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Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review

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Review

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Abstract

Adverse exposures during fetal life and the postnatal period influence physical, cognitive and emotional development, and predispose to an increased risk of various chronic diseases throughout the life course. Findings from large observational studies in various populations and experimental animal studies have identified different modifiable risk factors in early life. Adverse maternal lifestyle factors, including overweight, unhealthy diet, sedentary behavior, smoking, alcohol consumption and stress in the preconception period and during pregnancy, are the most common modifiable risk factors leading to a suboptimal in-utero environment for fetal development. In the postnatal period, breastfeeding, infant growth and infant dietary intake are important modifiable factors influencing long-term offspring health outcomes. Despite the large amount of findings from observational studies, translation to lifestyle interventions seems to be challenging. Currently, randomized controlled trials focused on the influence of lifestyle interventions in these critical periods on short-term and long-term maternal and offspring health outcomes are scarce, have major limitations and do not show strong effects on maternal and offspring outcomes. New and innovative approaches are needed to move from describing these causes of ill-health to start tackling them using intervention approaches. Future randomized controlled lifestyle intervention studies and innovative observational studies, using quasi-experimental designs, are needed focused on the effects of an integrated lifestyle advice from preconception onwards on pregnancy outcomes and long-term health outcomes in offspring on a population level.

Introduction

In the past decades, an accumulating body of evidence has shown that adverse exposures during the fetal and postnatal period may influence physical, cognitive and emotional development, and the risk of chronic diseases throughout the life course.[1] Large observational studies have shown that both low and high birth weight and preterm birth are associated with increased risks of obesity, cardio-metabolic diseases, asthma and mental health related disorders in later life.[1] These findings are supported by experimental animal studies.[1] Clearly, low and high birth weight and preterm birth are unlikely to be the causal factors per se leading to non-communicable diseases in later life. Birth weight and gestational age at birth are merely proxies of different fetal exposures and growth patterns and the starting point of childhood growth.

Observational studies have shown that early life covering the first 1000 days of life, including oocyte and sperm cell development in the preconception period, fetal growth in pregnancy and the postnatal development up to infancy, is a critical period for health outcomes throughout the life course. Adverse maternal lifestyle factors in the preconception period and during pregnancy are among the most common modifiable risk factors, which lead to a suboptimal in-utero environment predisposing to increased risks of pregnancy complications and long-term negative health consequences.[2–12] Among the most prevalent adverse maternal lifestyle factors are overweight, suboptimal dietary intake, sedentary behavior, smoking, alcohol consumption and stress.[2–12] These factors affect up to 15-50% of women and often cluster.[2–12] In the postnatal period and infancy, potential risk factors for adverse health outcomes in later life include rapid infant growth, lack of breastfeeding, suboptimal infant dietary intake and reduced sleep quality.[13–16] All these risk factors are more often present among families from a low socio-economic background.[16–20] Despite many observational studies in various populations which support these associations, it remains unclear whether lifestyle changes in early life improve pregnancy outcomes and long-term maternal and offspring health outcomes.

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Thus far, research on early life risk factors has focused on describing causes of ill-health. These findings urgently need to be translated to public health interventions. Randomized controlled trials are considered the gold standard for evaluations of health care interventions.[21] In this narrative review, we discuss the novel insights randomized controlled trials can provide to start translating these observational findings to public health strategies. We also discuss findings from previous randomized controlled trials focused on lifestyle interventions before, during and after pregnancy, and future directions for research on lifestyle interventions. This narrative review is a follow-up of the presentations and discussions at the preconference workshop of the past DOHaD World Congress 2017. This review is based on expert opinion as discussed in this workshop and a Medline search (through PubMed) up to January 2018 in order to identify relevant randomized controlled trials, meta-analyses and systematic reviews focused on lifestyle interventions before, during and after pregnancy. Used search terms included combinations of key words [free text and MeSH (Medical Subject Headings) terms](preconception lifestyle interventions, lifestyle interventions during pregnancy, postpartum lifestyle interventions, infant lifestyle interventions) in combination with the type of study (meta-analyses OR review OR systematic review OR intervention study OR randomized controlled trial). Articles were selected based on title and abstract, and workshop discussions.

Need for randomized controlled intervention studies

Although many observational studies in various populations have shown that early life is a major determinant of chronic diseases in adulthood, these studies do have important limitations.

First, the effectiveness and safety of lifestyle interventions in early life on the risk of chronic diseases in adulthood remains to be determined. Several observational studies have estimated the proportion of adverse perinatal outcomes that could potentially be prevented by reducing adverse maternal lifestyle characteristics in pregnancy, such as obesity and smoking.[7,22,23] For example, it is estimated that maternal overweight or obesity and smoking during pregnancy contribute to approximately 20% of stillbirths and up to 57% of common pregnancy complications.[7,22–24] Even though population attributable risks for long-term offspring health outcomes are less well-known, these population attributable fractions for pregnancy complications suggest that maternal lifestyle interventions would lead to improved pregnancy outcomes. However, randomized controlled trials are needed to assess whether intervention programs lead to meaningful maternal gestational lifestyle changes and improve short-term and long-term maternal and offspring health outcomes. These randomized controlled trials will also provide important insight into the safety of early life interventions. This is especially important for interventions targeting dietary intake, physical activity or using nutritional supplements. Thus far, mainly evidence from observational studies suggest that only extreme changes in maternal dietary intake or physical activity, such as severe caloric energy restriction, lead to adverse outcomes, but not small-to moderate changes.[25]

Second, randomized controlled lifestyle interventions trials can provide novel insights into the causality of observed associations. A major limitation of observational studies is confounding. Various family-based socio-demographic, nutritional, lifestyle and genetic characteristics may explain the observed associations of early life risk factors with adverse health outcomes in later life. Few observational studies used more sophisticated study designs to obtain insight into the role of confounding in these associations, such as sibling comparison studies, maternal-paternal offspring comparison analyses and Mendelian randomization studies.[26] Although for some early life exposures, such as maternal smoking, these more sophisticated observational studies suggest potential intra-uterine effects, for most early life exposures findings of different studies are conflicting and inconsistent. Randomized controlled trials are considered the gold standard to assess causality, but difficult to perform for some of these early life exposures, such as maternal prepregnancy obesity, breastfeeding or rapid infant weight gain. However, randomized controlled intervention studies targeting determinants of these exposures, such as dietary factors, physical activity or strategies focused on promoting healthy lifestyle, will already provide important new insights into the causality of these associations.

Thus, randomized controlled interventions studies are needed to provide novel insights into the effectiveness and safety of lifestyle interventions in early life to improve short-term and long-term maternal and offspring health outcomes and to assess causality of the associations of early life risk factors with health outcomes in later life.

Intervention studies before and during pregnancy

Preconception and pregnancy are critical periods for maternal and offspring health outcomes. Very little is known about the effectiveness of lifestyle interventions prior to pregnancy or in early-pregnancy. A review focused on the effectiveness of lifestyle interventions in women prior to pregnancy assessed the influence of different lifestyle interventions on behavior change and common pregnancy outcomes.[27] This review identified 19 randomized controlled trials with mainly interventions targeting one lifestyle factor, including alcohol consumption, smoking, nutrition and folic acid supplementation. The sample sizes in these randomized controlled trials were relatively small ranging from 97 to 786 participating women, except for folic acid supplementation trials in which up to 7905 women were included. Two randomized controlled trials were identified which provided lifestyle advice focused on multiple risk factors. These randomized controlled trials in the preconception period showed a reduction of maternal risk behavior, mainly based on self-reported data.[27] Mainly lifestyle interventions targeting behaviour to improve overall dietary intake, micronutrient intake and folic acid supplement intake had a positive effect on birth outcomes, but this was not consistently observed for the other lifestyle factors. Many of these randomized controlled intervention trials were performed among selected high-risk populations, which strongly limits the generalizability of these findings.[27] Also, there are no randomized controlled trials available in the preconception period comparing the effect of an individual intervention targeting one exposure to a lifestyle intervention program targeting multiple lifestyle factors simultaneously, which makes it difficult to assess potential benefits of an integrated lifestyle intervention program in the preconception period. A Cochrane review focused on the effectiveness of routine pre-pregnancy health promotion for improving pregnancy outcomes identified four trials with 2300 women in total.[28] This review concluded that little research has been performed in this area and there is a lack of evidence on the effects of pre-pregnancy health promotion on pregnancy

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outcomes. Recently, a multicenter randomized controlled trial among infertile obese women tested the effect of a preconception lifestyle intervention program which stimulated 5-10% weight loss by reducing caloric intake and increasing physical activity during a 6 month period or until pregnancy was achieved.[29] The intervention led to an average of 4.4 kg weight loss and significantly more ongoing pregnancies from natural conception, but did not lead to higher pregnancy rates, higher rates of vaginal birth of a healthy singleton at term or a reduction in pregnancy complications.[29]

During pregnancy, lifestyle intervention studies have mainly focused on lifestyle advice or nutritional supplementation to improve pregnancy outcomes. Major targets for lifestyle advice within randomized controlled intervention studies are maternal smoking, dietary intake and physical activity. A recent cochrane review suggested that maternal smoking cessation counselling led to a reduction in smoking in late pregnancy as compared to usual care and lowered the risk of delivering a low birth weight infant and admissions to the neonatal intensive care unit.[30] It could not be determined whether counselling increased the chance of smoking cessation when provided as one component of a broader maternal health intervention as compared to counseling on smoking only.

Dietary intake and physical activity have been targeted by multiple randomized controlled intervention trials, mainly among overweight and obese pregnant women. Six meta-analyses have been performed, assessing the impact of diet and physical activity advice on maternal and fetal pregnancy outcomes.[25,31–35] Dietary advice, delivered on an individual or group level, does lead to improved maternal dietary intake in pregnancy.[25] Physical activity adaptations seem to be more difficult to establish by advice, possibly due to pregnancy-related discomfort or maternal fear of harm by exercise for the unborn child.[25] Recently, an individual participant data meta-analysis showed that overall these types of dietary and physical activity lifestyle interventions during pregnancy reduce gestational weight gain by approximately -0.7 kg. However, these lifestyle interventions do not lead to improved maternal or fetal pregnancy outcomes, except a slightly lower risk of cesarean delivery and gestational diabetes.[36] These effects did not seem to differ by maternal prepregnancy body mass index category. Although one meta-analysis suggested that dietary interventions alone are more effective than combined dietary and physical activity interventions, this was not replicated in all meta-analysis.[25,36]

There is increasing awareness that maternal psychological distress during pregnancy is associated with maternal health risk behavior and adverse maternal and fetal pregnancy outcomes.[12] This lifestyle factor might be a new target for intervention studies. Thus far, only small (randomized controlled) trials and pilot studies have been performed targeting psychological distress, general- and pregnancy-specific-anxiety, pregnancy-related-discomfort and risk behavior.[37,38] These studies suggest that mind-body therapy may positively affect perceived maternal stress, anxiety symptoms, health risk behavior, pregnancy related pain and labor pain, utero-placental flow and birth outcomes, but these effects are often studied in small samples and findings are inconsistent across studies.

Next to maternal lifestyle advice in pregnancy, there is also a large number of intervention studies in pregnancy using maternal nutritional supplementation to improve pregnancy outcomes and offspring postnatal outcomes. Compliance and establishing meaningful alterations in maternal blood levels of various nutrients may be easier to achieve through supplementation than through lifestyle advice. Major attention has been given to vitamin D supplementation and polyunsaturated fatty acids supplementation in pregnancy. These trials have been performed in general and high-risk populations, such as pregnant women who had a previous IUGR pregnancy or a preterm born infant, and vary strongly in study size, type and timing of supplementation. A recent meta-analysis identified 43 small randomized controlled intervention trials, which assessed the influence of maternal prenatal vitamin D supplementation, mostly in the second half of pregnancy, on birth weight and risks of delivering a small size for gestational age infant or a preterm born infant.[39] The meta-analysis suggested that maternal vitamin D supplementation increased mean birth weight by approximately 58 grams and reduced the risk of small size for gestational age at birth (risk ratio 0.60, 95% confidence interval 0.40 to 0.90), but findings were not robust when sensitivity analyses and subgroup analyses were performed. There are inconsistent effects of maternal gestational vitamin D supplementation on neonatal bone development, infant anthropometric measures and wheezing or incident asthma.[40,41] Meta-analyses do not provide strong evidence that Omega-3 polyunsaturated fatty acids supplementation, mainly in the second half of pregnancy, leads to reduced risks of pre-eclampsia, preterm birth, intra-uterine growth retardation, gestational diabetes or perinatal mortality in general or high-risk populations.[42–45] Supplementation before 20 weeks gestation might have some beneficial effect on perinatal mortality.[42,43] No clear beneficial effects have been shown on offspring cognitive or cardio-metabolic development, but reduction in the risk of childhood allergic disease by prenatal omega-3 supplementation has been reported.[46–48] Among low- and middle income countries, various (double-blind) randomized controlled trials have been performed that assessed the influence of prenatal multiple micronutrient supplementation from second trimester onwards on birth outcomes and growth in the first years of life.[49] Although these studies among populations at risk of an suboptimal nutritional status, suggest a small positive effect on fetal growth and some birth outcomes, the effects on postnatal growth are small and do not seem to persist into childhood.[49–51]

Thus, lifestyle intervention studies in the preconception period and during pregnancy tend to show a positive effect on establishing maternal lifestyle changes and reducing health risk behavior. However, results on pregnancy, early postnatal and long-term outcomes are disappointing. These lifestyle intervention studies before and during pregnancy vary strongly in quality due to important limitations, as described in Table 1. Study heterogeneity and limitations make it difficult to interpret the findings of previous randomized controlled lifestyle intervention studies before and during pregnancy. Especially findings on longer-term outcomes need to be interpreted carefully as these studies suffered from high attrition rates.

Intervention studies after pregnancy

Postpartum lifestyle intervention studies have mainly focused on improving infants nutritional status in the first year of life to improve their short-term and long-term health. Also, some intervention studies targeted the postpartum period to improve long-term maternal health outcomes or maternal health for a potential subsequent pregnancy. These studies used lifestyle advice or nutritional supplementation as intervention.

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Table 1. Major limitations of previous randomized controlled lifestyle intervention studies in early life

• Timing of lifestyle intervention: ° Most studies have focused on the second half of pregnancy, which might be too late to improve maternal and offspring outcomes. ° No studies have compared effectiveness of interventions in single critical periods (preconception, pregnancy or postpartum) versus multiple critical periods.
• Type of lifestyle intervention: ° Most studies targeted a single lifestyle factor or two lifestyle factors. No studies compared this approach to an integrated lifestyle advice approach targeting multiple lifestyle factors. ° Methods used to deliver the intervention and the intensity of the intervention vary strongly across intervention studies.
• Many studies suffered from low compliance and low adherence to the lifestyle intervention.
• Most studies focused on a (single or composite) birth outcome and subjective measures of maternal behavioral change. Most studies did not assess: ° Biomarkers or physiological responses to measure the effect of the lifestyle intervention ° Long-term maternal and offspring follow-up outcomes ° Safety outcomes
• Most studies were performed in selected populations (e.g. obese women, women with a previous complicated pregnancy) without involvement of partners and lack of ethnic diversity. No lifestyle intervention studies have been performed on a population level.
• Most studies suffered from high attrition rates and lack of power to detect differences
• There is a large heterogeneity between randomized controlled intervention studies limiting the possibilities for meta-analyses and comparisons across these studies
• Risk of publication bias

One of the most well-known randomized controlled intervention studies focused on lifestyle advice in the postpartum period is the Promotion of Breastfeeding Intervention Trial (PROBIT). Naturally, due to ethical considerations, randomizing women and their infants to breastfeeding or formula feeding is impossible. The PROBIT trial uses an approach of health behavior promotion. This is a multicenter randomized controlled trial using cluster randomization in Belarus in which mothers with healthy term infants were randomized to a breastfeeding promotion intervention or usual care.[52] This study showed that the lifestyle intervention increased the duration and degree (exclusivity) of breastfeeding, and had a positive effect on the risk of gastrointestinal tract infections and atopic eczema at 1 year of age.[52] However, no significant reduction in respiratory tract infection at 1 year was present. Uniquely, long-term follow-up of mothers and their children participating in the PROBIT Trial has been conducted. Among mothers, it was shown that a longer duration of breastfeeding did not lead to clinically relevant changes in maternal BMI, body fat percentage or systolic blood pressure 11.5 years postpartum.[53] Among offspring, it was shown that longer breastfeeding duration and exclusivity of breastfeeding improved children's cognitive development at 6.5 years, but did not improve cardio-metabolic profile, lung function or risk of asthma at 11.5 years or 16 years.[54,55] Thus, this randomized controlled intervention study showed that promotion strategies are effective to improve breastfeeding duration and exclusivity and provides new evidence that strategies to improve duration and exclusive breastfeeding in early life might be causally related to cognitive development in childhood, but not to improved maternal or offspring long-term cardio-metabolic and respiratory outcomes.

In infancy, a few randomized controlled trials also aimed to target multiple environmental factors by stimulating parental lifestyle changes. A controlled multicenter intervention study with a historical control cohort in primary health care in Norway assessed the influence of an intervention program with lifestyle counseling during pregnancy and in the first two years of life targeting parental smoking cessation, optimizing N3-PUFA intake and reducing exposure to indoor dampness. The study showed that, at 2 years of age, the intervention program reduced parental smoking and increased N3-PUFA intake from supplements and oily fish, and led to lower incidence in parental reported doctor diagnosed asthma and use of asthma medication.[56] A randomized controlled trial among 802 families which assessed the influence of a lifestyle intervention program in the first two years of life targeting dietary intake, breastfeeding, activity and sleep to reduce excessive weight gain in infancy, did not show an effect on infant dietary intake or sleep outcomes, in line with other intervention studies targeting dietary intake in infancy.[57,58] The effect on childhood obesity risk remains to be assessed.

Lifestyle interventions by nutritional supplementation have been performed by supplementation of mothers who breastfeed, by supplementation or composition alterations of infant formula or by supplementation directly administered to the infant. Maternal supplementation during the breastfeeding period or formula supplementation with long-chain omega 3 poly-unsaturated fatty acids does not seem to effect infant cognition, growth or cardio-metabolic development.[59–61] With regards to composition of infant formula, randomized controlled intervention trials have mainly focused on lower protein content in infant formula which might lead to lower body mass index in infancy and childhood.[62,63] Mainly among risk groups and populations from low and middle-income countries, the influence of specific nutritional supplementations in the first years of life, such as vitamin A or iron, on various health outcomes has been explored in randomized controlled intervention trials and might have some positive effects on infant morbidity and mortality.[64–66] A Swedish randomized double blind controlled intervention trial among low birth weight infants, a population at risk of various adverse health outcomes in later life, explored the effect of iron supplementation from 6 weeks to 6 months of age on childhood neurocognitive development and blood pressure.[65,66] This study showed that iron supplementation might reduce the risk of behavior problems and systolic blood pressure, but did not affect infant IQ or diastolic blood pressure.

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Next to improving offspring health outcomes, the postpartum period can also be considered a window of opportunity to improve long-term maternal health outcomes and as an inter-pregnancy interval during which maternal health can be improved before the start of the next pregnancy. Multiple observational studies have shown that inter-pregnancy weight loss, even small amounts, reduce the risk of pregnancy complications in subsequent pregnancies.[67] Next to the PROBIT trial, a few randomized controlled lifestyle interventions trials have been performed in this period, especially focused on maternal weight reduction. A meta-analysis among 11 randomized controlled trials with 769 participants focused on stimulating exercise and dietary advice as lifestyle interventions, showed that these lifestyle interventions led to approximately 2.5 kg weight loss.[68] None of these randomized controlled intervention studies assessed long-term maternal health outcomes or effects on pregnancy outcomes in subsequent pregnancies.

Thus, randomized controlled trials in the postpartum period and infancy show that lifestyle intervention programs in this period may stimulate parents to make lifestyle changes and might have some beneficial effects on selected maternal and offspring short-term health outcomes. The effects of nutritional supplementations in early life seem limited, and mainly confined to more high-risk groups at risk of deficiency. The effects of these lifestyle interventions programs on offspring outcomes in adolescence and adulthood and long-term maternal health outcomes remain to be established.

Perspectives for future research on lifestyle interventions in early life

Current evidence from observational studies suggests that adverse maternal lifestyle factors during fetal life and maternal and infant lifestyle factors in the postpartum period lead to increased risks of adverse health outcomes for mother and child throughout the life course. Results from randomized controlled intervention trials targeting these lifestyle factors are inconsistent, but overall do not show a strong effect of lifestyle interventions on birth outcomes or maternal and offspring health outcomes. Yet, previous randomized controlled lifestyle intervention studies have major limitations and there remain important issues to be addressed (Table 1). These include the critical periods in which lifestyle interventions are delivered, the type of lifestyle interventions delivered, the targeted populations, collection of outcome data and power of the randomized controlled intervention trials (Table 2).

First, based on findings from observational studies and animal studies, the critical periods for lifestyle interventions need to be carefully identified. Based on current observational and animal studies, the preconception period and early-pregnancy appear to be major critical periods related to pregnancy complications and long-term adverse maternal and offspring health outcomes. This period involves the embryonic phase and is essential for development of the placenta and fetal organs. However, there is a paucity of well-designed randomized controlled intervention trials that target these specific critical periods. Indeed, it has been proposed that the lack of results from previous randomized controlled lifestyle intervention studies is at least partly due to their timing in pregnancy, in which they often target the second half of pregnancy.[3,27,67] This might simply be too late to improve pregnancy and long-term health outcomes, as suboptimal development has already begun from the start of pregnancy onwards. Future randomized controlled intervention trials need to start lifestyle interventions from preconception onwards and assess the influence of these interventions on the course of pregnancy, pregnancy outcomes and long-term maternal and offspring health outcomes. Whether lifestyle interventions in early-pregnancy instead of the preconception period have similar effects on maternal and offspring outcomes needs to be explored, as enrolment up to early-pregnancy may increase trial feasibility and applicability for clinical practice. Further randomized controlled intervention trials are also needed to compare the effectiveness of interventions around gestation or in infancy or in both periods for improving maternal and offspring outcomes. Advanced study designs, such as a factorial randomized controlled trial design, provide opportunity to answer these questions.

Second, the targeted lifestyle factors need to be critically evaluated to design the most optimal lifestyle interventions. Observational studies and animal studies can be used to identify the most critical lifestyle factors related to adverse maternal and offspring outcomes, to assess potential interactive effects between lifestyle factors, to determine their potential underlying mechanisms and to determine optimum of levels of certain lifestyle factors in relation to maternal and offspring outcomes. This will aid the development of more targeted lifestyle interventions. In addition, future randomized controlled intervention trials are needed to obtain insight in the most optimal methods of delivering lifestyle interventions and to compare the effects of interventions targeting a single lifestyle factor as compared to

Table 2. Key points for future research on lifestyle interventions

- Randomized controlled intervention trials need to target the critical periods identified by observational and animal studies, especially the preconception period and early-pregnancy
- Findings from observational studies, animal studies and previous randomized controlled intervention trials need to be used to design the most optimal lifestyle interventions.
- Advanced trial designs, such as a factorial randomized controlled trial design, need to be used to compare the effectiveness of lifestyle interventions targeting a single lifestyle factor versus an integrated lifestyle intervention program and to compare the effectiveness of lifestyle interventions in single critical period or multiple critical periods.
- Future randomized controlled trials need to focus on interventions on a population level, instead of only targeting selected populations.
- Future randomized controlled trials need to collect rigorous maternal and offspring outcome data, including short-term and long-term outcomes. A harmonized core outcome set needs to be established, which will allow future meta-analyses of randomized controlled lifestyle intervention trials.
- Future randomized controlled trials need to collect detailed information on socio-economic status to allow subgroup analyses and identify vulnerable populations
- Future randomized controlled intervention trials need to consider adequate power to assess short-term and long-term maternal and offspring outcomes in the design of their study, allowing a high attrition rate. In addition, information on why women decide to quit the study needs to be collected.

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lifestyle intervention programs targeting multiple lifestyle factors. Advanced and unique study designs, such as a factorial randomized controlled trial design or quasi-experimental evaluations will allow these detailed analyses. An example of this approach is the experimental birth cohort design in the Born in Bradford's Better Start Study, in which the effect of multiple early life interventions on children's social and emotional development, communication and language development, and nutrition and obesity risk are assessed within a birth cohort design.[69]

Third, future randomized controlled intervention trials need to carefully consider the population they are targeting. Thus far, most randomized controlled intervention trials have focused on selected populations, such as obese women or women who previously delivered an infant with macrosomia. It is also well-known that individuals who participate in randomized controlled trials are likely to differ in health behaviour and social characteristics from those who do not participate. Specific subgroups that might benefit from these lifestyle interventions might not be well-represented in previous randomized controlled trials. There is increasing awareness that public health problems, as obesity and disparities in pregnancy complications, result as a consequence of complex societal systems, and cannot be targeted by focusing on one lifestyle factor in a selected population.[70] Randomized controlled intervention studies need to target multiple elements across systems on a population level to identify novel intervention strategies with a large population impact. In the design of the study, specific attention needs to be given to the development of inclusion strategies focused on enrolling women from lower socio-economic status in the study, for example by collaborating with the municipality and district teams. Information about why women from more vulnerable populations decline to participate or drop-out of the study needs to be collected as much as possible. Well-defined socio-economic data needs to be obtained to allow posthoc subgroup analyses and identify specific vulnerable groups who might benefit most from lifestyle interventions. Subsequently, it would be of interest to design new randomized controlled trials or use innovative cohort designs with quasi-experimental evaluations specifically focused on identified vulnerable populations who might benefit most from lifestyle interventions and were not well-represented in previous trials.

Fourth, outcome assessment in future randomized controlled intervention trials needs to be optimized in the design of the study. In randomized controlled trials, usually a primary outcome and multiple secondary outcomes are included. In previous randomized controlled intervention trials, most studies focused on a birth weight related measure as primary outcome or a composite outcome consisting of a maternal and fetal pregnancy outcome, e.g. gestational diabetes and large size for gestational age infants. Secondary outcomes often include subjective measures of maternal behavioral change, other pregnancy outcomes and sometimes infant outcomes. Long-term follow-up of participants of these previous randomized controlled intervention trials will already provide novel insights into the effect of these lifestyle interventions on long-term maternal and offspring health outcomes. For future randomized controlled lifestyle intervention trials there is a need to move beyond the assessment of birth weight related outcomes and subjective behavioral change measures within the design of the study. Studies need to focus on rigorous measurement of maternal and fetal outcomes, including measures of compliance and lifestyle changes, e.g. questionnaires, biomarkers and physiological responses, detailed maternal and fetal pregnancy outcomes, long-term maternal and offspring health outcomes and safety measures. To maximize clinical interpretation of findings of future randomized controlled intervention trials, there is a need to develop a harmonized core outcome set for future reporting of clinical trials, which will allow comparisons between studies and individual participant data meta-analyses of these studies. This is particularly important to assess the effect of these lifestyle interventions on rare but clinically relevant outcomes, such as perinatal mortality, and long-term maternal and offspring health outcomes.

Finally, for future randomized controlled intervention trials the power needs to be carefully considered in the design of the study. Previous randomized controlled lifestyle intervention trials suffered from high attrition rates, especially in the intervention arms of the trials, reaching up to 20%. Often the previous randomized controlled intervention trials were underpowered to detect significant changes in various pregnancy outcomes. This is an even larger problem, when previous intervention trials also assessed postpartum and infant outcomes, where even higher attrition rates lead to a substantial lack of power to detect change. Future randomized controlled trials would improve if, in the design of their study, they determine adequate power for the primary outcome, allowing at least 20% maternal drop-out, but also estimate their power to assess long-term maternal and offspring outcomes considering substantial attrition rates. As this requires a large sample size, multicenter randomized controlled trials in national and international collaborations may be necessary as well as joint meta-analyses. In addition, information needs to be collected about why women decide to quit the study, which might provide important insight for future studies and implementation.

Conclusions

Over the past decades, lifestyle factors in the preconception period, during pregnancy and in the postpartum period have been identified as determinants of maternal and offspring health across the life course. Given the accumulating body of evidence, it is time to start tackling these causes of ill-health and to develop strategies to improve health of women and their offspring. Thus far, results from randomized controlled intervention trials targeting lifestyle factors in early life suggest that lifestyle interventions do lead to lifestyle changes, but overall these lifestyle interventions do not show a strong effect on maternal and offspring outcomes. Given the major limitations of these previous randomized controlled intervention trials and to advance the development of public health strategies, new well-designed randomized controlled intervention trials are needed. These new trials need to focus on interventions on a population level, targeting lifestyle in identified critical periods, with rigorous short-term and long-term maternal and offspring outcome assessments, and adequate statistical power.

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Conflicts of Interest. None.

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