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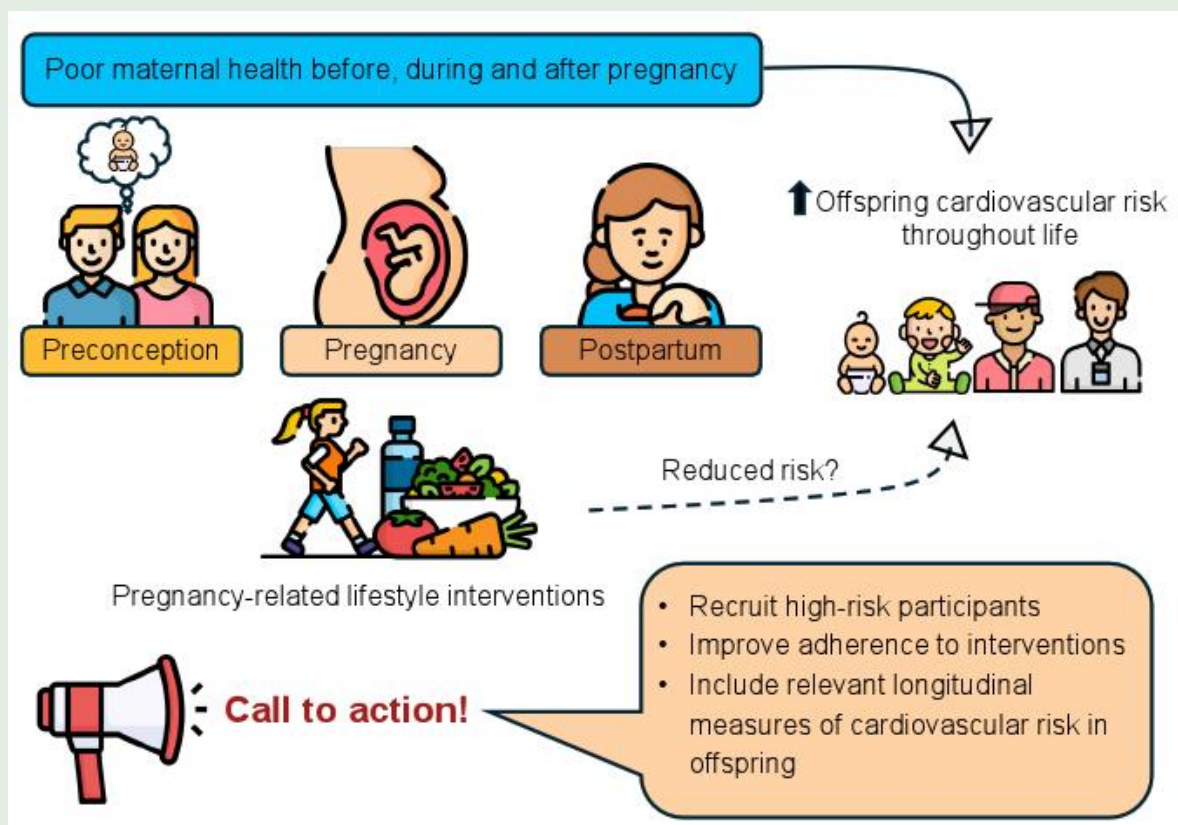
Adverse pregnancy outcomes, such as gestational diabetes, hypertensive disorders of pregnancy, fetal growth restriction, and prematurity, can increase the risk of future cardiovascular disease (CVD) in the offspring. This document aims to raise recognition of the impact of maternal health on offspring cardiometabolic health and to highlight research gaps on how to mitigate this risk via pregnancy-related lifestyle interventions. Lifestyle interventions initiated before, during, or after pregnancy hold great promise to prevent and manage adverse maternal outcomes. Still, there is limited evidence for the effect of such interventions on CVD-related outcomes in the offspring. In this document, we 'call for action' concerning research investigating how pregnancy-related lifestyle interventions can reduce CVD risk in the offspring. There is a need to overcome barriers to recruit individuals who need such interventions the most, to better design strategies for increased adherence, and to include relevant measurements in children.

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Graphical Abstract



Keywords

Cardiovascular disease • Metabolism • Hypertension • Epigenetics • Exercise • Diet • Nutrition • Sleep • Supplements • Behaviour change • Infant

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. With risk factors for CVD continuing to rise, identification and management of cardiovascular risk factors as early as possible are crucial. Adverse pregnancy outcomes, like hypertensive disorders of pregnancy, gestational diabetes, and obesity, are increasingly recognized as contributors to future CVD risk. These adverse pregnancy outcomes also increase the risk of future CVD for the offspring.^{1–3} Adverse pregnancy outcomes share many common risk factors and have pathophysiological similarities, including oxidative stress, inflammation, and endothelial dysfunction,⁴ all deemed modifiable with lifestyle changes. As such, various lifestyle interventions targeting the mother, from the preconception to the postpartum period, might influence their children's CVD risk. There is an urgent need for a better understanding of how lifestyle interventions can benefit the offspring's future cardiovascular and metabolic (cardiometabolic) health. Randomized controlled trials (RCTs) in this field are scarce and characterized by low recruitment, high drop-out rates, and low therapy adherence. To move this field forward, there is a need for well-designed RCTs that determine the impact of maternal interventions on offspring health and that consider barriers in this specific patient population.

In this document, we aim to raise awareness about the impact of maternal health on offspring CVD risk. To highlight lifestyle interventions during different pregnancy-related periods, we summarize the current knowledge on the effects of lifestyle interventions before, during, and

after pregnancy on offspring cardiometabolic health and highlight research gaps in this field. Our main focus is on hypertensive disorders of pregnancy, gestational diabetes, and obesity. We present and discuss the available evidence for the effects of dietary interventions, exercise and physical activity, multi-component interventions, and the impact of other lifestyle factors on offspring CVD risk factors. Furthermore, we 'call for action' for intervention studies that investigate the cardiovascular health of the children of mothers who are at risk of adverse pregnancy outcomes, including proposed interventions and relevant measurements in the children. We also discuss strategies to effectively reach individuals needing interventions focusing on overcoming pregnancy-specific barriers and designing feasible and effective interventions.

Methods

The document was initiated by the Childhood Cardiovascular Health Task Force of the European Association of Preventive Cardiology. The authors are members of this task force as well as other relevant invited healthcare professionals with expertise in the fields of cardiology, exercise physiology, obstetrics and gynaecology, and nutrition. The authors performed a comprehensive, non-systematic literature search using electronic databases. We selected and critically evaluated relevant publications to provide a summary of the evidence to date, focusing on systematic reviews and meta-analyses when available.

Impact of adverse pregnancy outcomes for offspring cardiovascular disease risk

During pregnancy, physiological adaptations promote the optimal growth and development of the placenta and the fetus. However, nearly 20% of births are complicated by an adverse pregnancy outcome such as hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, and fetal growth restriction, which all increase offspring CVD risk. Hypertensive disorders of pregnancy include pre-eclampsia, gestational hypertension, and chronic hypertension. Pre-eclampsia is characterized by hypertension, in addition to proteinuria and/or new-onset end-organ damage after 20 weeks of pregnancy. This serious adverse pregnancy outcome affects ~2–8% of pregnancies worldwide and poses substantial risks, including eclampsia, severe maternal organ dysfunction, (early) fetal growth restriction, preterm birth, and fetal demise.⁵ Gestational diabetes, characterized by hyperglycaemia manifesting during pregnancy, affects ~11% of pregnancies in Europe, with the highest rates in Eastern European countries, reaching 31.5%.⁶ Risk factors for gestational diabetes include maternal obesity and advanced age, as well as a family history of diabetes. Obesity during pregnancy is a growing concern, affecting roughly 15–25% of pregnant people in developed countries.⁷ Adverse pregnancy outcomes are a significant concern and an emerging risk factor for the development of CVD later in life in both mothers and their children.^{5,8–13} The underlying mechanisms for increased risk of CVD in the offspring after adverse pregnancy outcomes are not fully understood but are thought to include a combination of (epi-)genetic, molecular, and environmental factors (Figure 1).^{5,13} As such, cardiometabolic risks are

hypothesized to pass from the mother to the child through various pathways, including genetic inheritance, the *in utero* environment, and shared environmental risk factors after birth.^{2,14,15}

Concept of maternal intervention

Even subtle perturbations of homeostasis can cause marked alterations in developmental trajectories and therapeutic interventions during critical development periods may confer beneficial outcomes that persist in later life. Thus, interventions around the time of reproduction represent an attractive therapeutic strategy to reduce the long-term burden of chronic disease in future generations.¹⁶ Epidemiological studies have demonstrated that maternal (and paternal) behaviour and environment have a great impact on the risk of chronic disease of the child, as captured in the Developmental Origins of Health and Disease (DOHaD) hypothesis.¹⁷ According to this hypothesis, the *in utero* development heavily influences the infants' susceptibility for CVD later in life. Epigenetic modifications, including DNA methylation, histone modification, and non-coding RNA expression, play a role in metabolic programming and the development of CVD and metabolic disorders in the adult.¹⁸ Even if there are substantial experimental data in animals and observational data from humans supporting the DOHaD hypothesis, there is still a need to establish this concept in human intervention studies.¹⁹

Both the preconception period and pregnancy are critical time periods since any deviation from a normal environment can affect development by *in utero* imprinting. Indeed, lifestyle and therapeutic interventions during development, when an individual's phenotypic plasticity is highest, may be the most effective approach to prevent or mitigate CVD risk.¹⁶ Pregnancy is a crucial time to assess health, offering opportunities to

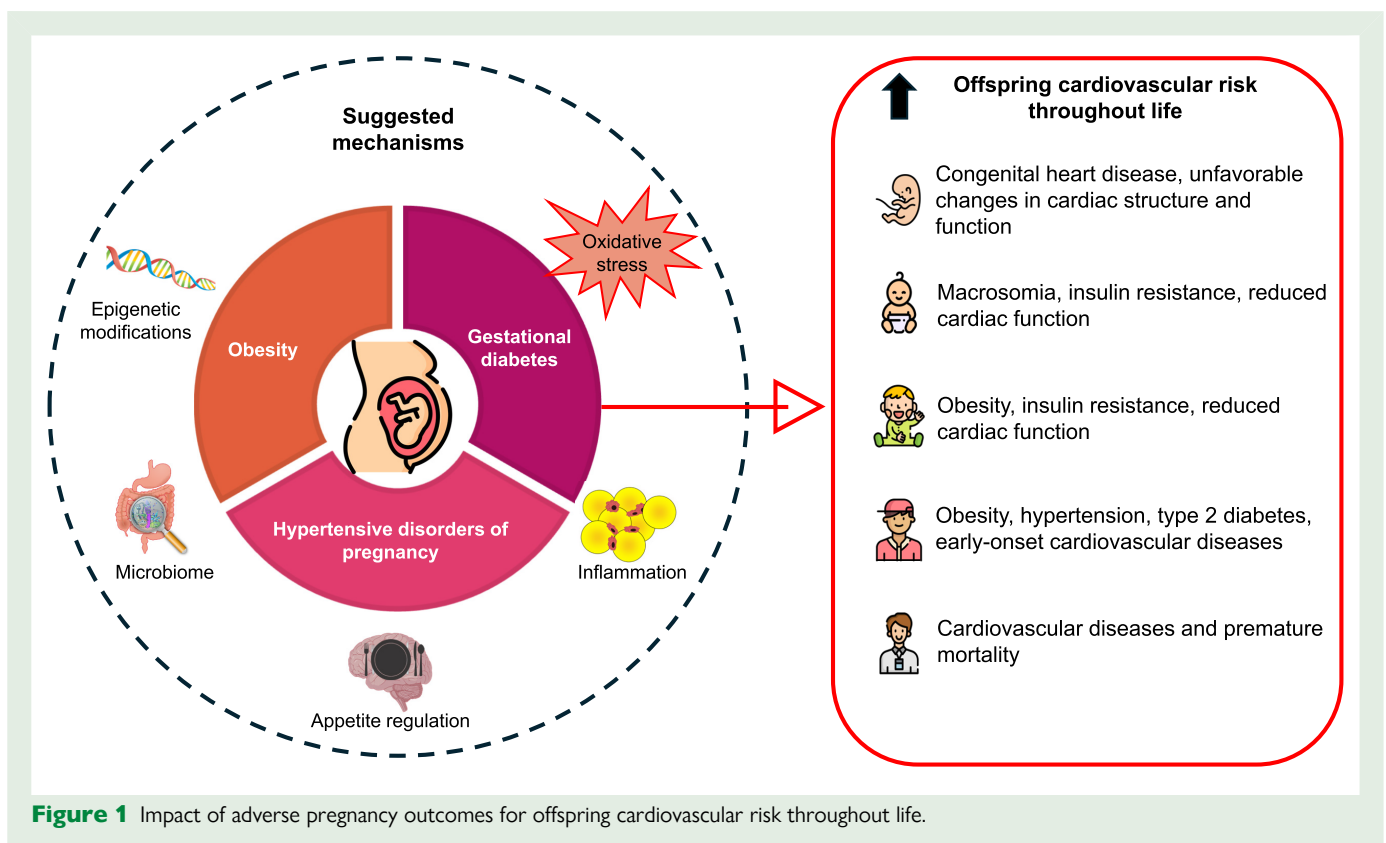


Table 1 State of the art and suggestions for future research on the effects of pregnancy-related lifestyle interventions and offspring cardiovascular risk

Limitations with previous studies	Suggestions for further research
Studies have had relatively short follow-up periods, and many children are lost to follow-up.	Long-term longitudinal follow-up studies to understand the long-lasting impact of maternal lifestyle interventions on offspring CVD risk. The use of digital health technologies to improve engagement, remote monitoring, and follow-up to reduce participant burden. Apply artificial intelligence to analyse large data sets to identify optimal lifestyle interventions.
Studies have been mainly observational, lacking a mechanistic understanding of the effect of maternal interventions on offspring CVD health.	In-depth research to elucidate the physiological pathways through which maternal lifestyle impacts offspring CVD health.
Adherence to interventions has been suboptimal.	Identify education tools and behaviour change strategies to enhance adherence.
Studies have mainly been implemented from the second trimester of pregnancy and until delivery.	Preconception and postpartum interventions. Optimizing timing and duration of interventions. Investigating whether interventions initiated during specific time periods have different outcomes.
Interventions have mainly focused on physical activity/exercise and/or diet.	Interventions that include other lifestyle factors, such as smoking, sleep, and stress/mental health.
Included participants are often highly educated and not representative of all socioeconomic, religious, and ethnic groups.	Specifically targeting high-risk populations and addressing potential disparities in access and outcomes.
Studies have mainly focussed on interventions in pregnant females.	Future studies should include both parents.

monitor and modify cardiometabolic health, as well as identify those at risk of adverse pregnancy outcomes. The risk of adverse maternal health varies across the world and is affected by a myriad of factors, including health systems, law, policies, socioeconomic factors, ethnicity, distance from a health facility, migration, and health literacy.²⁰

Ideally, a healthy maternal lifestyle is promoted as early as possible, preferably preconceptionally or in early pregnancy.¹⁸ There is growing awareness of the impact of maternal preconception health on offspring outcomes. Evidence from numerous observational human studies demonstrated that maternal health before conception impacts embryonic development, with lasting effects on the offspring.¹⁸ Still, interventions applied late in pregnancy or even postpartum can also have the potential to improve the offspring's cardiovascular health as the heart keeps on growing and maturing up to adolescence. Maternal lifestyle can influence child health through breastfeeding²¹ and also by shaping children's diet and lifestyle choices, which subsequently exert a profound impact on their cardiometabolic risk.²² Table 1 outlines some suggestions for further research on the effect of pregnancy-related lifestyle interventions on offspring CVD risk.

Types of lifestyle interventions and offspring cardiovascular health

Diet and nutritional supplements

The importance of the nutritional status during gestation is known and a balanced diet is accessible in Western countries. Nevertheless, many preconceptional and pregnant people fail to meet recommendations for vegetable and whole-grain intake, along with deficient intakes of micronutrients such as iron, calcium, and folic acid, and exceed the recommended fat intake.²³

Preconception

Despite the increased awareness of the impact of preconceptional maternal health on offspring outcomes, there are few RCTs that have

determined the effects of preconception dietary interventions on cardiometabolic health in the children.^{24–26} In a follow-up of the Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health ('NiPPER') study, supplementation with myoinositol, probiotics, and additional micronutrients preconception and in pregnancy reduced the incidence of infant rapid weight gain and obesity at 2 years,²⁵ indicating reduced CVD risk. In this study, Lyons-Reid *et al.* reported that infants in the intervention group had 24% reduced risk of experiencing rapid weight gain (>0.56 SD) in the first year of life. In contrast, a study from India in which low-income females were supplemented with micronutrient-rich foods preconceptionally and during pregnancy showed that body mass index (BMI) was increased relative to controls by 2%, fat mass index by 10%, and fat percentage by 7% among girls when they were 5–10 years old, compared with the control group.²⁴ Importantly, both these interventions stretched from preconception and throughout pregnancy, making it impossible to determine the separate effects of the preconception intervention on adiposity in the children. In summary, dietary interventions during preconception have shown conflicting results on infant body composition outcomes.

Pregnancy

A systematic review on the Dietary Approaches to Stop Hypertension (DASH) on neonatal outcomes among pregnant people with cardiometabolic disorders such as obesity, gestational diabetes, and hypertension concluded that the DASH diet reduced the risk of giving birth to an infant < 4 kg by 71% and the risk of macrosomia with 65%.²⁷ Some RCTs have also shown improved outcomes in the newborns after Mediterranean diet interventions.^{28,29} The Improving Mothers for a Better Prenatal Care Trial Barcelona (IMPACT BCN) demonstrated that a Mediterranean diet supplemented with extra virgin olive oil and walnuts from the second trimester until gestational weeks 34–36, resulted in a 42% lower odds of newborns with small for gestational age birth weight and a 36% lower odds of a composite adverse perinatal outcome, compared with usual care.²⁹ The Mediterranean diet group

received 2 L of olive oil per month and 15 g of walnuts daily, with personalized dietary training and advice regarding increased intake of whole-grain cereals, vegetables, fruit, and legumes. Also, in the The St Carlos RCT, a diet supplemented with extra virgin olive oil and pistachio nuts resulted in fewer premature, small for gestational age, and large for gestational age newborns.²⁸

Micronutrients play critical roles in fetal growth and development, and vitamin and mineral requirements increase during pregnancy. Evidence from RCTs suggests a positive impact of multiple micronutrient supplements with iron and folic acid on low birthweight and prematurity, particularly in areas at high risk for deficiencies.^{30,31} In populations where malnutrition is prevalent, nutritional interventions during pregnancy have shown mixed results on cardiometabolic outcomes in the offspring. A follow-up of 14-year-old adolescents born to participants in a Gambian RCT of protein supplementation during pregnancy showed no evidence of the intervention on offspring CVD risk factors, including body composition, blood pressure, insulin, or cholesterol concentrations. There was, however, a slight and probably not clinically relevant decrease in fasting plasma glucose (adjusted mean difference -0.05 mmol/L) among the adolescents in the intervention group.³² In the MINIMat trial from Bangladesh, children aged 4.5 years whose mothers had received a food supplement (powder made of roasted rice, roasted pulse, molasses, and soybean oil providing 608 kcal/day) from gestational week 9 had significantly lower apolipoprotein-B (-0.017 g/L), cholesterol (-0.079 mmol/L), and LDL (-0.068 mmol/L) levels than children born to mothers allocated to receive the same food supplements from around gestational week 20 (usual care).³³ The same study also showed that prenatal multi-micronutrient supplementation resulted in lower fasting concentrations of glucose (-0.099 mmol/L) and IGF-1 (-0.141 μ g/L), but also lower HDL (-0.028 mmol/L), compared with the usual-care iron + folate supplementation.³³

Supplementation of omega-3 fatty acids during pregnancy has not shown beneficial effects on offspring CVD risk outcomes. Maternal docosahexaenoic acid supplementation (200/800 mg daily) combined with dietary counselling for pregnant people with overweight/obesity did not reduce macrosomia or insulin resistance in neonates.³⁴ In line with this, a follow-up of children at 4 years of age after maternal supplementation with 400 mg docosahexaenoic acid from gestational weeks 18–22 until delivery did not affect non-fasting serum lipid or glucose concentrations.³⁵ Furthermore, another study suggested potentially adverse health effects from supplementation of 2.4 g $n-3$ ($\omega-3$) long-chain polyunsaturated fatty acids from pregnancy week 24 to 1 week after birth on offspring CVD risk factors at the age of 10 years.³⁶ In this study, children born to those in the intervention group had a 0.5 kg/m² higher BMI and 53% higher odds ratio of being overweight, along with increased fat mass, and a higher metabolic syndrome score, compared with the control group. Overall, there is evidence for beneficial effects of some dietary patterns in pregnancy on offspring cardiometabolic risk factors, including the DASH and Mediterranean diets, but weak evidence for any effect of micronutrient supplementation.

Postpartum

Consumption of human milk is associated with greater protection from excessive weight gain and obesity in childhood and later life and with reduced risk of type 2 diabetes.^{37,38} Human milk consumption, independent of duration or exclusivity, was also associated with ~ 4 mmHg lower blood pressure at 3 years of age in infants in the Canadian CHILD Cohort study.²¹ Furthermore, preterm infants randomly assigned to donated banked human milk had 4.2 mmHg lower

mean arterial blood pressure at age 13–16 compared with those receiving formula milk.³⁹ Additional follow-up in a subgroup of these participants at age 23–28 years showed that there were potential long-term cardiac benefits associated with human milk consumption, including greater left and right ventricular volumes and function compared with those who received formula as infants.⁴⁰ Maternal dietary intake during the lactation period can influence milk composition.^{41,42} How such diet-induced modifications to human milk can influence cardiometabolic risk in the offspring is, however, still unclear. One of the suggested mechanisms for a 'lactational programming' of the offspring's susceptibility to CVD later in life is that the maternal diet alters the composition of human milk oligosaccharides, which in turn shapes the infant's microbiome.⁴² In summary, consumption of human milk may reduce the cardiometabolic risk in offspring. More research is needed to establish the impact of maternal diet on milk composition and by extension offspring health.

Exercise and physical activity

Preconception

Engaging in physical activity or exercise before becoming pregnant is a key lifestyle change that can improve overall cardiometabolic health. As such, exercise patterns established *before* pregnancy significantly influence physical activity levels *during* pregnancy.⁴³ As the RCTs to date on preconception maternal physical exercise also included a dietary intervention,^{44–47} it is unclear whether isolated preconception exercise interventions influence offspring outcomes. Observational studies, however, show that physical activity before pregnancy is associated with reduced risk of pre-eclampsia, with 35% lower risk in those with high vs. low pre-pregnancy physical activity levels.⁴⁸ Pre-pregnancy physical activity is also associated with a 38% lower risk of gestational diabetes in those with high levels of physical activity vs. those with low levels.⁴⁹ There is little experimental evidence in humans on the effect of preconception exercise and physical activity on offspring cardiometabolic risk.

Pregnancy

The World Health Organization 2020 guidelines on physical activity and sedentary behaviour advocate that pregnant people should do at least 150 min/week of moderate-intensity aerobic physical activity for substantial health benefits.⁵⁰ Regular physical activity is a preventive and therapeutic method to reduce adverse pregnancy outcomes, without any known harm to fetal/neonatal health. In a meta-analysis including 37 RCTs and more than 8000 pregnant people, exercise interventions were shown to lower the risk of gestational diabetes by 38%, of gestational hypertension by 39%, and of pre-eclampsia by 41%.⁵¹ The same meta-analysis showed that pregnant people needed to accumulate at least 140 min/week of moderate-intensity exercise to achieve at least a 25% reduction in the odds of developing these three adverse pregnancy outcomes. Similar results were confirmed by other meta-analyses,^{48,52,53} but with some controversy remaining.⁵⁴ Some of the conflicting findings may be explained by the heterogeneity of study design and exercise programmes.⁵⁵ There have been concerns about physical activity leading to preterm birth and low birth weight. However, a meta-analysis of 20 RCTs and 21 cohort studies showed that physically active compared with inactive individuals have 10–14% reduced risk of preterm birth.⁵⁶ Another meta-analysis demonstrated that participants in exercise RCTs had 39% lower odds of macrosomia (having a baby > 4000 g), with no effect of exercise on growth restriction, preterm, or low birth weight.⁵⁷

Even if physical activity and exercise training during pregnancy reduce the risk of adverse pregnancy outcomes, there is much less evidence for the effects of exercise-only interventions on infant outcomes. A sub-analysis of exercise-only interventions included in a meta-analysis of the effects of lifestyle intervention during pregnancy and childhood weight and growth showed that the length of children of those who received physical activity interventions was ~0.5 cm greater across various age ranges between 1 and 12 months, but with no other differences compared with controls.⁵⁸ A secondary analysis of an RCT of individual education about healthy gestational weight gain and prescription of physical activity showed no significant between-group differences in BMI z-score or the proportion of over- or undernutrition (defined as BMI z-score $> \pm 2$ SD) at birth or the age of 5 years.⁵⁹ Furthermore, a follow-up at 7 years of age of children whose mothers participated in an RCT of structured exercise training during pregnancy failed to demonstrate any effect of maternal exercise on the children's height, weight, or physical activity.⁶⁰ Similarly, there were no differences in growth outcomes between 6-month-old infants of participants with overweight/obesity who were randomly allocated to a walking intervention during pregnancy vs. those in the control group.⁶¹ In contrast, 7-year-old children of mothers who participated in an exercise intervention between 20 and 36 weeks of gestation had increased total body fat (+3.2%), greater abdominal (+4.1%), and gynoid (+3.%) adiposity compared with controls.⁶²

A recent systematic review concluded that there is some evidence to suggest that lifestyle intervention in females with obesity may limit offspring cardiac remodelling.⁶³ However, studies that have investigated the effect of exercise training as an isolated intervention during pregnancy did not detect statistically significant differences in cardiac function parameters measured by echocardiography between the infants born to participants in the exercise groups vs. control groups.^{64,65} Some recent findings indicate that moderate-intensity resistance or endurance exercise training from gestational week 16 and throughout pregnancy may improve insulin signalling and cell respiration in infant mesenchymal stem cells.⁶⁶ In summary, physical activity and exercise training during pregnancy reduce the risk of macrosomia and are not associated with increased risk of growth restriction, preterm, or low birth weight. There is less evidence of beneficial effects for the offspring beyond the neonatal period.

Postpartum

Moderate-intensity aerobic exercise performed four to five times weekly for 12 weeks did not affect human milk volume or composition nor infant weight gain.⁶⁷ Findings in animals suggest that maternal exercise during lactation can have beneficial effects on offspring metabolic health and cardiac function, mediated through changes in the milk.⁶⁸ The effects of maternal exercise on milk composition are an area that deserves further investigation also in humans.⁶⁹

Multi-component lifestyle interventions

Although diet and exercise interventions can independently be promising pregnancy-related lifestyle interventions to reduce the risk of adverse pregnancy outcomes and, by association, improve offspring CVD risk, multidisciplinary treatment approaches may be more effective.

Preconception

A limited number of RCTs have examined the effects of preconception interventions involving diet and physical activity/exercise on the offspring's cardiovascular and metabolic health.^{45–47} The scarce existing

evidence is from follow-up studies of trials with different primary outcomes, hampering statistical power to determine the effect of these interventions. Children born to infertile individuals with obesity in the LIFEstyle study,⁴⁴ a multicentre preconception lifestyle intervention combining diet modifications with moderate physical activity, were followed up for several health outcomes.^{45–47} The LIFEstyle study intervention comprised a low-energy diet involving a 600 kcal/day reduction in energy intake and physical activity counselling with a target of 10 000 steps/day and at least 30 min of moderate-intensity exercise two or three times per week. At age 3–6 years, there were no differences in offspring cardiometabolic health outcomes, including BMI z-scores, blood pressure, arterial stiffness (pulse wave velocity), body composition, or circulating concentrations of lipids, glucose, or insulin, between the intervention group and the control group.⁴⁵ However, only 46 of the 305 eligible children attended the follow-up, which may have introduced bias in the results and prevented the detection of potential effects.

When children were 6.5–7.1 years old, children of participants in the intervention group had improved cardiac structure and function measured by echocardiography, including thinner intraventricular septum (-0.88 z-score), lower left ventricle mass index (-8.56 g/m²), and higher peak systolic and early diastolic annular velocity of the left ventricle (1.43 and 2.39 cm/s, respectively).⁴⁶ When assessed by magnetic resonance imaging, the left ventricular ejection fraction was also higher in the children in the intervention group compared with those in the control group (63.0% vs. 58.8%).⁴⁷ Since the intervention in the LIFEstyle study included both a dietary component and physical activity, it is unclear which component specifically influenced the outcomes in the offspring. Further work is needed to determine how scalable this form of intervention may be in the general population and whether benefits observed in childhood extend beyond cardiac remodelling. The ongoing BEFORE THE BEGINNING study may provide additional answers.⁷⁰ Overall, preconception multi-component lifestyle interventions may improve cardiac structure and function in infants, without clear effects on other cardiometabolic outcomes.

Pregnancy

There are some multi-component lifestyle intervention studies during pregnancy in which the infants have been followed up. In the Lifestyle in Pregnancy and Offspring (LiPO) study, the researchers reported no differences in any measures of body composition, blood pressure, fasting plasma glucose, insulin, high-density lipoprotein, or triglycerides between the intervention and control groups at the average age of 2.8 years.^{71,72} The intervention consisted of dietary counselling four times during pregnancy and encouragement to be physically active with moderate intensity for 30–60 min daily. The original trial included 360 participants with obesity who were recruited at 10–14 weeks of gestation, and 157 (52% of those eligible) were followed up. In contrast, infants born to participants in the intervention group in the FeLiPO study in Germany weighed 350 g less than those in the control group at 12 months of age.⁷³

Cardiovascular disease risk factors in children born to participants in the Australian LIMIT trial,⁷⁴ an RCT of the effect of a lifestyle intervention consisting of a combination of dietary, exercise, and behavioural strategies during pregnancy for pregnant people with overweight/obesity, have been investigated at several time points.^{74–76} *In utero*, the fetuses of participants in the intervention group had slower rates of subscapular adipose tissue deposition (-0.14 mm) between 28 and 36 weeks of gestation than those in the control group.⁷⁵ There was also a reduction in the chance of birth weight above 4.0 kg in the

intervention group (15%) vs. in the control group (19%).⁷⁴ However, at a later follow-up of the children, with the latest performed to date at the age of 8–10 years, there were no differences between offspring according to group in childhood obesity, other anthropometric measures, child dietary intake, or physical activity.^{77–79} The findings from the LIMIT trial follow-ups are in line with two 2021 meta-analyses that concluded that there is no evidence that lifestyle interventions during pregnancy modify the risk of early childhood obesity.^{58,80}

Follow-up of 3-year-old children born to participants in the UK UPBEAT multicentre RCT demonstrated that a lifestyle intervention comprising diet and physical activity in pregnant people with obesity prevented cardiac remodelling, with reduced intraventricular septum thickness (−0.03 cm), posterior wall thickness (−0.03 cm), and relative wall thickness (−0.02 cm), compared with children born to participants in the control group.⁸¹ However, results from a 5-year follow-up sub-study of the Finnish RADIEL study showed that children of participants in the intervention group had a less optimal metabolic profile compared with children in the usual care group.⁸² Participants in this study were included either before or during pregnancy and had pre-pregnancy obesity and/or previous gestational diabetes and the differences in offspring metabolic health were primarily related to lipid metabolism outcomes.⁸² In summary, multi-component lifestyle interventions can reduce the risk of macrosomia, but there is no evidence of reduced risk of obesity in older infants. Studies on other cardiometabolic outcomes have shown contrasting effects.

Postpartum

There is little research on the effect of postpartum lifestyle interventions on offspring outcomes. Lovelady et al.⁸³ showed that a daily energy restriction of 500 kcal combined with 45 min of exercise for 4 days per week did not affect the growth of the infants of breastfeeding people with BMI between 25 and 30 kg/m². The intervention in this study induced a weekly weight loss of ~0.5 kg between 4 and 14 weeks of postpartum. It is uncertain if higher volumes of exercise and/or greater energy deficiency will impact human milk and thus infant growth.

Other lifestyle factors

Additional modifiable lifestyle factors such as poor sleep, high stress, smoking, and alcohol consumption have also been shown to lead to adverse pregnancy outcomes and negatively impact offspring cardiovascular health. In a systematic review and meta-analysis including 120 studies and more than 58 million pregnant people with and without sleep disturbances, poor sleep quality, and short sleep duration were shown to be associated with adverse pregnancy outcomes including gestational diabetes, hypertensive disorders of pregnancy, and preterm birth.⁸⁴ All three of these adverse pregnancy outcomes are independently associated with short- and long-term CVD risk in the offspring, including hypertension, congenital heart disease, potentially adverse cardiac and vascular remodelling, and later life risk of heart disease, stroke, and cardiovascular-related mortality.^{85–87} In the study by Lu et al.,⁸⁴ the authors suggested that the underlying mechanism linking sleep disturbances with adverse pregnancy outcomes remains unknown, but could be due to up-regulation of oxidative stress, inflammation, and intermittent hypoxia, all of which are known to lead to poor placental perfusion and dysfunction.⁸⁸

At present, evidence on the efficacy of sleep interventions to reduce adverse pregnancy outcomes is limited, with lifestyle approaches including acupuncture, cognitive behavioural interventions for insomnia, and mindfulness, meditation, and yoga being explored.⁸⁹ Nevertheless, RCTs in the

field have been in small cohorts lacking adequate statistical power to test potential sleep benefits for reducing adverse pregnancy outcomes and improving offspring CVD risk. Interventions of this nature may also provide broader benefits for reducing prenatal stress, which has long been shown to lead to an adverse intrauterine environment for the developing fetus that puts them at increased risk of CVD.⁹⁰ More specifically, psychological distress and anxiety during pregnancy are associated with higher heart rate, triglycerides, and blood pressure levels in children, including higher systolic, diastolic, and mean arterial blood pressures.^{91,92} Although there is a growing body of evidence on the negative consequences of maternal stress during pregnancy, there is a lack of robust data on the relationship between maternal stress and obesity risk in offspring over the long term.⁹³ Furthermore, maternal bereavement due to child or family member loss during the prenatal period has been shown in large population-based registry studies to be associated with an increased risk of offspring heart failure by middle-age,⁹⁴ congenital heart defects,⁹⁵ and early-onset type 2 diabetes,⁹⁶ offering the possibility that targeted approaches to better manage maternal mental health and stress levels may have cross-generational benefits.

Smoking during pregnancy has been widely shown to have direct, negative impacts on cardiovascular health for both mother and child.⁹⁷ The effectiveness of generalized approaches to smoking cessation in pregnant people remains varied.⁹⁸ The greatest potential for preventing adverse pregnancy outcomes relevant to offspring CVD risk, such as low birth weight, is observed when smoking cessation is implemented before the second trimester⁹⁹ and is usually achieved by clinically led, individualized approaches involving behavioural, psychosocial, and pharmacotherapy interventions.¹⁰⁰ RCTs for smoking cessation show high relapse in the postpartum period, with 43% of participants who reported having ceased smoking at the end of their pregnancy having restarted by 6 months of postpartum.¹⁰¹ Breastfeeding appears to reduce relapse and may be a target for future interventions to maintain smoking cessation.¹⁰² Smoking negatively affects maternal milk supply and composition,¹⁰³ which may have downstream negative consequences for cardiovascular health given consumption of human milk has been shown to associate with lower blood pressure and preferential cardiac remodelling across the life course in the offspring, especially in children born preterm or to intrauterine growth restriction.^{104–106} Management of maternal stress and psychosocial behaviours may also be particularly beneficial to milk composition and breastfeeding success.¹⁰⁷ It was demonstrated in an RCT that a postpartum relaxation intervention reduced the stress scores and increased milk production among participants in the intervention group compared with controls, as well as increased infant postnatal weight gain.¹⁰⁸ In summary, maternal sleep, stress, smoking, and alcohol impact pregnancy outcomes and offspring cardiovascular health, with interventions like mindfulness, smoking cessation, breastfeeding support, and stress management offering potential benefits but needing further evidence.

Call to action

Recruitment to pregnancy-related interventions

There remain significant barriers to implementing pregnancy-related interventions for people in high-income and low-and-middle-income countries. Pregnancy outcomes in the USA remain among the worst in high-income countries despite spending more money on maternal health than any country in the world. From 1999 to 2019, maternal mortality rates doubled, with significant racial disparities.¹⁰⁹

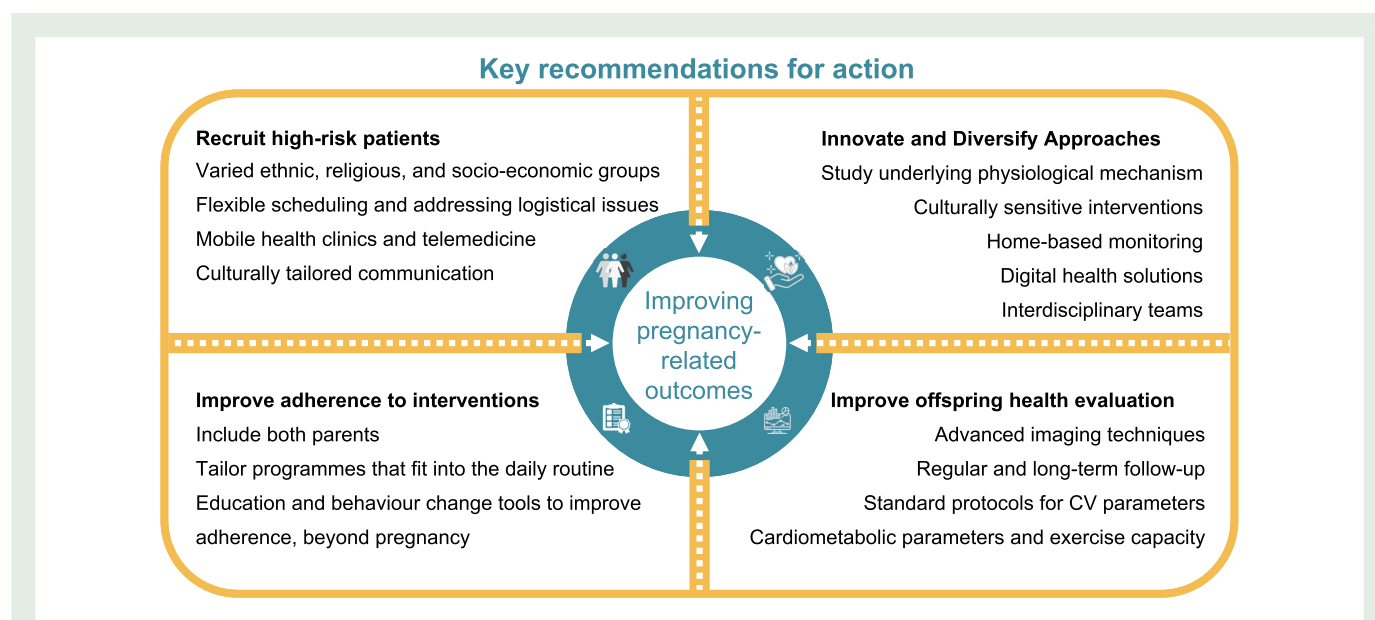


Figure 2 Key recommendations for pregnancy-related interventions aiming at improving offspring health. CV, cardiovascular.

Timing and receipt of antenatal care vary between ethnic groups, with insurance status, access to transport, migration, and other social factors likely playing a role.¹¹⁰ Even in countries with universal healthcare coverage, such as the UK, similar barriers exist. Despite a free at-the-point-of-use system, those suffering from social deprivation are less likely to engage with medical professionals and have poorer outcomes. In the UK, a national report demonstrated that the rate of neonatal mortality in the most deprived quintile was almost double that in the least deprived.¹¹¹ There also remains an increased neonatal mortality in babies with Black and Asian compared with White ethnicity. The reasons for this are likely multifactorial. Reaching these high-risk groups requires interventions that are accessible from early in pregnancy, culturally appropriate, affordable, and feasible with an associated education package that is easy to understand considering education and language barriers. Implementation of evidence-based recommendations on antenatal care screening is suboptimal in the WHO European Region, and it is necessary to increase the availability of such services in routine clinical practice.¹¹²

Antepartum care aims to provide comprehensive and regular care to pregnant people, addressing various aspects of their health and well-being to ensure optimal outcomes for both the mother and the newborn. A recent systematic review and meta-analysis showed that enhanced antepartum care interventions improved clinical outcomes for mothers and babies.¹¹³ Barriers to receiving regular antepartum services have included patient-specific factors such as social determinants of health including health literacy and agency, inadequate resources, negative attitudes towards healthcare, cultural factors, stigma and systemic factors related to racism, inadequate health system resources and service shortages, and access to care.¹¹⁴ A continuity of care model that promotes partnership between pregnant people and healthcare providers, through midwives and other clinicians, has been considered a core enabler for antenatal care services.¹¹⁵ Additional enablers include a welcoming health facility environment, flexibility in scheduling appointments, easier access and less distance to clinic facilities via public transportation, and parking availability. A welcoming environment at the clinic facilities where people feel accepted, trusted, and safe with positive communication experiences

in languages that are easily understood and early referrals for supportive services is important in enhancing the experience of the continuity of care model.^{115,116} Personal agency and wanting the best for the baby are the main motivators for most people receiving regular antenatal care. However, some will require additional support to overcome personal challenges that include social determinants of health factors such as intimate partner violence or financial stress.¹¹⁵ Overcoming cultural perceptions regarding exercise and diet through community programmes and regular home monitoring of blood glucose and blood pressure are key in the management of high-risk pregnancies.^{117,118} Successful innovations in reaching individuals in rural and underserved areas have included using mobile health clinics and technology innovations such as text messages in local languages and telemedicine services.¹¹⁹ The most frequently reported barriers to leisure-time physical activity during pregnancy include pregnancy-related symptoms, mother–child safety concerns, lack of information, and lack of social support.¹²⁰ These barriers should be targeted in future interventions.

In summary, the following actions should be taken for recruitment to interventions: (i) enhance antenatal care with mobile health clinics, telemedicine, and culturally tailored community educations to improve access for underserved populations; (ii) address social determinants of health through transport subsidies, flexible scheduling, and early referrals to support high-risk groups; (iii) implement home-based monitoring for high-risk pregnancies and promote targeted interventions for diet, exercise, and mental health barriers to improve maternal and offspring outcomes (*Figure 2*).

Types of interventions

Several key principles must be considered when designing pregnancy-related interventions to optimize feasibility and effectiveness. Firstly, the proposed interventions must be acceptable to pregnant mothers or those planning to conceive a child. Is the aim of the intervention a health priority for the local population, especially in low- or middle-income countries? Expectant mothers are less likely to agree to interventions without evidence or a strong scientific

rationale even if they have perceived benefits. The growing use of patient and public involvement initiatives is likely effective and must be specific to the setting for the proposed intervention.¹²¹ In addition, there must be consideration as to how practical and time-consuming the intervention is. For example, can they fit into a normal day-to-day routine, like lifestyle interventions such as physical activity or nutritional interventions?¹²² Utilizing trainers and buddies may also increase adherence.¹²³ For multi-component interventions, an interdisciplinary team should be formed, typically including experts in gynaecology and obstetrics, exercise physiology, nutrition, paediatrics, and midwifery. The team should also collaborate with other stakeholders, such as employers and family members. If interventions require contact with a healthcare professional, as with pharmacological interventions, this could take place during routine antenatal visits, especially in countries with universal healthcare. There are also opportunities to use digital tools where available, for example smart smartphone apps and websites to complement or follow up on interventions and to apply artificial intelligence to analyse large data sets. Digital tools would also reduce the need to present to research or healthcare facilities in person and may improve engagement. A systematic review of digital and combined digital and face-to-face interventions targeting weight, diet, supplementation use, and physical activity indicates the potential of such interventions to impact these modifiable behaviours.¹²⁴ Digital interventions for smoking cessation in pregnancy have also proven effective, especially those including specific behaviour change techniques.¹²⁵

Many high-risk populations are the hardest to reach due to poor access to healthcare. To overcome these barriers, buy-in from key stakeholders is required for interventions to be successful.¹²⁶ One of the key challenges when developing pregnancy-related interventions is determining what components to focus on. The results of many CVD prevention studies in other populations may have limited transferability as many trials included mostly male participants and also since pregnancy is a time with unique physiological changes.¹²⁷ Furthermore, if

intervention trials show maternal benefits, the next step is to show that these benefits also extend to the offspring. Critically, longer-term trials are required to demonstrate that any intervention in the pregnancy-related period influences the trajectory of CVD risk in their children (Figure 2). It may be decades before definitive results will be available. The cost of the intervention also needs to be defined. Even if the intervention trial is funded, are there benefits to the local healthcare systems? If the trial is successful, will it be possible to roll out the intervention in clinical practice? Integration of these interventions into national or international guidelines, along with the implementation of policy and population-level strategies, is essential for achieving long-term clinical benefits beyond individual patient care.

Measurements in the offspring during pregnancy and after birth

Detailed history taking

The cardiovascular health evaluation in the offspring should include taking a detailed history including maternal factors that affect fetal programming,¹²⁸ information regarding genetic cardiac disease in the family, and dietary history. A scoring system to evaluate maternal pre-pregnancy cardiovascular health has been proposed.¹²⁹ Furthermore, if assisted reproductive technology has been used, this may influence the offspring's cardiac structure and function.¹³⁰ Preterm birth elevates the risk for lifetime CVD¹³¹; however, preterm infants with higher consumption of mother's own milk have enhanced cardiac performance at 1 year of age.¹⁰⁵ This suggests that consumption of human milk may modulate cardiac mechanics in preterm-born infants and help in the normalization of the preterm cardiac phenotype.¹⁰⁵

Offspring examination

A comprehensive physical examination that includes inspection, palpation, and cardiac auscultation of the child is needed. In a clinical setting,

Table 2 Measurements to map the cardiovascular health of the offspring

Age	Basic measurements	Cardiac anatomy, structure and function	Other relevant parameters
Fetus	<ul style="list-style-type: none"> • Growth (AC, EFW, BPD, FL) • Uterine artery, middle cerebral artery and ductus venosus Doppler • Sex 	<ul style="list-style-type: none"> • Echocardiography¹³⁶ • MAPSE • TAPSE • IVSd 	<ul style="list-style-type: none"> • Heart rate • Fetal well-being • Biomarkers in umbilical cord blood
Neonate	<ul style="list-style-type: none"> • Growth (length, weight, BMI) • Apgar score • GA at birth • Postnatal age • Thriving • Sex 	<ul style="list-style-type: none"> • Echocardiography¹³⁷ • MAPSE • TAPSE • IVSd • Strain • FS 	<ul style="list-style-type: none"> • Blood pressure • Heart rate variability • Oxygen saturation • Body composition
Infant (<2 years)	<ul style="list-style-type: none"> • Growth (length, weight, BMI) • Development • Postnatal age • Thriving • Sex 	<ul style="list-style-type: none"> • Echocardiography¹³⁷ • MAPSE • TAPSE • IVSd • Strain • FS 	<ul style="list-style-type: none"> • Blood pressure • Heart rate variability • Oxygen saturation • Body composition

AC, abdominal circumference; BMI, body mass index; BPD, biparietal diameter; EFW, estimated fetal weight; FL, femur length; FS, fractional shortening; GA, gestational age; IVSd, interventricular septum diameter in diastole; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion.

we advise further evaluation if the history and physical examination findings suggest congenital or acquired heart disease. Blood pressure measurements are relevant but challenging in infants.¹³² Implementing a standardized approach, including choosing the right cuff size, could improve the accuracy.¹³³ Heart rate and heart rate variability have been used as surrogates of cardiac health and are feasible measures in neonates and infants.¹³⁴ Assessment of body composition and anthropometry may assist in identifying high-risk infants.¹³⁵

Fetal ultrasound including fetal echocardiography according to the guidelines provides important information about fetal growth, heart structure, and function.¹³⁶ Doppler ultrasound also provides information about placental function. Signs of intrauterine growth restriction must be detected and measured, as this may be associated with cardiovascular risks in early adulthood.¹³¹ We advise echocardiography according to the guidelines to evaluate cardiac anatomy, structure, and function in a research setting.¹³⁷ The use of myocardial function analysis and strain using speckle tracking may be beneficial.¹² Ultrafast ultrasound is a novel technique to evaluate cardiac remodelling including diastolic function and cardiac stiffness that can bring the field forward.^{138–140}

In a research setting, infant blood samples (i.e. glucose, lipid profile, and insulin levels) are often not ethically justifiable, unless samples are taken in the clinical ward. Umbilical cord blood sampling to examine metabolic and/or inflammatory markers may then be a gentle compromise. [Table 2](#) lists more specific widely available measurements to map the cardiovascular health of the offspring from fetal life until 2 years of age. Assessing these various parameters can indicate the development and function of the cardiovascular system already at an early stage.

Follow-up

Regular follow-up assessments after 2 years of age would be ideal to measure cardiometabolic health parameters as the child grows and develops. Cardiac magnetic resonance imaging studies have been used in research settings and have identified myocardial fibrosis and diastolic function abnormalities in young adults who were born preterm.¹⁴¹ Exercise testing in children before school age is difficult. However, knowledge of exercise capacity in small children is needed for a complete evaluation of their cardiometabolic health, and a detailed history can help. Most studies on exercise testing performed previously have been limited to children > 8 years; however, exercise field testing in younger children has been proposed, such as shuttle run tests.¹⁴²

Conclusions

Cardiovascular disease has origins in adverse environmental exposures during preconception, *in utero*, and early infancy, as suggested in the DOHaD concept.¹⁷ As such, lifestyle interventions before and during pregnancy, as well as early postpartum, may impact future susceptibility of CVD and other chronic diseases in the offspring. Although there is some evidence from intervention studies to suggest that maternal lifestyle can limit the offspring's risk of future CVD, there is a pressing need for high-quality longitudinal studies in this field. Most pregnancy-related interventions have focused on maternal outcomes, but such interventions have the potential to impact both mother and child. With this 'call for action' document, we aimed to increase awareness about the impact of maternal health on offspring CVD risk and stimulate the scientific community to undertake lifestyle interventions among people with increased risk of adverse pregnancy outcomes, including incorporating relevant longitudinal measurements in the offspring.

Author contributions

T.M., M.B., H.H., A.J.L., M.T., and E.V.C. contributed to the conception and design of the study. All authors participated in the writing of the manuscript and critically revised it. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

There is no data for this manuscript.

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