central obesity more commonly seen in LBW babies9. GDM is associated with several adverse outcomes such as congenital anomalies and large for gestational age (LGA) babies. Studies have also shown that children who were LGA at birth, and were exposed to an environment of maternal obesity or GDM, are at a high risk of developing metabolic syndrome in later life10. Programming effects can be seen even in childhood, as significantly higher insulin resistance, higher plasma total and LDL cholesterol and high systolic blood pressure were also observed among children (eight years old, n=477) with low birth weight11. While several risk factors for LBW which are not easily modified have been described, including preterm birth, intrauterine growth restriction, maternal short stature and twin pregnancies, several modifiable risk factors such as maternal nutritional status and smoking have been linked to future NCDs and obesity. Moschonis et al. (2008) 12 analysed data from a survey of 2374 Greek children (aged 1-5 years) and found that LGA babies were 4.59 and 2.19 times more likely to be overweight at 6 and 12 months of age, respectively, than children born at weight appropriate for gestational age. In collating evidence for prenatal programming of childhood obesity, Huang et al13 found that prenatal exposure to maternal smoking was significantly associated with an increased odds of childhood overweight and obesity, with most odds ratios ranging between 1.5 to 2.0.Other factors related to childhood overweight included paternal overweight and children not exclusively breastfed. Maternal nutritional status and pre-pregnancy weight are strong predictors of neonatal outcomes. Results of the pooled analysis of 12 observation studies (out of 34 studies included in one review 14) suggest that being underweight before pregnancy can increase the risk of preterm birth (RR 1.32, 95% CI 1.22-1.43) and SGA babies (RR 1.64, 95% CI 1.22-2.21). Liu et al.15, in a retrospective study of 5047 Chinese women, found that compared to women with a normal BMI, women who underweight had a higher risk for SGA babies (OR = 1.67 95% CI 1.07-2.61). Pre-pregnancy obesity on the other hand significantly increased the risk of preeclampsia (OR 2.28; 95% CI: 2.04-2.55) and GDM (OR 1.91; 95% CI: 1.58-2.32); and maternal overweight before conception was also significantly associated with perinatal outcomes such as macrosomia, LGA babies, neural tube defects and congenital heart defects.14

There is evidence for several maternal (and potentially paternal) risk factors such as over- or undernutrition, GDM and smoking that could lead to intermediate outcomes such as LBW or macrosomia, which increases the risk for childhood obesity and NCDs throughout the life course.16 There are signs that preconceptional interventions could provide benefit in this context, e.g. adopting healthy habits prior to conception has been associated with reduced risk of GDM and its complications 17. There is currently no high-quality evidence to confirm or quantify whether directed preconception health programs are beneficial in preventing NCDs in children. It is essential to determine what type of interventions have already been implemented, the appropriate setting/ context for such interventions, and whether these interventions helped in preventing adverse outcomes. In high-income settings, tackling issues such as overweight and lack of physical activity must also be considered pre-pregnancy as young preconceptional women and women with children are often less likely to engage in interventions for preconception care.18 In LMICs the age of first pregnancy remains low and undernutrition leading to stunted growth is a major cause of LBW babies in such regions.19 Added to this, rapid urbanisation and development has led to a change in diet and lifestyle leading to an increase in NCDs in countries such as India and China where LBW is still a pressing issue. To achieve optimal fetal growth, improving maternal nutrition is of utmost importance. The World Health Organization’s (WHO) Commission on Ending Childhood Obesity (ECHO)8 considers preconception and pregnancy care as a core component of the strategy to prevent childhood obesity. This includes improving parents’ lifestyle before conception, maternal health and nutrition before and during pregnancy, treatment of gestational diabetes, supporting breastfeeding and improving infant feeding practices.

# Aim

The objective of this report is to prepare a narrative review of existing evidence for preconception interventions to prevent childhood obesity and other risk factors for non-communicable diseases in children, based on previous systematic reviews.

# Methods

An initial scoping review suggested that there were few studies with the primary aim of evaluating the effect of interventions to prevent prenatal risk factors on outcomes such as childhood obesity, so we considered intermediate outcomes discussed above that were associated with future NCD risk and obesity in children. We included systematic reviews, which evaluated observational and experimental studies, focusing on prevention of maternal risk factors such as GDM, type 1 and 2 diabetes, maternal malnutrition (under and overnutrition), maternal weight and pregnancy-related outcomes such as birthweight. The following exclusion criteria were applied to reviews, as well as to studies included in the original reviews - focus on a different period of the life course e.g. starting in pregnancy, studies evaluating treatment for NCDs, focus on specific clinical conditions such as pre-eclampsia, focus on IVF and studies identifying risk factors in the preconception period.

This review was part of a series of reviews conducted for different periods in the life course aimed at identifying interventions to prevent childhood obesity and later NCDs. A search was conducted in May 2016 in PubMed and the Cochrane Library, including the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (DARE) to identify pertinent systematic reviews published between 2006 and 2016. The search was repeated in 2018 January to update the review. Data were extracted from each systematic review and summarised in a Table (Appendix 1) for relevant maternal, neonatal and child health outcomes. Other outcomes considered in the original review that did not address NCD-related risk factors or outcomes were not extracted. The evaluation was done by one author. We did not attempt to pool the results from the reviews due to differences in populations considered for each outcome, variations in variables considered and in the settings of interventions. Pooled results of meta-analyses were however extracted, and a qualitative summary of findings is reported for reviews where meta-analysis was not conducted. We conducted a ROBIS evaluation (Table 1 and Appendix 2) of each systematic review to assess risk of bias during the review process. The ROBIS tool20 was completed in 3 phases to (1) Assess relevance of the review (Population, intervention, comparator and outcomes or equivalent) (2) Identify concerns with the review process (3) Judge risk of bias in the review (High/ Low or Unclear).

# Results

Fifteen reviews were identified including five Cochrane reviews; two of the papers 3,14 were part of the same systematic review. Not all reviews were systematic reviews of interventions, thus integrative reviews of observational studies also formed a part of this report. All reviews were published between 2007 and 2016 and included studies from high-income countries and LMICs. Ten reviews14,21-29 focused specifically on preconception and/ or inter-conception periods. Three reviews26,30,31 focused on interventions in different reproductive stages to prevent gestational diabetes, two of which27,28 focused on women with pre-existing diabetes mellitus and one on overweight and obese women. The most variation was in terms of outcomes considered (maternal, fetal and neonatal). None of the studies included in the 16 reviews directly addressed the aim of the present review – i.e. preventing childhood obesity using preconception interventions. Two reviews3,14 were part of a larger study investigating the state of preconception health services for a range of outcomes including maternal smoking cessation, neonatal mortality etc. Together, the 16 reviews report results from over 250 studies (54 trials), only a portion of which contributed to the meta-analysis when performed in each review. The overall risk of bias was low for 13 of the reviews (Appendix 4). Reasons for high risk of bias included lack of well-defined eligibility criteria and appraisal and quality assessment methods. It must be noted that since all reviews were not systematic reviews, but also included scoping reviews. Table 2 provides a summary of selected reviews along with the interventions and outcomes considered.

There was a lack of consensus in terms of defining the population to be included in the preconception period. Dean *et al.* 3 propose that ‘the preconception period should be defined as a minimum of 1-2 years prior to the initiation of any unprotected sexual intercourse that could possibly result in a pregnancy. This would extend through the care provided in early pregnancy (peri-conception care) and the postnatal period until the next pregnancy’. Studies often include the post-partum period, early pregnancy and peri-conceptional periods as part of preconception care. Other authors 32, who considered the peri-conception group, used the first trimester (<12 weeks of gestation) to select their target populations and highlighted this as a critical period to access women from LMICs who often do not seek antenatal care before 12 weeks. The post-partum period was also considered as part of the preconception period for the next pregnancy in three reviews 21,26,30. This provides potential for interventions aiming to support recent mothers with issues such as excess weight gain in order to have positive outcomes in the next pregnancy. We present a qualitative synthesis of interventions based on the outcomes considered in each selected review.

### **Table 1. Results of ROBIS assessment for risk of bias**

|  |  |  |  |
| --- | --- | --- | --- |
|  | *PHASE 1* | *PHASE 2* | *PHASE 3* |
| **REVIEW** | ***Relevance******(PICO)*** | ***Study eligibility criteria*** | ***Identification and selection of studies***  | ***Data collection and study appraisal*** | ***Synthesis and findings*** | ***Risk of bias in the review*** |
| A R. A.Adegboye et al. (2013) | Yes | Low | Low | Low | Low | Low |
| M. Agha, R. A. Agha, J. Sandell (2014)  | Yes | Low | Low | Low | Low | Low |
| S. V. Dean, Z. S. Lassi, A. M. Imam, Z. A. Bhutta (2014)  | Yes | Low  | Low | Unclear | Low  | Low |
| J. M DiNallo, D. S Downs (2007)  | Yes | High | High | High | High | High |
| N. Hussein, J Kai, N. Qureshi (2016)  | Yes | Low | Low | Low | High | Low |
| A. Imdad, Z. A. Bhutta (2012)  | No | Low | Unclear | Low | Low | Low |
| N. Opray, R. M. Grivell, A. R. Deussen (2015)  | Yes | Low | Low | N/A | N/A | Low |
| S. Temel, S. F. van Voorst, B.W. Jack, S. Denktas, E. A. P. Steegers (2014) | Yes | Low | Low | Low | Low | Low |
| J. Tieu, et al(2013)  | Yes | Low | Low | N/A | N/A | Low |
| J. Tieu, et al(2010)  | Yes | Low | Low | Unclear | Low | Low |
| D.K. Tobias et al (2011)  | Yes | Low | Low | Low | Low | Low |
| U. Ramakrishnan (2012)  | Yes | Low | High | Low | high | High |
| H. A Wahabi (2010)  | Yes | Low | Low | Low | Low | Low |
| M. Whitworth(2009)  | Yes | Low | Low | Low | Low | Low |
| N Hemsing, L Greaves, N Poole (2017) | Yes | Low | Low | Unclear | Low | Low |

### **Table 2. Characteristics of systematic reviews included**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Citation (Year) | Exposures/ Intervention | Population | Outcomes\* | Summary of results and MA (if meta-analysis was carried out) |
| A R. A.Adegboye et al.21 (2013) | Nutritional and exercise interventions, community based and individual | Women in the post-partum period (up to 24 months after childbirth for this review).  | 1. Change in body weight2. Percentage of women who returned to pre-pregnancy weight or lost weight retained after childbirth3. Women who achieved a healthy weight or weight loss of clinical significance4. Change in percentage body fat5. Change in fat free mass6. Change in cardiorespiratory fitness | Pooled analysis was not possible due to heterogeneity and variation in interventions.Results of subgroup analyses:i. Change in body weight in kgs:*Usual care versus Diet:* MD: -1.70 kg 95% CI (-2.08, -1.32)*Usual care versus Exercise:* MD: -0.10 kg; 95% CI (-1.90 to 1.71)*Usual care versus Diet + Exercise:* MD -1.93 kg; 95% CI -2.96 to -0.89*Diet versus Diet plus exercise :* MD 0.30 kg ; 95%CI -0.06 to 0.66ii. Percentage of women who returned to pre-pregnancy weight or lost weight retained after childbirth - RR 2.00 (95%CI 1.31 to 3.05)Other results included a change in percentage of body fat (not significant) in the diet groups and significant improvement in cardiorespiratory fitness (MD in VO2 max 6.73 mL/kg/minute95% CI 4.28 to 9.17) in the exercise groups.  |
| M. Agha et al. (2014)33 | Behavioural interventions for weight management during pregnancy | Women of child-bearing age planning to get pregnant and/or those who were already pregnant | Primary outcome measure was gestational weight gain. Secondary measures included postpartum weight retention, postpartum weight loss, infant birth weight and gestation week of delivery. | Compared to standard care, women in intervention groups gained lesser weight during pregnancy.Pooled results for GWG: MD -1.66 kg (95% CI -3.12 to -0.21) |
| S. V. Dean et al. (2014)14 | Any form of preconception care | Women in the reproductive age group (aged 15 to 49) | Congenital anomaliesNutritional risk factors for adverse birth outcomes – maternal pre pregnancy weight | Maternal overweight before conception were also significantly associated with perinatal outcomes such as macrosomia, large-for-gestational age babies (OR 1.63, 95% CI 1.51-1.76)Pooled results of 3 RCTs suggest a protective effect of Folic acid supplementation to prevent NCDs: RR = 0.31 (0.14, 0.66)Multivitamin supplementation to prevent NCDS: RR = 0.51 (0.31, 0.82) |
| DiNallo et al. (2007)30  | Exercise related interventions, biological interventions (Exercise + insulin therapy) | Studies included pregnant adults, postpartum adults and non-pregnant adults | No specific outcomes related to NCDs reported | Pre-pregnancy exercise was associated with GDM risk reduction |
| N. Hussein et. Al (2016)23 | Advice on nutrition, lifestyle, folate intake, smoking or alcohol; screening for genetic disorders or diabetes | Women of reproductive age including women who had existing medical, obstetric or genetic risks | 1. Improvement in knowledge2. Improvement in self-efficacy and health locus ofControl3. Improvement in maternal risk behaviour4. Improvement in adverse pregnancy outcomes | Results were not significant for adverse pregnancy outcomes.Improvement in self-efficacy along with eating healthier food (OR: 1.757, P=0.008) being physically active (OR: 2.185, P=0.0001) and perceived higher preconception control of birth outcomes (OR: 1.916, P=0.031)Significant improvement in exercise self-efficacy was seen (difference in score 15.4; 95% CI: 13.74 - 17.06) and internal health locus of control (HLOC) scores (difference in score 6.4; 95% CI: 5.41–7.39)No pooled analysis due to heterogeneity |
| A. Imdad, Z. A. Bhutta (2012)34 | Interventions including dietary advice to increase protein intake or supplementation of protein | Pregnant women and women attending pre-natal clinics | 1. Birthweight2. SGA3. LBW | 1. BirthweightMean difference 73.78g [30.42, 117.15]2. SGARR 0.68 [0.51, 0.92]3. LBWRR 0.68 [0.51, 0.92]Results of a subgroup analysis show that balanced protein energy supplementation was more effective in malnourished women (MD 100 g [95% CI 53, 147]) than in adequately nourished women (MD 37 g [95% CI -34, 99]). |
| N. Opray et al (2015)24 | Interventions for improving pregnancy outcomes for women who are overweight or obese | Women who are not pregnant, but of reproductive age with BMI >/=to 25 kg/m2. | Large for gestational age infants, maternal and infant outcomes | Zero studies were included in the final report.  |
| S. Temel et al (2014)25 | Any type of intervention | Not specified | Risk/protective factors for adverse outcomes considered are:Folic acid supplementationSmokingAlcoholNutrition | A supplemental food programme among women with low income and nutritionally at risk in their inter-pregnancy interval showed a positive effect on birth weight and birth length35 |
| J. Tieu, et al(2013)26 | Any type of interconception intervention for women with GDM | Women in the reproductive age group who have been diagnosed with GDM in a previous pregnancy | Expected primary outcomes were Maternal GDM, mode of birth and neonatal outcomes such as LGA, macrosomia perinatal mortality | No completed trial met the inclusion criteria, and one ongoing clinical trial was identified.Results of the ongoing trial are not available |
| J. Tieu, et al(2010)27 | Any type of preconception care for diabetic women | Women of reproductive age with pre-existing diabetes mellitus (type I or type II) who were not pregnant during the trial | Metabolic control by HbA1c levels | Results of one trial: Reported as mean change from baseline: -1% no 95% CI reported. |
| D.K. Tobias et al. (2011)31 | Physical activity before and during pregnancy | Women in the reproductive age group | Diagnosis of Gestational Diabetes Mellitus | Prepregnancy physical activity OR = 0.45 (0.28-0.75) and early pregnancy physical activity OR = 0.76 (0.70 – 0.83) was associated with a lower odds of GDM (pooled results of subgroup analyses) |
| U. Ramakrishnan (2012)32 | Nutritional interventions | Periconceptional women | SGALow birthweightBirthweightBirth defects | An increased risk of delivering a SGA infant (adjusted RR: 1.7 [95% CI 1.1, 2.6]) among underweight women (BMI < 18.5 kg/m2) was reported in one studyNo significant differences were found between women receiving folic acid supplementation 12 weeks before gestation and those who received other trace elements |
| H. A Wahabi (2010)28 | Preconception care for diabetic women | Women of reproductive age group with type I or type II diabetes | 1. First trimester mean value of Glycosylated Haemoglobin3. SGA4. Macrosomia5. Congenital Malformations | When compared to groups with no preconceptional care:1. First trimester mean value of Glycosylated HaemoglobinMD -2.43 (-2.58, -2.27)2. MacrosomiaRR = 1.03 (0.81, 1.30)3. Small for Gestational AgeRR = 0.26 (0.05, 1.41)4. Congenital MalformationsRR 0.25(95% CI 0.15-0.42) |
| M. Whitworth(2009)29 | Health promotion | Women of childbearing age | Small for gestational age | Lower risk of SGA babies for women in intervention group (One trial)RR=1.30 (95%CI: 0.83, 2.04)Other results included improved maternal behavioural outcomes such as risky drinking and smoking (non-significant) |
| N Hemsing, L Greaves, N Poole (2017) | Any preconception/ interconception intervention | Women of childbearing age | All outcomes reported in studies were included | An intervention based on risk assessment delivered by a midwife suggested that preconception care prior to conception was associated with less weight gain reported prior to conception.Web based interventions showed an increased knowledge of preconception behaviours at 6 months follow up. Overall, group health education interventions showed promise with significant improvements in preconception health knowledge, and in obesity and diabetes knowledge.  |

## **Nutritional supplementation**

Four of the 16 studies included in a review by Imdad *et al.* included preconceptional women as part of the eligible population 34*.* Results of the meta-analysis showed a positive effect of balanced protein-energy supplementation on birthweight compared with control groups [MD 73 (g) (95% CI: 30, 117)]. The results of a subgroup analysis based on nutritional status of the mother (which would have pertained pre-pregnancy) showed that benefits of supplementation on birthweight were more prominent in undernourished women (MD 100 [95% CI 53, 147]) than adequately nourished women (MD 37 [95% CI -34, 99]). In an extensive review of preconception care to avoid risk factors with known adverse outcomes Temel *et al.* 25 included 44 studies that explored lifestyle-related risk factors and other routine preconception services. Interventions that included individual counselling sessions, provision of supplements, public campaigns and food fortification led to a lower risk of congenital anomalies. Evidence for multivitamin supplementation and birthweight and SGA are of low quality but show promise. Results from prospective studies in Korea, Thailand, Netherlands and China have reported a decreased risk for LBW after periconceptional micronutrient supplementation32. One RCT (Hungary, n=5502) provided multivitamin supplementation with folic acid and other vitamins (for the intervention group), along with supplements containing trace elements (control group), to periconceptional women36. However, there was an increase in birthweight compared to the general population in both groups.

## **Physical activity**

Results of a review that included 23 studies 14 involving diet and/or exercise-based interventions to reduce weight in women suggest that interventions that incorporated calorie restriction and physical activity, along with mentoring, brought about sustained weight loss. All studies were controlled trials and women in the intervention group lost an average of up to 3.5 kg. A Cochrane review 21 evaluated the effectiveness of diet and exercise-based interventions for weight reduction in women after childbirth and found significant results among the diet, exercise or diet plus exercise groups compared to standard care. There was a strong association between change in maternal body weight post-pregnancy and diet based interventions [MD -1.70 (-2.08, -1.32)]. In a review of observational studies that explored the relationship between physical activity and development of GDM 31, the meta-analysis indicated a lower risk of gestational diabetes among women who were in the high physical activity groups compared to those in the lower ones (pooled OR 0.45; 95% CI 0.28–0.75). However, heterogeneity was significant (I2=82%). Early pregnancy physical activity was also associated with a significant 24% lower risk of GDM in the high activity groups compared with the lowest activity group. There was also an inverse association between involvement in vigorous physical activity before pregnancy, compared to no vigorous activity, but the pooled estimate was not significant (0.55 [0.21–1.43]). There is weak evidence supporting a protective effect of brisk walking and stair climbing in early pregnancy and risk of GDM, and a non-significant risk of GDM among women who reported high sedentary time pre-pregnancy and early pregnancy (<2 hours/ week of total physical activity)31.

## **Routine preconception health promotion**

Pre-conception care is defined as ‘any intervention provided to women of childbearing age, regardless of pregnancy status or desire, before pregnancy, to improve health outcomes for women, newborns and children’ 1. Two reviews 25,29 explored the effectiveness of routine prepregnancy health promotion and preconception care. Temel et al. assessed a multiple risk factor approach for inter-conceptional women preparing for pregnancy and suggest that preconception care (in any setting) was associated with maternal behaviour change such as increased intake of multivitamins (self-reported) one month before pregnancy and cessation of alcohol consumption three months before pregnancy. Observational studies conducted among subfertile patients in a hospital-based setting also suggest that preconception counselling led to an increased intake of fruit and vegetables among couples. Other self-reported changes include smoking cessation and weight reduction (mean = 6.1kg, SD 3.6). While the generalisability of hospital-based studies on a subfertile population is low, the studies had a low risk of bias. One Cochrane review 29 assessed the effectiveness of routine health promotion on several MNCH outcomes. Results of four trials (n=2300 women) showed no strong evidence of a difference between groups for congenital anomalies or weight for gestational age, when compared to women who received no preconceptional interventions. The interventions consisted of health education, varying in number of sessions and duration of each session and only one study followed up women through pregnancy. A significantly lower rate of binge drinking (risk ratio 1.24, 95% CI 1.06 to 1.44) was noted after health promotion interventions.

**Birthweight**

Seven reviews 14,23,28-30,32,34 considered parameters related to weight or size of the newborn as a primary outcome. LBW was included in four reviews 23,29,32,34, SGA in four28,29,32,34, macrosomia in one 28 and birthweight in three reviews30,32,34.

Anaemia was an important risk factor for LBW in LMICs, and results of one review 14 identified six studies that utilised a range of interventions to prevent or treat anaemia in the preconception period. Folic acid was often supplied along with iron and similar results were observed in Vietnam and Bangladesh where a significant reduction in anaemia was seen. Trials in Vietnam 37 have also shown a significant decrease in LBW babies (OR= 0.29, 95% CI 0.10 - 0.81) in intervention groups who received deworming along with weekly iron and folic acid. An increased risk of LBW babies is also seen in adolescent pregnancy, short inter-pregnancy intervals, pre-eclampsia and advanced maternal age38.

Pooled results from five studies34 showed a reduction of 32% in the risk of LBW in the intervention group compared with control [Relative Risk = 0.68 (95% CI 0.51, 0.92)]. There was also a significant reduction of risk for SGA babies [RR 0.66 (95% CI 0.49, 0.89)] in the intervention groups (nine studies reporting data, GRADE-Low). The Cochrane review by Whitworth *et al.* (2009)29 however found a non-significant reduction in risk of births where babies were SGA in the intervention group after PCC (RR 1.30, 95% CI 0.83 to 2.04). This result is based on the finding of one RCT39 that included multicomponent pre-pregnancy counselling with discussion of health and lifestyle issues, preparation and timing for pregnancy. The study, conducted in Australia, did not find any beneficial outcomes and birth weight in the second birth (post intervention) was significantly lower (-97.4 g) among infants in the intervention arm. The results could partly be attributed to the non-significant increase in preterm births in the intervention group. Observational studies also suggest that preconceptional and periconceptional vitamin and mineral supplementation reduces the risk of LBW and SGA babies and preterm deliveries. Overall, the strength of evidence for birthweight is very low and that for SGA is low.

## **Gestational weight gain and post-partum weight loss**

Three reviews 21,24,33 assessed the effectiveness of interventions with the objective of weight loss or achieving a healthy weight for women in different stages of reproduction. A Cochrane review 21 evaluating the effectiveness of dietary and exercise-based interventions for weight reduction in women after childbirth considered secondary outcomes such as maternal body composition and cardio-respiratory fitness. The meta-analysis for subgroups based on comparison groups show that women who took part in a diet (one trial, MD -1.70 kg; 95% CI -2.08 to -1.32), or diet plus exercise intervention (7 trials; MD -1.93 kg; 95% CI -2.96 to -0.89) showed significant weight loss compared to women in the usual care group. One trial that compared diet alone versus diet plus exercise groups showed no difference in the degree of weight loss (MD 0.30 kg; 95% CI -0.06 to 0.66). Maternal cardio-respiratory fitness significantly improved (high-quality evidence) in the exercise groups (four studies, MD V02max: 6.73 mL/kg/minute 95% CI 4.28 to 9.17) and diet plus exercise groups (two trials, MD V02max: 3.76 mL/kg/minute; 95% CI 1.46 to 6.07), compared to usual care. Significant improvement in fat-free mass (MD 0.88 kg; 95% CI 0.06 to 1.69) was seen among women who were in the exercise group compared to usual care in two trials. Though diet alone was effective in reducing weight post-partum, it also reduced fat-free mass as participants in the diet only group lost significantly more fat-free mass than women in usual care (one trial, MD -0.90 kg 95% CI -1.38 to -0.42). Women who followed a dietary and exercise programme were significantly more likely to return to prepregnancy weight (RR 2.00 95%CI 1.31 to 3.05). A high-quality review of 15 studies to reduce and prevent obesity, in women who were overweight, obese or severely obese, by Agha *et al.* 33 included preconceptional (one study n = 692) and pregnant women. When intervention groups were compared to standard maternity care for the outcome of gestational weight gain (GWG), lower GWG was seen in the intervention groups (MD -1.66 kg; 95% CI -3.12 to -0.21 kg). Interventions delivered in early pregnancy were more effective than those delivered later during pregnancy. There was considerable heterogeneity between studies in GWG group (P< 0.00001 I2 = 86%). No significant effect of interventions were seen on subgroup analysis including women from all weight groups, but when obese pregnant women were considered a significantly lower GWG compared to standard care was observed (MD -4.65; 95%CI -8.74 to -0.56). One study 40 focused on the preconceptional period and results suggest that women in the intervention group gained significantly lower weight (MD −17.95; 95%CI −33.42 to −2.49) compared to those in the control group over a 12 month follow up period. This was not significant after controlling for pre-pregnancy obesity (MD −10.46; 95% CI −24.27 to 3.36).

There is high-quality evidence supporting the findings for cardio-respiratory fitness, return to pre-pregnancy weight and change in fat-free mass, moderate evidence supporting interventions that helped women achieve a healthy BMI post-partum, change in body weight and change in percentage of body fat. The strength of evidence for preventing GWG through preconception interventions is based on the findings of one study, and is low.

**Gestational Diabetes and interventions for diabetic women**

Three reviews 26,30,31 considered outcomes related to GDM and two 27,28 considered women with pre-existing diabetes mellitus as their target population. A review28 of preconception care for diabetic women to improve both maternal and fetal outcomes included 20 studies (one controlled trial). Preconception care in this case included interventions such as counselling/ health education for diabetes, multivitamin and folic acid supplementation and glycaemic control with insulin. Results of a meta-analysis suggested that preconception care is effective in lowering HbA1c in the first trimester of pregnancy by 2.43% (95% CI -2.58, -2.27). Four trials were included in this analysis with high heterogeneity (P<0.00001, I2=97%). There was no effect on reducing the risk for macrosomia or SGA babies, but a significantly lowered risk of congenital malformation (RR 0.25; 95% CI 0.15-0.42). A Cochrane review included only one trial41 assessing the effectiveness of an intervention (n=53 adolescents) for diabetic women and found a lowered HbA1c level compared to baseline (very low-quality evidence as outcome data addressed in case of metabolic control was incomplete). A review of 16 studies 42 not included in this review of reviews that evaluated control of pre-existing DM during pregnancy, report that all studies that presented results of blood sugar control (glycosylated haemoglobin HbA1, HbA1c, and GHb, or fasting and postprandial capillary blood glucose) found preconception care to be associated with improved control in early pregnancy. In type 1 diabetics, long-term intensive insulin prior to conception was more effective in achieving blood sugar control at conception than conventional insulin therapy with conversion to intensive therapy just prior to conception. A review of exercise-based interventions in preventing GDM **30** reports that among women with GDM, exercise decreased the need for insulin and improved cardiorespiratory fitness. A 45% reduction in risk of GDM was found among pre-pregnancy exercise groups (co-relational studies). However, findings of this review are largely based on observational studies - 24 studies were included of which four were intervention studies. They provide very low quality evidence for the benefits of exercise to prevent GDM. The studies also showed high inconsistency in reporting study outcomes and characteristics. Certain studies reported outcomes in terms of birth weight and mean gestational age at delivery (inconsistent results), and need for insulin or dosage of insulin therapy. Prospective studies showed protective effects of moderate to vigorous exercise before pregnancy 43,44. A prospective study 44 reported that, among 1428 incident cases of GDM, there was a significant inverse association between vigorous activity and the risk of GDM (after controlling for common confounders like BMI and diet). Women with a high screen time (spent 20 h/week or more watching television) but who did not perform vigorous activity had a significantly higher GDM risk than women who spent less than 2 h/week watching television and were physically active (multivariate RR, 2.30; 95% CI, 1.06-4.97). A Cochrane review did not identify any eligible trials evaluating the effectiveness of inter-conception interventions among women with a history of GDM. Tobias *et al.* (2011)31 identified seven pre-pregnancy and five early pregnancy studies that looked for the effect of physical activity on risk of GDM. Pooled results of the pre-pregnancy studies showed a significantly decreased likelihood of GDM among women with high levels of physical activity. Exercise in early pregnancy had a significantly protective effect (OR = 0.76; 95% CI 0.70–0.83), along with pre-pregnancy exercise (OR = 0.45; 95% CI 0.28-0.75). However, pre pregnancy exercise is by itself a strong predictor of exercise during early pregnancy and this could have influenced the findings in the early pregnancy groups. This review however did not include any RCTs and was based on low-quality evidence from observational studies. The confounders considered by each study also varied with only two studies assessing family history of DM and one conducting a dietary assessment. Physical activity was measured using the Stanford Seven-Day PA Recall and other standardised PA questionnaires. Preconception care was also associated with fewer maternal hospitalizations and reduced utilization of neonatal intensive care. Considering the adverse outcomes of GDM, they represent a group who could potentially benefit from intervention to prevent the condition before pregnancy. However, our review found a lack of good quality experimental studies on these issues.

## **Smoking**

Four of the reviews3,23,25,29 included preconception interventions for smoking cessation. Women were three times more likely to quit smoking, five to six times more likely to consume folic acid and 71% more likely to breastfeed if they had been part of a preconception lifestyle modification intervention. There is poor quality evidence supporting self-reported behaviour change outcomes related to risky drinking and smoking after preconception interventions 25. The intervention included smoking cessation advice at a preconception consultation, counselling and provision of material with information. Whitworth *et al29.* found no significant effect of intervention on smoking cessation when compared to the control groups.

## **Behaviour change interventions**

Three reviews 23,25,29 reported studies that had outcomes related to maternal behaviour change. A recent review of eight RCTs 23 exploring the effects of preconception interventions suggests that multifactorial and single risk interventions improved maternal knowledge, self-efficacy, health locus of control and risk behaviour. The interventions consisted of multifactorial or single reproductive health risk assessments, education and counselling, and the frequency ranged from single short sessions to intensive sessions over several weeks. Five studies recruited women planning a pregnancy. An intervention based on a 15-min computerized-assisted counselling session on preconception folate supplementation with a bottle of free folate tablets showed that women’s knowledge regarding the protective effect of folate for birth defects improved (OR: 4.19; 95% CI: 1.98– 8.85). Preconception counselling on multifactorial health risks also showed a beneficial effect. The strength of evidence for increased knowledge following preconceptional interventions is moderate, but ranges from low to very low for other behavioural outcomes considered by Hussein *et al.* (2016). Significant improvement in self-efficacy (exercise), along with healthier food intake (OR = 1.757, P=0.008) was also observed.

Agha *et al.* report that preconceptional interventions based on behaviour change could be effective in reducing GWG in obese women, but no evidence was found for overweight or morbidly obese women33. Such interventions did not have an effect on postpartum weight loss or retention, gestation week of delivery and infant birth weight in overweight, obese and morbidly obese women. One study focusing on preconceptional women from this review 40 reported a significantly higher intake of daily multivitamins including folic acid among women in the intervention group and who were more likely to have lower weight and BMI (after a 12 month follow-up). Women who participated in the intervention and gave birth to singletons during the follow-up period had lower average pregnancy weight gain compared with controls. The Strong Healthy Women behaviour change intervention40,45 in the Central Pennsylvania Women’s Health Study was included in several of the reviews23,24,29, being one of the few experimental studies which met the objective of the present review. Education was provided (by bi-weekly small group sessions) in a way to motivate women by linking current health-related behaviours and the future health of the woman, her child, and her family generally. Short-term results suggested that women in the intervention group were significantly more likely than controls to report higher self-efficacy for eating healthy food (OR=1.9; p=0.01), greater intent to eat healthy foods (OR=1.75; p= 0.008) and be more physically active (OR=2.18; p<0.001). Results of the long-term follow up40 (6- and 12-months) suggest that participants were significantly more likely than controls to use a daily multivitamin with folic acid and to have lower weight and BMI. Among those who gave birth to singletons during the follow-up period, women who participated in the intervention had lower average pregnancy weight gain compared with controls (Mean Difference −17.95 (−33.42, −2.49); p=0.023). Although the intervention effect was no longer significant when controlling for pre-pregnancy obesity, the adjusted means show a trend toward lower weight gain during pregnancy in the intervention group.

# Discussion

Not all reviews identified and included in this report addressed the aim of the present review, which was to collate evidence on preconception intervention to prevent future childhood obesity and NCD risk. Although preconception care has been successfully used for interventions related to folic acid and iron supplementation, micronutrient intake and balanced protein and energy supplementation, very few interventions targeted prevention of maternal obesity before pregnancy to prevent adverse pregnancy outcomes or aimed to prevent obesity or NCD risk in children. Few outcomes such as LBW or GDM, which previous studies have associated with high risk of future NCDs, were reported in the reviews included. However, it is clear from the results of this review that preconception services do have the potential to reach women in need.

There is a lack of definition of limits for excess weight retention after pregnancy, along with the recommended period to achieve a healthy weight post-partum. Although weight loss would ideally be achieved before pregnancy, most studies focused on the pregnancy and post-partum periods for achieving weight loss 21,33. Long-term follow up studies 46 have shown that women who achieved pre-pregnancy weight within 6 months post-partum had gained less weight 10 years after childbirth than women who retained postpartum weight (2.4 kg gain vs.8.3 kg gain). Thus, failure to lose pregnancy weight gain by six months postpartum can be considered an important predictor of long-term obesity in women.

The Mumbai Maternal Nutrition Project 47 was a randomised controlled trial that evaluated a complex intervention to improve women's dietary micronutrient quality before conception and throughout pregnancy, with the aim of increasing birth weight in a high-risk Indian population. This intervention included the provision of a daily snack made from green leafy vegetables, fruit and milk (treatment group) or low-micronutrient vegetables (control group) from before pregnancy until delivery, in addition to the usual diet. Results show no significant effects on birthweight although its distribution appeared to change: there was a 48g increase in mean birth weight and a reduction in LBW incidence of 24%. The intervention effect was larger on birthweight in mothers of higher BMI. There was also a significant protective effect against GDM (prevalence of 7.3% in intervention group vs. 12.4% in controls [OR: 0.56; 95% CI: 0.36, 0.86]). Interventions at a population level such as mass information campaigns or food fortification are seen to be effective, especially for nutritional outcomes3,14,25. Multi-component interventions usually take a while to improve outcomes, but have shown better results when personal counselling was included 3,14. Since large-scale food fortification is a cost-effective method in LMICs, Dean et al (2014) recommended that fortification trials (folic acid, iron and other micronutrients) should also consider MNCH outcomes while evaluating effectiveness. The techniques used in the successful interventions consisted of physical activity and diet counselling by trained professionals, supplemented by motivational talks on weight management, feedback on the progress of participants and weight monitoring during pregnancy. Providing balanced protein energy supplementation has also shown promise in improving maternal and neonatal outcomes in LMICs. Though pre-pregnancy underweight was a significant risk factor for adverse neonatal outcomes 14, a shortage of evidence for studies targeting undernourished and underweight women before pregnancy is noted. While there is a need for educational programmes, especially in low-income settings, knowledge, awareness and beliefs about preconception care do not necessarily lead to preconception health practice18.

Several observational studies were limited by a lack of baseline measures, or measures taken at least at two time points. It is essential that studies evaluating preconception interventions should consider post-pregnancy follow up, to assess differences in outcomes between women who became pregnant over the course of the study and those who did not. In addition, process evaluations of preconception interventions have shown that the prevalence estimate for engagement with preconception services ranged between 18.1% through to 45% depending upon the chronic health condition examined.48

There was significant heterogeneity between studies for each outcome considered, possibly due to differences among study populations or methodology affecting the results. There is ambiguity regarding the generalisability of interventions. While certain interventions had a robust study design, it is still not clear how replication in another setting might be accomplished. Strong cultural influences are associated with lifestyle behaviours, and quality of delivery of an intervention depends on the mode of delivery, content and dosage. 29 Studies were often of poor quality with small sample sizes 21,33.

The paucity of intervention trials, especially in LMIC settings is significant. Studies have recommended that preconception care should address the overall socioeconomic and cultural barriers/ structural factors along with biological, medical and lifestyle risk factors 3. The interventions in the USA, Netherlands, Australia, and Hungary were mainly based in healthcare facilities with trained staff delivering services; whereas community-based services targeting women in the reproductive age group and providing health education about pregnancy and child health, with help from women’s support groups, were more common in LMICs such as India, Pakistan and Nepal3,14. Other risk factors for LBW and preterm delivery 49,50 that are common in LMICs such as indoor air pollution from cooking stoves also need to be addressed. The review by Dean et al (2014) draws attention to the gap in preconception care in Sub-Saharan Africa and South Asia and recommends that providing comprehensive care could help overcome the lack of uptake of routine services due to issues such as gender inequality3,14. They also describe an expanded framework that links women’s empowerment to healthy pregnancy outcomes by providing adequate care for adolescent girls and women before and between pregnancies. In their conceptual framework Ramakrishnan et al.32 identify adolescence, the preconception period before first pregnancy and the inter-pregnancy interval after first delivery as key entry points for interventions, especially in resource-poor settings. Differences in healthcare systems among high-income countries could also lead to a lower likelihood of replication of effective trials. It is important to note that with economic, technological and social transformations taking place in LMICs such as India, the burden of under- and over-nutrition is increasing, and interventions developed in such countries must be culturally specific and based on nationally relevant evidence.51

The chief limitations of the findings from this review of reviews stem from the small number of trials identified for preconception preventive interventions for childhood obesity and NCDs. The studies included varied in the population studied, intensity, type and frequency of intervention and patient compliance. This limits the ability to combine and compare findings across studies or to establish a consistent trend in results. As a review of reviews, relevant experimental studies that were not included in the original reviews were potentially missed out in this report too. However, this report provides a useful overview of preconception intervention for various target groups that have shown promise globally and offers key insights for those providing care to women in the reproductive age group, including adolescents.

**Recommendations and implications for public health strategies**

Pregnancy and planning for pregnancy provides the motivation to adopt a healthy lifestyle among women and the studies included this review demonstrate a lack of knowledge regarding the impact of malnutrition on pregnancy outcomes in many women and communities. Despite guidelines on folic acid intake before pregnancy, only half of all women use folic acid before conception and thus do not achieve protective levels 14. Significant gaps in women’s knowledge among those with chronic health conditions and the impact of diseases on pregnancy was found 25. Since pregnancies are often unplanned, improving women’s nutritional and weight status in the early reproductive years becomes vital. Birth cohort studies providing longitudinal data will be helpful in assessing changes in behaviour and health outcomes throughout the childbearing years. However, preconception interventions need to be incorporated into efforts using a life course approach, and addressing other environmental and socioeconomic determinants of health,52 and must not rely on women’s individual responsibility and cause further stigmatisation.

Studies identified in this review have not followed up the participants with adverse outcomes such as LBW, and have issues such as incomplete outcome data and a lack of data on long-term effects of interventions. Although we have focused on quantitative studies, incorporating qualitative methods in the initial stages would enable an examination of women’s preferences and needs regarding preconception care service delivery, including availability and access. Most of the evidence for the effectiveness of preconception interventions comes from the primary care setting. It is possible that much of this learning can be transferred to other settings (such as community settings). Existing platforms such as family planning services can be utilised to identify preconceptional women and to provide health education and counselling related to healthy diet and lifestyle, and to optimise maternal, neonatal and child health outcomes. This is especially relevant in LMICs and should include young mothers and newlywed couples. We recommend high-quality data collection from the inception of the studies including anthropometric and biological markers for both parents and in newborns, including for example longitudinal epigenetic markers, markers of cardiometabolic fitness, growth and body composition in children during follow up.

# Conclusion

A key finding of this review is the paucity of interventions in the preconception period in contrast to the myriad of interventions during pregnancy. We aimed to assess the effectiveness of those interventions which have been conducted but are unable to suggest a particular model due to the dearth of studies meeting our criteria. There is substantial evidence for maternal underweight and overweight, diabetes and smoking in the preconceptional period leading to negative outcomes such as LBW, macrosomia and congenital anomalies. Weight gain during pregnancy is an important risk factor for future NCDs in the mother and child, and this review provides moderate evidence supporting the effectiveness of exercise-based interventions in the preconception (postpartum) period to reduce weight gained during previous pregnancy. Risk factors in parents associated with childhood obesity and later NCD risk such as an unhealthy diet, smoking and lack of physical activity originate prior to pregnancy and are often carried forward through gestation and the post-partum periods. Hence, the preconception period is key to bringing about behaviour change. Adopting a life course approach provides the potential to prevent the risks for obesity in children, which further affects their growth and physical and mental development. Since there are very few trials targeting this period to reduce the risk of passage of NCDs, HeLTI provides the opportunity to implement an RCT/ cohort study that would provide long-term follow up after a preconceptional intervention. Sustaining the intervention through pregnancy, postpartum, infancy and childhood should be considered.

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