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REVIEW

Reducing intergenerational obesity and diabetes risk

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Abstract

To address the intergenerational transmission of obesity and diabetes, strategies promoting the health of women of reproductive age appear to be urgently needed. In this narrative review, we summarise what has been learned from many prenatal clinical trials, discuss the emerging evidence from preconception clinical trials and highlight persistent gaps and critical future directions. Most trials tested prenatal interventions that resulted in a limited gestational weight gain of ~1 kg and reduced gestational diabetes by 20–30%. These interventions also reduced macrosomia by 20–40% but had little-to-no impact on other offspring outcomes at birth or beyond. Far fewer trials tested preconception interventions, with almost all designed to improve conception or live-birth rates in overweight or obese women with infertility rather than reduce intergenerational risks in diverse populations. Preconception trials have successfully reduced weight by 3–9 kg and improved markers of glucose homeostasis and insulin resistance by the end of the intervention but whether effects were sustained to conception is unclear. Very few studies have reported offspring outcomes at birth and beyond, with no evidence thus far of beneficial effects on offspring obesity or diabetes risks. Further efforts to develop effective and scalable strategies to reduce risk of obesity and diabetes before conception should be prioritised, especially for diverse and under-resourced populations at disparately high risk of obesity and diabetes. Future clinical trials should include interventions with high potential for dissemination, diverse populations, thorough maternal phenotyping from enrolment through to conception and pregnancy, and rigorous assessment of offspring obesity and diabetes risks from birth onwards, including into the third generation.

Keywords Clinical trials · Diabetes · Intergenerational · Obesity · Offspring · Preconception · Pregnancy · Review

Abbreviations

DALI	Vitamin D and Lifestyle Intervention for Gestational Diabetes Mellitus Prevention
LIMIT	Limiting Weight Gain in Overweight and Obese Women during Pregnancy study
RADIEL	Finnish Gestational Diabetes Prevention Study
UPBEAT	UK Pregnancies Better Eating and Activity Trial

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Introduction

The rising prevalence of obesity and type 2 diabetes at increasingly younger ages [1–3] suggests that modifiable exposures beginning very early in life, even before birth, may contribute to this growing public health problem. As reviewed in *Diabetologia*'s 2019 special issue 'A life course perspective on diabetes: developmental origins and beyond', offspring exposed to rising maternal weight or dysglycaemia in utero exhibit increased body size, adiposity and diabetes risks from birth onwards [4]. This observational evidence in humans is supported by experimental animal studies demonstrating that fetal exposure to maternal diabetes, obesity or an obesogenic diet increases weight, adiposity, dyslipidaemia, hyperinsulinaemia and cardiovascular dysfunction across the life course [5–7]. Following adverse exposures, a major concern is that children will later enter their own reproductive years with chronic disease and expose the next generation to adverse intrauterine environments, triggering a vicious, self-perpetuating cycle.

Over the last 20 years, the scientific community has examined how this intergenerational disease cycle can be

addressed. In non-pregnant humans, diet and physical activity modification can significantly reduce body weight and progression to type 2 diabetes [8, 9]. In animals, reproductive experiments have shown that diet and physical activity modification immediately before or during pregnancy reverses maternal metabolic dysfunction and mitigates the adverse impact of maternal obesity on offspring outcomes [10–12]. Yet, comparative evidence for prenatal or preconception interventions to reduce the intergenerational disease cycle in humans is limited, despite commendable efforts. In this narrative review, we summarise learnings from the many prenatal clinical trials, discuss the emerging evidence from preconception clinical trials and highlight persistent gaps and critical future directions.

Summary of prenatal interventions

1. Prenatal lifestyle interventions limit gestational weight gain by ~1 kg and prevent gestational diabetes by 20–30% but have had little impact on offspring outcomes up to 8 years of age
2. The majority of eligible women decline to enrol in prenatal intervention trials, resulting in selective samples with limited generalisability
3. Focusing trials on women most likely to benefit and tailoring interventions to individual phenotypes will be key to identifying successful prenatal strategies

Interventions during pregnancy

The potential for lifestyle modification during pregnancy to improve maternal/offspring health has been evaluated in nearly 100 trials worldwide. The most conclusive evidence is provided by large trials, including the Australian Limiting Weight Gain in Overweight and Obese Women during Pregnancy (LIMIT) study ($N = 2152$ women with pre-pregnancy BMI ≥25 kg/m^2; primary outcome of large-for-gestational age births), the UK Pregnancies Better Eating and Activity Trial (UPBEAT) ($N = 1555$ women with pre-pregnancy BMI ≥30 kg/m^2; primary outcomes of gestational diabetes and large-for-gestational age births), the pan-European Vitamin D and Lifestyle Intervention for GDM Prevention (DALI) study ($N = 436$ women with pre-pregnancy BMI ≥29 kg/m^2; primary outcome of gestational weight gain) and the Finnish Gestational Diabetes Prevention Study (RADIEL) ($N = 293$ women with pre-pregnancy BMI ≥30 kg/m^2 or history of gestational diabetes; primary outcome of gestational diabetes). Below, we summarise major findings from these key studies, along with the average effects reported by comprehensive meta-analyses, and discuss implications for continued prenatal efforts (see also Text box: 'Summary of prenatal interventions').

Impact on gestational weight gain The collective evidence from prenatal interventions affirms that lifestyle modification (vs usual care) can reduce gestational weight gain albeit with a modest 1 kg mean reduction (as reported in a 2017 meta-analysis of 81 studies encompassing a total of >17,000 women) [13]. This meta-analysis included the LIMIT [14] and UPBEAT [15] studies but not the more recent DALI [16] and RADIEL [17, 18] trials, though the latter studies had relatively consistent findings (effects of −2.0 kg and −0.6 kg, respectively). The questionable strength of a causal relationship between improving prenatal diet and physical activity behaviours and reduced gestational weight gain [19, 20] has presented a challenge to achieving more robust trial outcomes. For example, even trials demonstrating improved behaviours in the intervention vs control group (e.g. reduced energy intake [−699 kJ/day (167 kcal/day)] [15], +10–20 min/day of activity [15–17, 21]) lacked corresponding impact on weight gain. While larger behavioural changes may be needed to modulate gestational weight gain, this may prove difficult given the minimum weight gain needed to support fetal development [22] and psychosocial barriers to lifestyle change while pregnant [23, 24]. Alternatively, the true potential of these prenatal trials may have been obscured by limited reach, as the 20–40% of eligible women who enrolled [14–16] were likely filtered for those who were highly motived to improve behaviours even when assigned to control conditions. Yet, attrition remains problematic even in this selective group (e.g. ~25% of intervention participants received <35% of the programme in some trials [14, 15]), reducing confidence that broader enrolment could produce larger effects. Instead, the clinical significance of this modest effect of prenatal interventions on gestational weight gain must be judged by the downstream effect on other maternal and offspring outcomes.

Impact on gestational diabetes As with gestational weight gain, the collective evidence from prenatal studies indicates that lifestyle modification can prevent gestational diabetes to some degree, with meta-analyses estimating risk reductions of 20–30% vs control groups [25, 26]. Yet, one study found that behavioural interventions must be provided to 88 pregnant women (costing more than UK£13,000 [~€15,000]) to prevent one case [27], impeding potential uptake by clinics due to limited cost-effectiveness. Every 1 kg reduction in gestational weight gain resulting from lifestyle intervention is associated with just 7% risk reduction for gestational diabetes [26], indicating that limiting weight gain among overweight/obese pregnant women is not the key to gestational diabetes prevention.

Rather, the greatest success occurred among women at highest risk of gestational diabetes, such as those with a history of the condition [17] or additional risk factors (e.g. Asian race or Hispanic ethnicity) [26]. For example, compared with the control group, the RADIEL trial reported a 35% risk reduction with the intervention in a sample in which 33% of the participants had a history of gestational diabetes [17], while the UPBEAT trial showed that in a sample in which 4% of participants had a history of gestational diabetes, the lifestyle intervention had no effect compared with control [15]. These findings suggest that improved identification of women most likely to benefit from an intervention is critical for effectiveness. Indeed, prior trials may have been impaired by the inclusion of women unable to benefit from prevention efforts (i.e. those having gestational diabetes at enrolment). The excellent prevention associated with the intervention in RADIEL was restricted to women with normal glucose tolerance at enrolment (~13 weeks' gestation) [17]; a subsequent analysis including all women in the study (of whom 32% had pathological OGTTs at enrolment) revealed that the intervention had no impact (RR 0.88 [95% CI 0.61, 1.26]) [18]. In the DALI study, more women were excluded due to prevalent gestational diabetes at 15 weeks of gestation than the proportion who had newly developed gestational diabetes at 24–28 weeks (27% vs 21%) [16]. This highlights the population burden of early pregnancy dysglycaemia and the need to intervene before 15 weeks of gestation [28] or even before conception. Lack of measures to exclude women with gestational diabetes at enrolment was also likely to be problematic for the LIMIT and UPBEAT trials. Further, significant heterogeneity exists in gestational diabetes, with varying contributions from insulin resistance and impaired insulin secretion across gestation [29] that may require tailored behavioural targets (e.g. increased physical activity for insulin resistance vs limited carbohydrate intake for impaired insulin secretion). Given the high cost and burden of delivering prenatal interventions, focusing on women most likely to benefit and tailoring interventions to individual phenotypes may greatly aid future prenatal efforts.

Impact on offspring outcomes The modest success of prenatal interventions for regulating gestational weight gain and preventing diabetes have not translated to clear offspring benefits. In some studies, macrosomia has been reduced by 20–40% vs control groups [14, 30] but birthweight and the prevalence of large-for-gestational age deliveries have been found to be unchanged following intervention [13–16, 18, 30]. Neonatal adiposity is also increasingly being studied as a more sensitive marker of intrauterine exposures than size at birth [31] but has been inconsistently affected by prenatal interventions (i.e. a positive finding in the DALI study [32] but no effect in the LIMIT trial [33]). Above all, reports of improved maternal outcomes without corresponding neonatal impact [15–17], and vice versa [14], suggest that further efforts to improve intergenerational outcomes through prenatal lifestyle interventions may be futile [20]. This conclusion is further supported by the lack of impact on obesity-related outcomes when offspring have been followed into childhood [34, 35]. Although the UPBEAT trial reported a modest 5% reduction in subscapular skinfold thickness at 6 months [36], other outcomes were not significantly improved. In contrast, the RADIEL trial reported worsened lipid profiles among offspring of women in the intervention group at age 5 years compared with control counterparts [37], despite no impact of the intervention on gestational weight gain or diabetes. However, this result may be spurious, particularly as only half of the offspring were followed through to 5 years of age, such that confirmatory evidence appears needed. Nonetheless, the effect was notably prominent in male offspring and those exposed to gestational diabetes. At the same time, the bulk of evidence alleviates concerns that prenatal interventions might impair fetal growth and development, as adverse outcomes such as small-for-gestational-age births, hypoglycaemia requiring treatment, respiratory distress, and neonatal intensive care unit admission have not increased vs comparator groups [13, 18, 21, 30]. Overall, considering the observational evidence that maternal obesity and diabetes risks around the time of conception are more strongly related to offspring outcomes than prenatal factors [38], a shift in focus towards earlier intervention, namely before conception, is warranted.

Interventions during the preconception period

Relatively few trials have targeted intergenerational diabetes and obesity risks during the preconception period, with most having been designed to improve conception or live-birth

Summary of preconception interventions

1. Preconception lifestyle interventions reduce maternal weight by 3–9 kg and improve dysglycaemia prior to pregnancy, but effects at conception and throughout gestation are relatively unknown
2. Very limited evidence of impact on offspring outcomes beyond birth is available, with current studies showing no clear benefit
3. Prior studies enrolled overweight/obese women with infertility, limiting generalisability
4. Scalable preconception strategies that are effective for diverse and under-resourced populations are needed

rates in overweight/obese women with infertility or polycystic ovarian syndrome. Initial weight-loss outcomes from these trials have been well reported given relevance to fecundity but reporting on other intergenerational obesity and diabetes risks has been limited, as discussed below (see also Text box: 'Summary of preconception interventions').

Impact on maternal weight Preconception lifestyle interventions have resulted in weight loss of 3–9 kg [39–44], while combined lifestyle and medication (metformin [45], phentermine [46], sibutramine [47] and/or orlistat [47, 48]) interventions have resulted in 6–8 kg weight loss compared with control groups. This impact over 3–6 months is commendable, although women pursuing fertility treatments may be more motivated to lose weight than the broader population of women of reproductive age, limiting generalisability. Further, most effect estimates were based on end-of-intervention measurements, which may not have persisted until pregnancy. For example, a trial conducted in Sweden, Denmark and Iceland achieved a mean weight loss of 9.1 kg between enrolment and the first oocyte retrieval in 152 intervention participants (compared with a gain of 1.2 kg in 153 control participants), with nearly all of the weight (8.6 kg) being regained over the subsequent 24 months [40]. Intervention effects on weight at conception were unreported for the 27% of women who conceived after the index cycle [49]. The LIFEstyle trial in the Netherlands did not prospectively assess weight during the 18 months of fertility treatments that followed the 6 month intervention [42] but did report that maternal weights available at 8–12 weeks' gestation for 244 women (76% of the 321 who conceived) were significantly reduced from baseline for intervention participants (−4.1 kg vs −1.0 kg for intervention vs control participants) [50]. Given the likelihood of weight regain following lifestyle interventions [51], it is important that studies of preconception interventions include frequent assessments to accurately capture maternal weight at conception.

Impact on maternal dysglycaemia Few preconception trials have evaluated maternal dysglycaemia at the end of interventions, around conception or during pregnancy, despite the growing prevalence of pregestational type 2 diabetes, impaired fasting glucose or impaired glucose tolerance in women of reproductive age [52]. The LIFEstyle study (N = 577) reported lower fasting insulin (89.9 vs 104.6 pmol/l) and insulin resistance (HOMA-IR 3.12 vs 3.72) at 3 months and lower fasting glucose (5.32 vs 5.41 mmol/l) at 6 months in the intervention group compared with the control group [53]. Similarly, Karimzadeh and Javedani reported lower fasting insulin at 6 months in the lifestyle intervention group compared with women treated with metformin (N = 343) [41], and Legro et al reported lower glucose and higher insulin sensitivity at 4 months in the lifestyle + weight-loss medication group compared with the control group (N = 149) [47]. For all three studies, these effects occurred alongside significant weight reductions (e.g. −3.4 kg at 3 months and −5.0 kg at 6 months [53]), suggesting that preconception interventions that successfully reduce weight also benefit glucose homeostasis and insulin sensitivity before pregnancy. Other studies reported non-significant improvements in glucose, insulin or insulin sensitivity following significant weight loss in the intervention groups [39, 48], although smaller samples (n < 100) may have limited the power. Dysglycaemia in early pregnancy has not been evaluated for preconception interventions, and no study has reported an impact on gestational diabetes incidence [42, 47]. Thus, whether preconception lifestyle and/or pharmacological interventions have a persistent beneficial effect on maternal glucose homeostasis, insulin sensitivity or dysglycaemia remains unknown. There is promising evidence from retrospective and case–control studies of surgical interventions to reduce weight prior to pregnancy that substantial reductions in BMI (8–15 kg/m^2) sustained to conception reduce gestational diabetes incidence by nearly 70% [54]. Yet, surgical weight loss is unfeasible as a population health strategy and is associated with serious consequences [55]. Hence, evaluation of the glycaemic impact of modest weight loss following non-invasive preconception interventions is urgently needed.

Impact on offspring outcomes Only three preconception trials reported offspring outcomes [42, 47, 49], with just one (thus far) continuing follow-up beyond birth [49]. There have been no differences between lifestyle or pharmacological interventions and control arms in incidence of pre-term births, small-for-gestational age neonates or other adverse outcomes (e.g. jaundice, intensive care unit admission) [47, 49, 50], alleviating safety concerns for such interventions. In contrast, bariatric surgery prior to pregnancy is associated with increased rates of perinatal mortality, pre-term birth and small-for-gestational age neonates [55], further shifting support towards non-invasive strategies. Yet, there is currently no evidence suggesting that non-invasive preconception interventions benefit offspring. Despite notable weight loss (4–10%) by the end of the interventions, there have been no differences in birthweight [42, 47, 49] or large-for-gestational-age births [42] between intervention and comparator arms. Further, Kluge et al reported no difference in offspring weight at 2 years of age for the Nordic countries trial [49]. Achieving sufficient analytical power for offspring outcomes is a challenge for preconception trials given that women may not conceive during the follow-up period, even those receiving infertility treatments as part of the protocol. Of the three aforementioned studies, offspring outcomes were assessed for just 19–50% [42, 47, 49] of the randomised women, with the highest conception rate being achieved in the study with the longest follow-up (18 months post-randomisation) and more

intensive infertility treatment [42]. Other indicators of offspring obesity and diabetes risks (body composition, rapid growth, insulin resistance, glucose metabolism) have not been assessed, limiting the conclusions that can be drawn about the impact of preconception interventions on offspring.

Approaches needed for future studies

The existing evidence from many trials indicates that prenatal interventions have limited potential to reduce intergenerational obesity and diabetes risks (see Text box: 'Summary of prenatal interventions'), pushing a need to gather additional evidence from preconception interventions to inform public health initiatives (see Text box: 'Summary of preconception interventions'). As efforts shift towards the preconception period, we urge researchers to consider the following clinical trial design elements that may overcome current challenges (Table 1, Fig. 1).

Improving representativeness Inclusion of a diverse group of women at highest risk of intergenerational obesity and diabetes is necessary for maximising population impact. Preconception studies to date have enrolled women of predominantly non-Hispanic white race/ethnicity and higher educational attainment [40, 42, 47], precluding generalisation of results to minority or under-resourced women with disparately high obesity during peak child-bearing years [56]. Further, trials have focused on women with obesity and/or polycystic ovarian syndrome who are pursing infertility treatments, thus excluding the ~80% of overweight/obese women without impaired fecundity [57] and women not seeking infertility treatments for cultural, religious or socioeconomic reasons [58]. Broader inclusion criteria and targeted recruitment efforts in high-risk communities can increase the external validity of study results. The low reach of the target populations thus far suggests that any potential impact would similarly be limited if translated into practice. Among fully eligible women, approximately one-third decline to participate in preconception trials [40, 42] and two-thirds decline to participate in prenatal trials [14–16], suggesting that core elements of these studies (i.e. intervention components and data collection procedures) have limited appeal to the target population. Patient-centred outcomes research and similar methods [59] appear critical for designing protocols that are acceptable and

Table 1 Overview of approaches needed for future preconception studies addressing the intergenerational transmission of obesity and diabetes

Aspect	Challenges to date	Potential solutions
Population representativeness	Focus restricted to overweight/obese women with infertility Diverse women and women with low-income have been under-represented Suboptimal uptake among eligible women	Use broader inclusion criteria Target recruitment in high-risk communities Use patient-centred research methods to make interventions (and research protocols) more appealing, personally relevant and convenient
Scalability and sustainability	Wide variability in intervention intensity across studies Cost and staff burden under-reported but often appear high Most intensive, costly interventions are unlikely to be fully disseminated, even if effective Previous trials have included relatively low-risk women	Prioritise potential for widespread dissemination when designing interventions Report cost and other resources needed for delivering intervention to inform future uptake Target women at highest risk of gestational diabetes to increase efficiency of trials and impact of future dissemination
Maternal outcomes assessment	Reliance on self-reported or medical record data for periconceptional weight outcomes Limited data on periconceptional dysglycaemia outcomes Limited follow-up throughout pregnancy	Rigorously phenotype women at enrolment and around conception Include frequent weight monitoring, emphasising remote data collection to reduce burden Evaluate dysglycaemia at enrolment, shortly after conception and in late pregnancy Coordinate with clinical providers to capture follow-up during pregnancy
Offspring outcomes assessment	Reliance on measurements of total size at birth from medical records Very limited data beyond birth Impact on intrauterine programming mechanisms is unknown	Evaluate growth, body composition and fat deposition from birth onwards Assess dysglycaemia and cardiometabolic outcomes in childhood, adolescence and adulthood Characterise postnatal environment and health behaviours to identify direct and indirect effects Enrol large preconception samples to increase power for offspring outcomes Follow-up into third generation to assess transgenerational impact

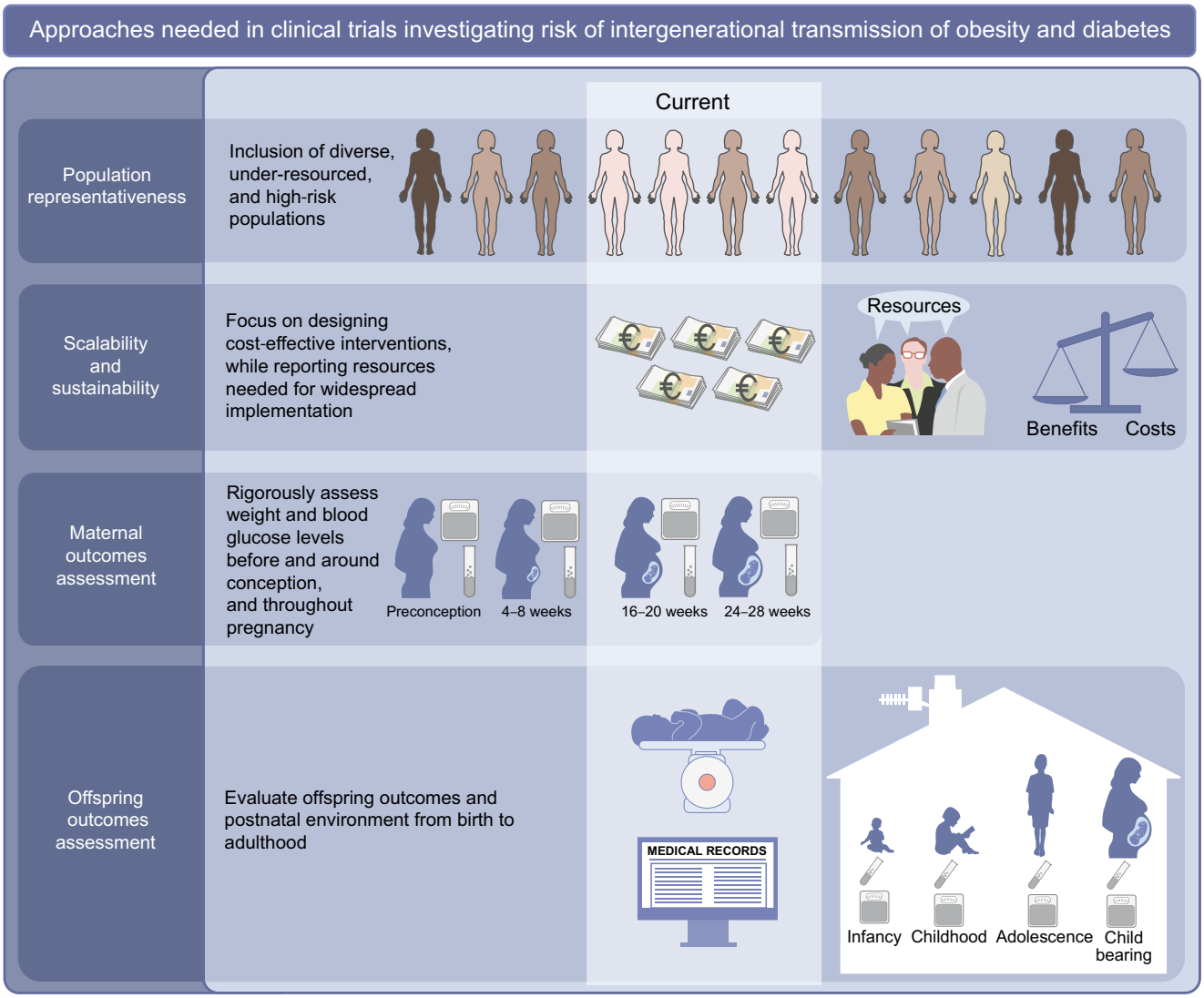

Fig. 1 Approaches needed in clinical trials investigating risk of intergenerational transmission of obesity and diabetes. Prior clinical trials investigating risk of intergenerational transmission of obesity and diabetes have been: (1) restricted to women of predominately non-Hispanic, white race/ethnicity; (2) expensive to implement; (3) focused on mid- and late-prenatal assessments; and (4) limited to offspring assessments at birth, and mainly from medical records. Further efforts to develop effective and scalable strategies to reduce obesity and diabetes risks before conception should be prioritised, including approaches that: (1) include diverse, under-resourced, and high-risk populations; (2) have cost-effective interventions, while reporting resources needed for widespread implementation; (3) rigorously assess weight and blood glucose levels before and around conception; and (4) evaluate offspring outcomes and the postnatal environment from birth to adulthood. This figure is available as a downloadable slide

appealing to women of reproductive age, thereby facilitating efficient recruitment, high retention and study completion.

Designing for dissemination Given the widespread burden of obesity and diabetes risks in women of reproductive age, designing interventions with high potential for scaled and sustainable implementation should be prioritised. Preconception trials have used a range of approaches of varying intensity to target weight loss, ranging from pharmacotherapy [47, 48] to study-provided meals or liquid meal replacements [40, 47]. Staff burden has varied considerably, with more intensive one-on-one interventions and food provisions having lower potential for scaled sustainability. The cost of preconception interventions has not been reported. Costs of lifestyle interventions aimed at reducing obesity and preventing type 2 diabetes in non-pregnant adults have been reported to be approximately USD$300–900 per participant for in-person group programmes and somewhat lower for online (virtual) programmes [60]. While investigators report on efficacy of maternal obesity and diabetes risk reduction for offspring health outcomes, they should also report on intervention cost, scalability and sustainability to further guide decisions made by providers, funders and policymakers. Similarly, the efficiency of trials (and subsequent public

health practices) could be improved by focusing on women at highest risk of gestational diabetes.

Improving measurement of maternal weight and blood glucose Maternal phenotyping at conception and throughout pregnancy is needed to assess the sustained impact of preconception interventions, particularly for weight and dysglycaemia.

Frequent weight monitoring from enrolment onwards is needed to accurately evaluate BMI at around the time of conception, given that weight regain is common [51]. Measurements made in person are the gold standard but are burdensome, while pre-pregnancy weight obtained by self-report or from medical records has limited validity despite common use in practice [61, 62]. Home scales equipped with cellular or Bluetooth technologies to automate data transfer may be a promising adjunct to limited in-person weighing, especially if incorporated into the intervention as a self-monitoring strategy. However, as self-weighing alone is associated with small but measurable weight loss [63], in future studies, one control arm should include self-monitoring for comparison with other control participants not receiving in-home scales. Additionally, coordination with care providers could enable researchers to obtain research-quality weights at all prenatal encounters.

Maternal blood glucose levels should similarly be evaluated at enrolment and regularly thereafter following clinical diagnostic protocols (e.g. fasting blood glucose, OGTT, HbA_{1c}) supplemented with perinatal clinical care records, if available. HbA_{1c} testing is the least burdensome for repeated measurement, as fasting and frequent monitoring are not required, with the added benefit that samples obtained in the first trimester reflect the average glucose levels around the time of conception. HbA_{1c} is increasingly tested at the first clinical prenatal encounter [64] and growing evidence suggests that a HbA_{1c} ≥39–41 mmol/mol (≥5.7–5.9%) in early pregnancy predicts gestational diabetes, pre-eclampsia, major congenital anomaly, perinatal death and increased neonatal size [65, 66]. Limitations to HbA_{1c} testing both within and beyond pregnancy include increased erythrocyte production, iron deficiency and genetic variations in haemoglobin [67], which should be considered by researchers and clinicians alike when interpreting results. Given that the heterogeneity of gestational diabetes is not reflected by HbA_{1c} levels [68], evaluation of glucose–insulin homeostasis, insulin resistance and glucose tolerance via OGTTs before and closely after conception is the most rigorous approach by which to characterise the glycaemic milieu of the early intrauterine environment. However, the burden on participants of multiple OGTTs must be considered, as this may adversely impact enrolment and retention of priority populations.

Focusing on offspring follow-up Rigorous assessment of offspring obesity and diabetes risks from birth onwards is necessary. This includes growth, body composition and fat deposition; fasting and postprandial glucose metabolism and insulin sensitivity; and cardiometabolic factors such as BP, lipids and inflammation. Characterising the postnatal environment and offspring health behaviours is important to enable us to understand the direct effects of preconception interventions on offspring via improved intrauterine exposures vs indirect effects via altered postnatal exposures. While it is possible that maternal obesity and diabetes risks are only temporarily reduced following intervention, given the difficulty of maintaining improved health behaviours and weight loss over the long term, studies of siblings with discordant intrauterine exposures [69, 70] suggest that even temporary shifts in maternal health can have lifelong implications for offspring. To obtain sufficient data for a rigorous evaluation of offspring, preconception studies will require significant investments in starting sample size and follow-up duration. An as-yet untapped strategy for increasing the efficiency of such trials is to focus on offspring outcomes that are highly sensitive to intrauterine exposures. Specifically, offspring body composition at birth appears to be more sensitive than total weight to modifiable intrauterine exposures, including maternal obesity [71], gestational diabetes [31], and prenatal diet [72] or physical activity [73]. Neonatal adiposity (% fat mass) also tracks over time [74] and predicts offspring BMI and overweight/obesity status from ages 2 to 6 years [75], demonstrating the prognostic significance of even small differences at birth. At the same time, to definitively determine the impact of preconception interventions on intergenerational obesity and diabetes risks, future preconception trials must include rigorous evaluation of offspring outcomes, with extended follow-up into childhood, adolescence and the reproductive years, plus continued follow-up into the third generation to assess transgenerational impact.

Summary

Strategies to reduce the public health burden of obesity and diabetes are urgently needed and have prompted a focus on improving maternal health in recent decades. However, prenatal interventions have had little success in reducing intergenerational obesity and diabetes risk factors. The limited available evidence from preconception intervention trials indicate that weight loss prior to conception is attainable by women with obesity and infertility. Unfortunately, these trials have largely excluded diverse populations. In addition, the impact of the interventions on maternal obesity and diabetes risks at conception and offspring risks at birth and beyond have not been rigorously assessed. Moreover, the potential for widespread implementation has not been reported. Further efforts to develop effective and scalable strategies to reduce obesity and diabetes risks before conception should be prioritised,

especially for diverse and under-resourced populations at disparately high risk of obesity and diabetes. There is a variety of potential strategies to improve the quality of evidence, which is key to this effort.

Supplementary Information The online version contains a slide of the figure for download available at https://doi.org/10.1007/s00125-020-05341-y.

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