Maternal cardiovascular disorders and offspring cardiovascular disease across the life course

Romy Gaillard[†] & Vincent Jaddoe

Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, Netherlands.

[†]e-mail : r.gaillard@erasmusmc.nl

Abstract | Obesity, hypertension, type 2 diabetes mellitus and dyslipidaemia are highly prevalent among women of reproductive age and contribute to complications in >30% of pregnancies in Western countries. An accumulating body of evidence suggests that these cardiovascular disorders in women, occurring before and during their pregnancy, can affect the development of the structure, physiology and function of cardiovascular organ systems at different stages in the embryo and fetus. These developmental adaptations might, in addition to genetics and sociodemographic and lifestyle factors, increase the susceptibility to cardiovascular disease throughout the life course. In this Review, we shed light on our current knowledge of the influences of maternal cardiovascular disorders, before and during pregnancy, on offspring cardiovascular development, dysfunction and disease from embryonic life until adulthood. We discuss findings from contemporary large-scale observational studies that provide insights into specific critical periods, evidence for causality and potential underlying mechanisms. Furthermore, we focus on priorities for future research, which include defining optimal cardiovascular and reproductive health in women and men before their pregnancy; identifying specific embryonic, placental and fetal molecular developmental adaptations from early pregnancy onwards; developing novel prediction models based on preconception, early pregnancy and infancy characteristics to identify individuals with an adverse cardiovascular risk profile; and performing randomized, controlled trials (RCTs) in both women and men from preconception onwards in order to

optimize cardiovascular health for future generations. Together, these approaches will contribute to stopping the intergenerational vicious cycle of cardiovascular disease development.

[H1] Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide[1]. Research on cardiovascular risk factors and treatment has been focused predominantly on adults, given the large clinical burden of cardiovascular disease on the elderly population. However, in the past three decades, an accumulating body of evidence has suggested that numerous events occurring in early life could contribute to cardiovascular health and disease[2]. The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that developmental adaptations in early life that occur in response to an adverse in utero environment can increase susceptibility to cardiovascular dysfunction and disease in later life[2]. Maternal cardiovascular disorders that occur before and/or during pregnancy, such as obesity, hypertension, diabetes mellitus and dyslipidaemia, are important modifiable risk factors for an adverse in utero environment, which might lead to adaptations during embryonic and fetal development that can result in an increased risk of cardiovascular diseases in later life[2,3]. In line with the DOHaD hypothesis, large-scale observational studies have shown that both low and high birth weight are associated with an increased risk of obesity, hypertension, coronary heart disease and type 2 diabetes in adulthood[4-6]; these findings suggest that both restricted and excessive nutritional in utero environments might lead to cardiovascular damage later in life[2].

Approximately one in three women of reproductive age have a preclinical or clinically overt cardiovascular disease, with the majority of these women suffering from more than one cardiovascular disorder[3,7-10]. Although accumulating evidence suggests that the cardiovascular disorders in these women have important implications for the health of their future offspring, the potential of novel preventative strategies has yet to be capitalized on, probably attributable to the limitations in our understanding of the mechanisms linking cardiovascular risk factors in the mother with cardiovascular disease in the offspring. In this Review, we shed light on what is currently known about the influence of maternal cardiovascular disorders, occurring before and during pregnancy, on cardiovascular

development and disease in offspring, from embryonic life until adulthood. We first summarize findings from contemporary large-scale observational studies, and then discuss insights into critical periods, evidence for causality and potential underlying mechanisms Finally, we discuss the priorities for future research on this topic, including potential public health and clinical strategies to optimize cardiovascular development from early life onwards and to stop the intergenerational vicious cycle of cardiovascular diseases.

[H1] Cardiovascular health before and during pregnancy

The AHA defined the concept of 'ideal cardiovascular health' using four cardiovascular variables: BMI, blood pressure (BP), total cholesterol level and fasting glucose concentration[1]. This approach has now also been adopted by the American College of Obstetricians and Gynecologists to assess the cardiovascular health of women of reproductive age[11]. These four cardiovascular risk factors strongly correlate with a diagnosis of obesity, hypertension, dyslipidaemia and diabetes, respectively, which can occur both before and during pregnancy. The prevalence of numerous cardiovascular disorders in women before and during pregnancy in Western countries is summarized in **Table 1.**

Pregnancy is considered a physiological stress test; the growing fetus imposes an increased physiological burden on the woman's cardiovascular system and numerous physiological cardiovascular adaptations need to occur in order to sustain fetal growth and development (**Box 1**)[11]. The placenta has a crucial role in regulating these adaptations and acts as an active interface between the maternal and fetal environment[12]. The physiological cardiovascular adaptations that occur during pregnancy has been reviewed previously[12]. Briefly, regardless of maternal BMI before conception, women normally gain weight during pregnancy, owing to increased fat accumulation and circulating blood volume, extracellular fluid expansion, and growth of the fetus, placenta and uterus[13]. Circulatory adaptations that occur during pregnancy include a decrease in vascular resistance, an increase in cardiac output and an expansion in blood volume, which together results in high tissue perfusion and a physiological decrease in BP during the first half of pregnancy, with an increase thereafter[12]. The architecture of the utero–placental and feto–placental circulation is established from early pregnancy onwards, which facilitates a high-flow and low-resistance placental circulation from the end of the first

trimester onwards that is crucial for fetal oxygen and nutrient supply[14]. Furthermore, major metabolic adaptations take place to ensure adequate nutrient supply for the developing placenta and fetus throughout pregnancy. The first half of pregnancy is characterized by an anabolic phase that increases the storage of lipids, which is needed to ensure adequate nutrient availability for the placenta and fetus later in the pregnancy and for breastfeeding in the postnatal period[12]. The second half of pregnancy is characterized by a catabolic phase, characterized by reduced insulin sensitivity, the breakdown of fat stores and an increase in the concentration of glucose, amino acids, fatty acids and triglycerides, all of which are required for placental and fetal nutrient supply at the time of the highest fetal growth rate[12]. Inadequate cardiovascular adaptations during pregnancy can result in increased risks of gestational hypertension or pre-eclampsia, gestational diabetes and gestational hyperlipidaemia, all of which contribute to an adverse intra-uterine environment for the offspring[11].

[H1] Link between maternal health and offspring health

Ideally, studies on the associations of maternal cardiovascular disorders before and during pregnancy with cardiovascular disease in the offspring should assess clinical cardiovascular end points. However, such studies will need to be prospectively designed to include participants from preconception or pregnancy onwards, with seven decades or more of follow-up of the offspring and will need large sample sizes, which is not always feasible given the high financial costs. Record linkage and registry studies might provide follow-up data on the offspring, but are hampered by limited data on sociodemographic and lifestyle factors across the life course. Therefore, prospective cohort studies that have been performed thus far often focus on measures of cardiovascular development and dysfunction from early life onwards, and include outcomes such as growth trajectories, BMI, body fat distribution, BP levels, and glucose and lipid concentrations measured during childhood or adolescence. Although these risk factors might have not direct clinical consequences that manifest in the first three decades of life, they are known to track from childhood into adulthood and to be related to cardiovascular risk in adulthood[15-18]. Moreover, cardiovascular risk factors including obesity, glucose intolerance and hypertension that are present during childhood are associated with increased

rates of premature death from endogenous causes[17,18]. **Figure 2** provides an overview of cardiovascular development over the lifetime and measurements obtained in cohort studies to assess cardiovascular dysfunction and disease.

In this section, we describe findings from mainly observational studies that focus on the link between maternal cardiovascular disorders occurring before and during pregnancy with offspring cardiovascular outcomes from early life to adulthood. These cardiovascular outcomes include congenital cardiac anomalies, obesity, high BP, impaired glucose tolerance and dyslipidaemia during childhood and adulthood, and cardiovascular diseases and mortality in adulthood.

[H2] Obesity and excessive gestational weight gain

Obesity before or early in pregnancy is associated with offspring cardiovascular dysfunction across the life course (**Table 2**)[13]. A meta-analysis of 18 observational studies showed that maternal overweight and obesity were associated with increased risks of offspring cardiovascular anomalies, with the strongest associations present for septal anomalies and transposition of the great arteries[19]. Findings from a meta-analysis of 250,000 mother–offspring pairs from various population-based prospective cohort studies involved in the EU Child Cohort Network showed that prepregnancy overweight and obesity were associated with higher risks of childhood obesity from 2–18 years, with the strongest associations at the higher ages[20]. Up to 41.7% of overweight or obesity in children was linked to maternal overweight and obesity[20]. A 2022 meta-analysis of 140,000 mother–offspring pairs from prospective cohort studies showed that every 5 kg/m^2 increase in maternal prepregnancy BMI was associated with a 1.9 mmHg increase in systolic BP and 0.5 mmHg increase in diastolic BP in the offspring, which was independent of BMI in the offspring[21]. A separate systematic review that identified 12 studies assessing the link between maternal prepregnancy BMI and childhood glucose metabolism, lipid profile, cardiac and vascular development during childhood (aged 2–18 years) also showed that a higher maternal prepregnancy BMI is associated with an adverse cardiovascular profile during childhood in the offspring, which was partly explained by increased childhood BMI[22]. Unsurprisingly, this adverse cardiovascular profile during childhood was carried into the adult years[22]. **A** study that assessed the birth records of 37,000 individuals showed that maternal obesity (BMI >30)

at the first antenatal visit was associated with an increased risk of premature mortality (HR 1.35, 95% CI 1.17–1.55) and hospital admissions for cardiovascular events (HR 1.29, 95% CI 1.06–1.57) in adult offspring compared to offspring from mothers without obesity[23]. Another similar study also found that maternal obesity at the first antenatal visit was linked to a threefold increased risk of type 2 diabetes in the offspring in adulthood[24]. The findings from all these studies were adjusted for family-based sociodemographic and lifestyle factors, but data on offspring BMI and lifestyle factors were not available, which increases the potential for residual confounding[23,24].

Excessive gestational weight gain is most often classified according to the National Academy of Medicine (NAM) guidelines.[25] The NAM guidelines define optimal gestational weight gain ranges by maternal prepregnancy weight status according to the lowest risks of cesarean delivery, postpartum weight retention, preterm birth, small or large for gestational age at birth, and childhood obesity[25]. However, the use of the NAM guidelines to define excessive gestational weight gain might have important limitations in research settings[13]. First, results from a large-scale, individual participant-level meta-analysis involving >190,000 mother–offspring pairs from population-based prospective cohort studies in the EU Child Cohort Network suggest the NAM guidelines might be suboptimal for women with obesity[26]. When the lowest risks of pre-eclampsia, gestational hypertension, gestational diabetes, cesarean delivery, preterm birth, and small or large size for gestational age at birth were taken into consideration, the optimal amount of gestational weight gain for women with obesity measured in this study was lower than the NAM guidelines.[26] Second, given that the NAM guidelines combine prepregnancy BMI and gestational weight gain, it iss not possible to disentangle the separate associations of maternal prepregnancy BMI and gestational weight gain with offspring outcomes.[13] Findings from another meta-analysis involving **162,129** mother–offspring pairs from Europe, North America and Australia showed that excessive gestational weight gain was associated with a higher risk of the offspring being overweight or obese in childhood, as compared to mothers with optimal gestational weight gain[20]. This association was present across the full range of total maternal gestational weight gain and was independent of prepregnancy BMI, but the association was weaker than the association of maternal prepregnancy overweight and obesity with childhood overweight and obesity[20]. Results from two meta-analyses together involving >150,000 mother–offspring pairs from

mainly prospective studies suggest that the association between excessive or total gestational weight gain and offspring BP and insulin sensitivity could be explained by offspring BMI.[21,27] Several observational studies have also shown that higher gestational weight gain is related to increased adiposity in adult offspring, independently of maternal prepregnancy BMI, but not to other cardiovascular risk factors in adulthood once offspring BMI is considered[28-31]. To date, no studies have investigated the link between gestational weight gain and cardiovascular disease outcomes in the adult offspring.

Together, these findings indicate that being overweight or obese before pregnancy and excessive gestational weight gain are independently associated with markers of adverse cardiovascular health in the offspring, from fetal life until adulthood. Of note, prepregnancy obesity is more strongly related to adverse offspring outcomes than excessive gestational weight gain. As prepregnancy obesity often occurs alongside other maternal cardiovascular risk factors, obesity needs to be taken into account when the associations of other maternal cardiovascular disorders with offspring outcomes are studied.

[H2] Hypertensive disorders

Gestational hypertensive disorders, which include gestational hypertension and preeclampsia, are a leading cause of maternal and fetal mortality worldwide[32]. Gestational hypertension is defined as hypertension after 20 weeks of gestation in previously normotensive women, whereas preeclampsia is defined as gestational hypertension with the addition of proteinuria (Table 1) [32]**.** However, studies focused on the associations of hypertensive disorders before and during pregnancy with offspring cardiovascular outcomes are scarce (**Table 2**). Findings from a population analysis involving >1,900,000 mothers and neonates showed that pre-eclampsia was associated with a higher risk of congenital heart defects, most commonly septal defects[33]. Early-onset pre-eclampsia (diagnosed before 34 weeks gestation) is often more severe than late-onset pre-eclampsia, and has been associated with an increased risk of severe congenital heart defects[33]. A population-based study involving >2,200,000 mother–infant pairs that used data from the Canadian Institute for Health Information showed that

pregestational hypertension is also independently associated with an increased risk of congenital cardiac anomalies[34]. These analyses were adjusted for other maternal chronic conditions, obesity and age, but no information on maternal medication use was available[34]. An individual participant-level meta-analysis of 160,000 mother–offspring pairs from population-based prospective cohort studies showed that offspring exposed to pre-eclampsia had a lower BMI in early childhood (2 to 5 years) , but a higher BMI in mid-to-late childhood (5 to 18 years) [35]. Furthermore, offspring exposed to gestational hypertension had a higher BMI throughout their childhood[35]. Importantly, these associations were fully attenuated after adjusting for maternal prepregnancy BMI[35]. A meta-analysis of data from 24 published studies showed that offspring from mothers with pregestational hypertension, gestational hypertension or pre-eclampsia had higher BP levels in childhood and adulthood as compared to offspring from mothers with BP levels in the normal range before and during pregnancy [36]. The investigators demonstrated that the association between maternal hypertensive disorders and offspring BP remained present after adjustment for potential confounders, including maternal weight, age, offspring birth weight, sex and childhood BMI[36]. However, findings from studies on the relationship between gestational hypertensive disorders and offspring body composition, cardiac remodelling, systemic vascular dysfunction and metabolic disturbances in childhood are inconsistent, possibly explained by discrepancies in study designs, differences in study populations, the timing of outcome assessment and the extent of adjustment for sociodemographic, lifestyle and birth characteristics[37-41]. A population-based cohort study that assessed data from >2,400,000 individuals born in Denmark with a follow-up duration of up to 40 years showed that offspring born from mothers with pregestational hypertension, gestational hypertension or pre-eclampsia had a higher risk of early-onset cardiovascular diseases, especially hypertension and myocardial infarction, compared with offspring born to mother with normal BP levels[42]. The offspring of mothers with severe and early-onset pre-eclampsia had the highest cardiovascular risk[42]. These analyses were adjusted for maternal characteristics, but no data on lifestyle factors in the offspring were available, leading to increased potential for residual confounding[42]. Furthermore, data from the Helsinki Birth Cohort similarly showed that offspring exposed to pre-eclampsia or gestational hypertension had a higher risk of hypertension and stroke[43].

[H2] Diabetes and hypercholesterolaemia

Pregestational type 1 and type 2 diabetes and gestational diabetes expose the fetus to an adverse utero environment that is characterized by hyperglycaemia, and have been identified as important risk factors for impaired cardiovascular health in the offspring (**Table 2**). A 2022 meta-analysis that included data from >80 million participants showed that the risk of congenital heart defects was 3.5 times higher in the offspring of women with pregestational diabetes and 1.5 times higher in the offspring of women with gestational diabetes[44]. The rate of glycaemic control in the mothers is related to the risk of congenital heart defects in the offspring, and the associations are independent of maternal prepregnancy BMI[44,45]. Findings from an individual participant-level meta-analysis involving>160,000 mother–offspring pairs from prospective population-based cohort studies suggest that offspring exposed to gestational diabetes were more likely to be overweight or obese during childhood compared with offspring from mothers without gestational diabetes, but this association was fully explained by maternal prepregnancy BMI[35]. A similar finding was reported in a meta-analysis of 20 observational prospective and retrospective studies involving >26,000 children, in which the offspring of mothers with type 1 diabetes had a higher childhood BMI compared with offspring of mothers without diabetes; of note, this relationship remained even after adjusting for maternal prepregnancy BMI[46]. Two meta-analyses of mainly prospective cohort studies showed that the offspring of mothers with type 1 diabetes or gestational diabetes had higher systolic BP levels in childhood compared with the offspring of mothers without prepregnancy or gestational diabetes, which again could be partly explained by prepregnancy maternal BMI[46,47]. Finally, two meta-analyses that assessed 7 prospective and 25 retrospective studies showed that offspring from mothers with type 1 diabetes or gestational diabetes had a higher risk of abnormal glucose tolerance from childhood to early adulthood, but not dyslipidaemia, **c**ompared with offspring from mothers without diabetes[46,47]. A limitation of these studies was that the role of maternal prepregnancy BMI or family-based lifestyle factors were not always accounted for. A large Danish population-based study showed that the offspring of mothers with pregestational or gestational diabetes had a 29% higher rate of early-onset cardiovascular diseases, such as hypertension, with slightly stronger associations for pregestational diabetes[48]. This increased risk was present from childhood into early adulthood, and most prevalent in

the offspring of mothers with diabetic complications or comorbid cardiovascular diseases. Importantly, these observed associations could not be explained by maternal sociodemographic and lifestyle factors, or offspring birth characteristics, but no information on offspring BMI or lifestyle factors was available[48].

The role of hypercholesterolaemia before or during pregnancy on offspring cardiovascular health has not been as well-researched as the aforementioned roles of maternal obesity, hypertensive disorders and glucose intolerance on offspring cardiovascular health. Autopsy studies performed two decades ago showed that maternal hypercholesterolaemia before and during pregnancy was linked to an increase in fetal plasma cholesterol levels during the first half of pregnancy and a greater formation of atherogenic lesions in the fetal aorta[49,50]. These studies suggest that LDL oxidation and formation of fatty streaks already occurs from early fetal life onwards and is influenced by the maternal gestational lipid profile. A study involving 310 mother–offspring pairs using medical records showed that maternal gestational hypercholesterolaemia was associated with BMI, atherosclerotic risk and the severity of acute myocardial infarction of the offspring in adulthood; however, this study did not adjust for confounder variables such as maternal prepregnancy BMI or lifestyle-related factors[51].

[H2] Maternal subclinical cardiovascular risk factors

Obesity, hypertension, diabetes and dyslipidaemia are examples of the clinical manifestations at the extreme end of the maternal cardiovascular risk spectrum. Results from previous studies suggest that the associations are not limited to these clinical disorders, but seem to be present across the full range of maternal cardiovascular risk factors from preconception onwards. For example, findings from the Generation R Study, a prospective cohort study involving ~6000 mother–offspring pairs in the Netherlands from early pregnancy onwards with detailed follow-up data, demonstrated that a higher maternal prepregnancy BMI across the full range, not just overweight or obesity, in women before pregnancy is related to increased birth weight, total body fat, increased organ fat accumulation and an adverse cardiovascular profile (high android fat mass percentage, high blood pressure, low HDL-cholesterol, high triglycerides, high insulin) in the offspring from age 5 to 10 years[52-54]. Furthermore, independent of maternal prepregnancy BMI, a small increase in maternal glucose concentrations in the

first trimester of pregnancy was related to a higher birth weight, increased glucose concentrations and small changes in ventricular cardiac development in the offspring during childhood, but not related to childhood body composition or lipid profile[55-58]. Furthermore, after adjusting for maternal prepregnancy BMI and childhood BMI, higher maternal BP levels in each trimester of pregnancy was related to higher BP levels and arteriolar and microvasculature alterations throughout childhood in the offspring[59,60] In line with these findings, results from the HAPO study[61], a multicentre observational study focused on optimizing diagnostic criteria for gestational diabetes, showed that both maternal BMI and glucose concentration in mid-pregnancy were across the full range independently and additively associated with an increase in childhood body fat and waist circumference in the offspring. Moreover, higher maternal glucose concentrations in mid-pregnancy were also associated with impaired childhood glucose metabolism in the offspring, independent of maternal and childhood BMI and a family history of diabetes[62]. Several population studies in individuals without diabetes have shown that higher maternal glucose concentrations within the normal range in the first half of pregnancy are associated with increased risks of congenital heart defects in the offspring, whereas no link was found between maternal prepregnancy BMI across the full range and risk of congenital heart disease in the offspring[63-66]. Studies focused on the relationship between maternal cardiovascular risk factors across the full range with adult offspring cardiovascular outcomes are scarce, but the available data show that the association between a higher maternal prepregnancy BMI with adverse cardiovascular development in the offspring persists into adulthood[28,30].

Taken together, these findings demonstrate that the spectrum of maternal cardiovascular risk factors, from subclinical to clinical disease, and from preconception onwards, are associated with increased risks of congenital heart defects and suboptimal cardiovascular development in the offspring. A better definition of optimal maternal cardiovascular health from preconception onwards, which considers both pregnancy and offspring outcomes, is needed for the development of prevention strategies.

[H2] Limitations of observational studies

The associations between maternal cardiovascular disorders before and during pregnancy with cardiovascular dysfunction and disease in the offspring are consistent across various higher-risk populations, such as hospital-based populations, populations with low socio-economic status and lower-risk populations, such as population-based samples, with clear dose-response relationships reported by well-designed prospective cohort studies. These findings are supported by animal studies, which provide strong mechanistic evidence that in utero derangements caused by cardiovascular disorders present in the mother before and during pregnancy, such as hyperglycaemia, inflammation and impaired placental vascular function, are involved in regulating offspring cardiovascular risk[13,67,68]. However, given that there is no perfect animal model for human placentation and in utero cardiovascular development, the extrapolation of findings between species is difficult[67,68], and findings from animal models can only be interpreted together with data from studies in human populations.

Importantly, findings from observational studies are limited by selection bias (owing to selective responses and follow-up), misclassification and residual confounding. In particular, the screening, diagnostic and treatment protocols for gestational disorders have changed over time and differ between Western countries. Underascertainment can not only lead to differences in the assessment of the prevalence of gestational disorders between studies, but might also result in a weaker association of these conditions with offspring cardiovascular outcomes. The most pronounced limitation of observational studies is residual confounding. Given that the correlation between cardiovascular disorders in women before and during pregnancy and cardiovascular health in offspring is at least partly explained by family-based genetic, sociodemographic and lifestyle factors, establishing the developmental programming effects in the offspring that are directly caused by maternal cardiovascular disorders is challenging.

Numerous sophisticated study designs have been used to obtain further insight into the role of confounding in these observed associations, including Mendelian randomization, sibling comparisons, maternal and paternal offspring comparisons, and offspring follow-up from RCTs[13]. However, none of these approaches can be considered as the gold standard for mother–offspring studies on causality. Depending on the exposures of interest, not all of these study designs can be conducted, but findings

from these studies need to be interpreted collectively to improve our understanding of the causality of these associations in human populations.

Mendelian randomization studies use genetic variants, which are known to be robustly associated with the exposures of interest and not affected by confounding, as the instrumental variable for a specific maternal cardiovascular exposure, including maternal BMI and BP, glucose and cholesterol levels[69]. The presence of associations of both the exposure themselves and the unconfounded genetic variants related to these exposures with the outcomes of interest provide evidence of a causal relationship[69]. A large meta-analysis using data from 18 birth cohorts showed that genetic variants related to higher maternal BMI and glucose concentrations were linked with higher offspring birth weight, whereas genetic variants related to higher maternal systolic BP were linked with a lower birth weight[70]. However, the associations of these genetic variants with offspring cardiovascular risk factors in later life are unclear and do not consistently demonstrate potential in utero programming effects[71-73]. A challenge for these Mendelian Randomization studies remains the small numbers of participants in the studies focused on long-term offspring cardiovascular health. In addition, for several exposures of interest, the genetic variants that are suitable for instrumental variables analyses in Mendelian Randomization studies have yet to be identified.

Sibling comparison studies attempt to better control for potential confounding factors that are shared within families, but might differ between pregnancies[74]. These studies compare siblings born from different pregnancies, but from the same mother and father. Using this approach, the comparison is focused on differences in pregnancy-related exposures, in the setting of similar family-based genetic and sociodemographic factors. These studies have mainly focused on the effect of maternal weight status during pregnancy on offspring cardiovascular health, and showed that maternal prepregnancy weight loss and lower gestational weight gain are related to lower risks of being overweight and having an adverse cardiovascular profile among siblings[75-79]. A study involving 135 sibling pairs with 40 years of follow-up showed that associations of gestational hypertensive disorders with offspring cardiovascular health were reduced in the sibling analyses compared with the associations seen in observational studies, whereas associations of maternal (pre)gestational diabetes with early-onset offspring cardiovascular diseases remained significant in the sibling analyses[42,48]. The limitations of

these sibling comparison studies include small samples sizes and the fact that other maternal characteristics might also change over time and differ between pregnancies and siblings.

A third approach involves the comparison of the strength of associations of maternal and paternal cardiovascular risk factors with offspring cardiovascular outcomes. Stronger maternal–offspring associations suggest direct in utero programming mechanisms, whereas similar or stronger paternal–offspring associations more strongly suggest a role for shared family-based genetic, sociodemographic and lifestyle-related factors[52]. Most of the studies employing this design have focused on the comparison of associations of maternal and paternal BMI with childhood cardiovascular risk factors and have shown conflicting results[80]. For example, within the Generation R Study, a higher maternal BMI and BP levels are more strongly associated with childhood obesity and adverse cardiovascular profile, respectively, than paternal BMI and BP levels[40,52,59]. However, the associations of maternal BP levels during pregnancy with early signs of atherosclerosis were similar as those for paternal BP levels[40].

RCTs are crucial for the translation of research findings into clinical practice. Given the randomization approach, RCT can also be considered as optimal method to take into account the presence of confounding variables. RCTs are difficult to perform when maternal cardiovascular disorders are the major exposures of interest, but those that are designed to influence determinants of cardiovascular risk and disorders, such as diet, physical activity and medical treatment, provide a model to assess their potential effect on both maternal health during pregnancy and offspring health[81]. Findings from RCTs that have been conducted during pregnancy suggest that such interventions might have small positive effects on maternal lifestyle habits and cardiovascular health, but the potential beneficial effects on offspring cardiovascular health remains unclear[81-83]. For example, an individual-participant-level meta-analysis of seven RCTs involving 2,383 mothers who were overweight or obese and their offspring showed that maternal lifestyle interventions during pregnancy do not reduce the risk of early childhood obesity[83]. Of note, however, the influence of these interventions on offspring outcomes was difficult to establish using this data, owing to major limitations of the trials assessed, such as low compliance to the intervention, short follow-up periods, high attrition rates and study heterogeneity.

Together, results from animal studies and observational studies in human populations suggest that maternal cardiovascular disorders occurring before and during pregnancy are associated with offspring cardiovascular development, function and disease risk, beyond the shared family-based genetic, sociodemographic and lifestyle factors. The underlying causal mechanisms of the observed associations have yet to be established.

[H1] Critical periods for cardiovascular adaptations

The identification of specific critical periods for early-life cardiovascular developmental adaptations is important for understanding both the biological mechanisms involved and the potential for intervention strategies. Rather than a single period that leads to programming of cardiovascular disease in later life, the development of cardiovascular disease seems to be the result of cumulative effects of cardiovascular adaptations occurring across the life course, starting in the earliest phases of life (**Figure 1**). Specific critical periods in early life that are relevant for future cardiovascular disease seem to be the preconception period (3 to 12 months before pregnancy) and early pregnancy in the mother (first three months of pregnancy), and the infancy period (months 0 to 24) in the offspring. These are all time periods characterized by the rapid development of the gametes, embryo and placenta, and by transition into different stages during the life course in the offspring.

Findings from historical famine cohort studies showed that the first trimester is a critical period during which the effects of severe maternal undernutrition can lead to increased risks of hypertension, impaired glucose tolerance and DNA methylation changes in the offspring in adulthood[84,85]. In line with these findings, analyses of repeated weight exposure data before and during each trimester of pregnancy suggest that maternal weight before pregnancy, and to a lesser extent during the first trimester, are associated with adverse body fat outcomes in school-aged children[53,86]. Similarly, early pregnancy was suggested as a critical period that dictated the effects of maternal weight on offspring BMI and BP levels in two population-based prospective cohort studies from the UK and Greece[87,88]. In line with BMI during pregnancy, maternal BP and glucose and lipid concentrations during the first half of pregnancy were associated with offspring cardiovascular outcomes during childhood[55-59,89]. Together with results from the Generation R Study showing that a

higher prepregnancy BMI was associated with greater childhood abdominal, pericardial and liver fat content, and higher BP and insulin levels[52,53], findings from the studies above suggest that cardiovascular health in women, just before or very early in pregnancy, might be most relevant for programming cardiovascular health in the offspring[90,91].

Accumulating evidence shows that apart from the prepregnancy or early pregnancy stage in the mother, the early infancy period is another critical timepoint for the development of cardiovascular diseases in childhood and beyond[92]. **A**nalyses of directly measured growth data showed that both children born small for gestational age but had a large weight gain in infancy and children born large for gestational age and had a large weight gain in infancy have a higher BMI and adverse body fat distribution by school age compared with children with normal fetal and infant growth[93]. These findings are in line with results from the PROGRAMM study[94] showing that rapid weight gain, especially in the first 3 months of life, is associated with risk factors for cardiovascular disease and type 2 diabetes in early adulthood. Furthermore, a study involving >1,200 mothers and children showed that lower-than-average fetal growth (specifically crown-to-rump length) in the first trimester was associated with a higher risk of clustering of cardiovascular risk factors in childhood[95]. Longitudinal growth analyses showed that compared with school-aged children without a clustering of cardiovascular risk factors, those with clustering had smaller fetal growth from first trimester onwards, but a higher childhood weight growth[95]. These findings are supported by another study with a long-term follow-up showing that low birth weight, followed by rapid weight gain after birth and into childhood, is especially associated with cardiovascular disease in adulthood[6]. Taken together, numerous critical timepoints, specifically the preconception period, early pregnancy and early infancy seem to be dictate disease susceptibility, and might interact with events later in life to contribute to the development of cardiovascular diseases.

[H2] Potential underlying mechanisms

As mentioned above, the reported relationship between maternal and offspring cardiovascular risk factors is at least partly explained by shared family-based genetic, sociodemographic and lifestyle factors, which must be taken into account when this relationship is assessed. In addition to these

family-based factors, early-life developmental adaptations might portend additional risk. **Figure 2** shows the potential mechanisms involved in the developmental adaptations and subsequent cardiovascular risk factors and diseases in the offspring as a result of impaired maternal cardiovascular health during the preconception period and pregnancy. In this section, we describe the crucial roles of gamete development in the preconception stage, early placentation and embryonic development, and the mismatch between fetal and childhood growth.

The cardiovascular health of parents might trigger developmental adaptations that affect the offspring from the preconception period, which includes important events such as the completion of the meiotic maturation of oocytes, differentiation of spermatozoa, fertilization, and resumption of mitotic cell cycles in the zygote, marking the transition from the parental to the embryonic genome, and the onset of embryonic development[96,97]. This process takes a few weeks, and is characterized by extensive changes in embryonic morphology, epigenetic reorganization and alterations in metabolism. Animal studies have demonstrated that poor maternal diet, hyperglycaemia and dyslipidaemia around the time of conception can negatively affect embryonic development and increase offspring cardiovascular disease risk across the life course[98-100]. Furthermore, findings from studies in assisted reproductive technology suggest that being overweight and having insulin resistance can modify cytokine, hormone and metabolite concentrations in the ovarian follicular fluid, which can adversely affect oocyte maturation and subsequent embryo quality[101]. When compared to women with a normal weight, women with obesity have smaller oocytes, which produce blastocysts with increased triglyceride and reduced glucose consumption[102]. Therefore, maternal cardiovascular health and nutrition can affect ovary quality and reserve, oocyte quality and blastocyst production. Whether these adverse changes can subsequently affect embryonic and fetal cardiovascular development is not yet known.

The embryonic period, defined as the first 8 weeks of pregnancy, is characterized by rapid cardiac and vascular development, during which two endocardial tubes develop into a complete four-chamber beating heart. Given these rapid changes, the cardiovascular system might be particularly susceptible to developmental adaptations that have long-term consequences for cardiac function and disease in later life. Results from a population-based study showed that age, BP, hematocrit levels,

smoking and the use of folic acid supplements in women during the early stages of pregnancy are all associated with first-trimester fetal growth, measured by crown-to-rump length[103]. Furthermore, animal studies in pigs, sheep, rats and mice have shown that embryonic or fetal blood flow is an important stimuli for cardiovascular development, through its effects on cardiac growth and hypertrophy, smooth cell proliferation and elastogenesis [67,68,104]. In human, changes in placental and fetal blood flow patterns have been shown to influence fetal growth and cardiovascular outcomes in the offspring during childhood[105,106]. Consequently, embryonic development can be modulated by numerous maternal lifestyle and nutrition factors and might be a critical period for cardiovascular development and subsequent cardiovascular health in later life.

The placenta is the active interface between the maternal and fetal environment and the key regulator of fetal nutrition, growth and cardiovascular development from early pregnancy onwards[68]. Placental disturbances might be another key factor by which maternal cardiovascular disorders can lead to cardiovascular developmental adaptations in the offspring[68]. Fetal nutrition and growth are determined by the nutrient transfer capacity of the placenta, which depends on nutrient concentration gradients, the availability of nutrient transporters, and placental blood flow and morphology[68]. The fetoplacental vascular bed is another major direct determinant of fetal cardiac development, vascular development and endothelial function[68]. Fetoplacental vasculogenesis starts 15 days after conception and is followed by angiogenesis, which continues until term, resulting in a well-branched fetoplacental vascular network by the time the baby is born[14]. Placental angiogenesis hormones, including vascular endothelial growth factor, placental growth factor and soluble vascular endothelial growth factor receptor 1 have crucial roles in the regulation of vasculogenesis and angiogenesis[14]. Impaired levels of the angiogenesis growth factors are associated with adverse birth outcomes, an increased risk of major congenital heart defects and small changes in offspring microvasculature and left ventricular cardiac development[107-111]. This association is strongest among children born preterm or small for their gestational age[109,110]. Long-term follow-up data showing the importance of placental function on offspring cardiovascular health are not yet available, but large historical cohort studies have shown that both low and high placental weight, crude estimates of placental function, are linked to cardiovascular disease in adulthood[68].

Both children born large for gestational age and children with low birth weight, followed by rapid weight gain in the infancy period seem to be at risk for an adverse cardiovascular risk profile, with these distinct growth patterns associated with different body fat distributions. Children with a small size at birth, followed by rapid weight gain in infancy were reported to have the highest ratio of android fat to gynoid fat, indicating an adverse body fat distribubtion] and increased visceral and liver fat, whereas those with both high birth weight and high infant growth rate had the highest childhood BMI, fat mass index and abdominal fat content[93,112]. The fetal and childhood growth patterns associated with optimal cardiovascular health still needs to be established.

[H1] Future directions

An overwhelming body of evidence has shown that maternal cardiovascular disorders present before and during pregnancy are associated with early-life developmental adaptations and cardiovascular health in the offspring throughout their life[2,90, 91]. After almost four decades of DOHaD-related research, the focus should be on how to translate findings into the clinic to help define optimal health parameters during the first 1,000 days of development[113] (Box 2).

First, the optimal levels of specific cardiovascular-related exposures that are related to cardiovascular health in the offspring, especially from the preconception period onwards, need to be identified. Such studies should include both women and their partners, given that the role of the father in determining offspring health is often overlooked. Small studies suggest that higher paternal BMI is associated with reduced sperm motility, sperm abnormalities (such as higher levels of reactive oxygen species and alterations in sperm DNA methylation), reduced serum testosterone and increased estradiol concentration [114-116]. Reduced sperm DNA integrity might be associated with suboptimal embryonic development and decreased pregnancy rates[117]. In addition to sperm-related mechanisms that might influence developmental programming in the offspring, seminal plasma composition might also affect embryonic, placental and offspring development[118]. Therefore, future studies should focus on the potential influence of paternal cardiovascular health in the preconception period on sperm and semen quality markers and cardiovascular development and health in offspring, and the underlying developmental programming pathways. The maternal and paternal contributions to offspring

development should be assessed both independently and in combination. Large-scale cohort studies conducted during the preconception or pregnancy period provide an unique opportunity to assess various life course models focused on early life exposures in relation to e outcomes in later life. The wealth of data from high-quality prospective cohort studies facilitates collaboration between cohorts using original data for individual participant data meta-analyses.[119]

Second, non-invasive imaging approaches, including 3D virtual reality tools, could be used to identify novel placental, embryonic and early fetal cardiovascular and metabolic adaptations[120,121] (**Figure 3**). These advanced imaging approaches might provide detailed assessment of cardiovascular development during the first 8 weeks of life[120,121]. Furthermore, the development of the placental vascular bed can be assessed in relation to vascular function in later fetal and postnatal life[122], which could be combined with histological and functional placental characteristics to establish placental nutrient transfer capacity[68].

Third, advances in novel omics approaches in large cohort studies, next to already availabile genome-wide association studies, will enable furtherprogressing DoHAD research[123]. For example, epigenetic modifications might have a role in the link between early-life exposures and health outcomes in later life. Life course studies beginning in early life are useful for studying the role of such modifications[123]. DNA methylation is the most studied epigenetic mechanism in population-based research. Key challenges for genome-wide methylation studies include tissue specificity, cell type adjustment, issues of power and comparability of findings, genetic influences and exploring causality and functional consequences given that the first few weeks of embryonic life are characterized by rapid changes in methylation, such genome-wide methylation studies might assess DNA methylation changes in the fetus in response to maternal and paternal cardiovascular markers and how these changes contribute to cardiovascular development, dysfunction and disease from early life onwards. Rapid advances in the application of cell-free fetal DNA methylation can facilitate this approach[124]. In addition to epigenome studies, hypothesis-free approaches for metabolomics, proteomics and microbiome studies can be used to assess the association between parent–offspring health outcomes from preconception onwards. A collaborative effort to collate and assess findings from different study types is paramount for propelling this field of research forward.

Fourth, in addition to recognizing the underlying mechanisms, risk selection based on genetic predisposition, environmental factors and biological pathways might facilitate the identification of groups at high risk of future disease from early life onwards. Prediction models based on exposures from the preconception period, early pregnancy and infancy that include both maternal and paternal factors in different critical periods might be helpful in identifying groups at risk of an adverse cardiovascular risk profile. Preventative strategies, beyond lowering BMI, should be targeted at high-risk children to optimize cardiovascular health from any early age[125].

Finally, RCTs that include both women and men before and during pregnancy to optimize the cardiovascular health of future generations are needed. To date, results from RCTs do not consistently show a strong benefit of lifestyle interventions targeting BMI during pregnancy on maternal and offspring health outcomes[81]. These intervention studies might have missed the most critical period for implementing these lifestyle changes, as previous observational studies suggest that maternal cardiovascular health before pregnancy is most strongly related to the cardiovascular health of the offspring. Therefore, intervention studies that integrate lifestyle changes, such as improving the diet and reducing stress, should be conducted in both the mother and father from the preconception period onwards. The inclusion of fathers in future intervention studies might be an good approach to improve compliance of both parents to intervention programmes.

[H1] Conclusions

Maternal cardiovascular disorders during the preconception period and pregnancy seem to lead to embryonic and fetal cardiovascular developmental adaptations, which predispose the offspring to an increased risk of cardiovascular dysfunction and disease throughout the life course and leads to an intergenerational vicious cycle of cardiovascular disease. The adverse influence of the maternal in utero environment on offspring health is not limited to maternal clinical cardiovascular disorders, but present across the full range of maternal cardiovascular risk factors, including BMI, glucose levels and lipid profile. **W**ell-designed human studies are urgently needed to identify the extent of causality of these observed associations and the mechanisms underlying the developmental adaptations from embryonic life onwards. Novel prevention strategies focused on improving maternal and paternal

cardiovascular health from preconception onwards might to improve the long-term cardiovascular health of future generations.

REFERENCES

1 Lloyd-Jones, D. M. *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* **121**, 586-613 (2010).

2 Gluckman, P. D., *et al*. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* **359**, 61-73(2008).

3 Lloyd-Jones, D. M. *et al.* Status of Cardiovascular Health in US Adults and Children Using the American Heart Association's New "Life's Essential 8" Metrics: Prevalence Estimates From the National Health and Nutrition Examination Survey (NHANES), 2013 Through 2018. *Circulation* **146**, 822-835 (2022).

4 Curhan, G. C. *et al.* Birth weight and adult hypertension and obesity in women. *Circulation* **94**, 1310-1315 (1996).

5 Curhan, G. C. *et al.* Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* **94**, 3246-3250 (1996).

6 Barker DJ, *et al*. Trajectories of growth among children who have coronary events as adults. *N Engl J Med*. **353**:1802-9 (2005).

7 Robbins, C. L. *et al.* Screening low-income women of reproductive age for cardiovascular disease risk factors. *J Womens Health (Larchmt)* **22**, 314-321(2013).

8 Deputy, N. P., *et al*. Gestational Weight Gain - United States, 2012 and 2013. *MMWR Morb Mortal Wkly Rep* **64**, 1215-1220 (2015).

9 Flegal, K. M., *et al*. Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA* **315**, 2284-2291(2016).

10 Ford, N. D. *et al.* Hypertensive Disorders in Pregnancy and Mortality at Delivery Hospitalization - United States, 2017-2019. *MMWR Morb Mortal Wkly Rep* **71**, 585-591 (2022).

11 Brown, H. L. *et al.* Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists: A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation* **137**, e843-e852 (2018).

12 Ramlakhan, K. P., Johnson, M. R. & Roos-Hesselink, J. W. Pregnancy and cardiovascular disease. *Nat Rev Cardiol* **17**, 718-731(2020).

13 Gaillard, R. Maternal obesity during pregnancy and cardiovascular development and disease in the offspring. *Eur J Epidemiol* **30**, 1141-1152 (2015).

14 Burton, G. J., *et al*. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta* **30**, 473-482 (2009).

15 Juhola, J. *et al.* Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *J Pediatr* **159**, 584-590 (2011).

16 Chen, X. & Wang, Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation* **117**, 3171-3180 (2008).

17 Reilly, J. J. & Kelly, J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes (Lond)* **35**, 891-898 (2011).

18 Franks, P. W. *et al.* Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med* **362**, 485-493 (2010).

19 Stothard, K. J., *et al*. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* **301**, 636-650, (2009).

20 Voerman, E. *et al.* Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. *PLoS Med* **16**, e1002744 (2019).

21 Eitmann, S. *et al.* Maternal overnutrition elevates offspring's blood pressure-A systematic review and meta-analysis. *Paediatr Perinat Epidemiol* **36**, 276-287 (2022).

22 Kankowski, L. *et al.* The Impact of Maternal Obesity on Offspring Cardiovascular Health: A Systematic Literature Review. *Front Endocrinol (Lausanne)* **13**, 868441 (2022).

23 Reynolds, R. M. *et al.* Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* **347**, f4539, (2013).

24 Lahti-Pulkkinen, M. *et al.* Consequences of being overweight or obese during pregnancy on diabetes in the offspring: a record linkage study in Aberdeen, Scotland. *Diabetologia* **62**, 1412-1419 (2019).

25 Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines; Rasmussen KM, Yaktine AL, editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US); 2009.

26 LifeCycle Project-Maternal, O. *et al.* Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. *JAMA* **321**, 1702-1715 (2019).

27 Eitmann, S. *et al.* Maternal overnutrition impairs offspring's insulin sensitivity: A systematic review and meta-analysis. *Matern Child Nutr* **16**, e13031 (2020).

28 Hochner, H. *et al.* Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation* **125**, 1381-1389 (2012).

29 Mamun, A. A. *et al.* Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. *Circulation* **119**, 1720-1727 (2009).

30 Reynolds, R. M., *et al.* Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood. *J Clin Endocrinol Metab* **95**, 5365-5369 (2010).

31 Tequeanes, A. L., *et al*. Maternal anthropometry is associated with the body mass index and waist:height ratio of offspring at 23 years of age. *J Nutr* **139**, 750-754 (2009).

32 Khedagi, A. M. & Bello, N. A. Hypertensive Disorders of Pregnancy. *Cardiol Clin* **39**, 77-90, (2021).

33 Auger, N., Fraser, W. D., Healy-Profitos, J. & Arbour, L. Association Between Preeclampsia and Congenital Heart Defects. *JAMA* **314**, 1588-1598 (2015).

34 Liu, S. *et al.* Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. *Circulation* **128**, 583-589 (2013).

35 Patro Golab, B. *et al.* Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: an individual participant data meta-analysis. *Lancet Child Adolesc Health* **2**, 812-821 (2018).

36 Yu, H. *et al.* Association between hypertensive disorders during pregnancy and elevated blood pressure in offspring: A systematic review and meta-analysis. *J Clin Hypertens (Greenwich)* **24**, 1397-1404 (2022).

37 Rice, M. M. *et al.* Pregnancy-Associated Hypertension and Offspring Cardiometabolic Health. *Obstet Gynecol* **131**, 313-321 (2018).

38 Geelhoed, J. J. *et al.* Preeclampsia and gestational hypertension are associated with childhood blood pressure independently of family adiposity measures: the Avon Longitudinal Study of Parents and Children. *Circulation* **122**, 1192-1199 (2010).

39 Andraweera, P. H. & Lassi, Z. S. Cardiovascular Risk Factors in Offspring of Preeclamptic Pregnancies-Systematic Review and Meta-Analysis. *J Pediatr* **208**, 104-113 e106 (2019).

40 Wiertsema, C. J., *et al*. Childhood Blood Pressure, Carotid Intima Media Thickness, and Distensibility After In Utero Exposure to Gestational Hypertensive Disorders. *J Am Heart Assoc* **11**, e023163 (2022).

41 Kuciene, R. & Dulskiene, V. Associations of maternal gestational hypertension with high blood pressure and overweight/obesity in their adolescent offspring: a retrospective cohort study. *Sci Rep* **12**, 3800 (2022).

42 Huang, C. *et al.* Maternal hypertensive disorder of pregnancy and offspring early-onset cardiovascular disease in childhood, adolescence, and young adulthood: A national population-based cohort study. *PLoS Med* **18**, e1003805 (2021).

43 Kajantie, E., *et al*. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. *Stroke* **40**, 1176-1180 (2009).

44 Zhang, T. N. *et al.* Risks of specific congenital anomalies in offspring of women with diabetes: A systematic review and meta-analysis of population-based studies including over 80 million births. *PLoS Med* **19**, e1003900 (2022).

45 Oyen, N. *et al.* Prepregnancy Diabetes and Offspring Risk of Congenital Heart Disease: A Nationwide Cohort Study. *Circulation* **133**, 2243-2253 (2016).

46 Kawasaki, M. *et al.* Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. *PLoS One* **13**, e0190676 (2018).

47 Pathirana, M. M., *et al*. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero: systematic review and meta-analysis. *J Dev Orig Health Dis* **11**, 599-616 (2020).

48 Yu, Y. *et al.* Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. *BMJ* **367**, l6398 (2019).

49 Napoli, C. *et al.* Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest* **100**, 2680-2690 (1997).

50 Napoli, C. *et al.* Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet* **354**, 1234-1241 (1999).

51 Cacciatore, F. *et al.* Maternal hypercholesterolaemia during pregnancy affects severity of myocardial infarction in young adults. *Eur J Prev Cardiol* **29**, 758-765 (2022).

52 Gaillard, R. *et al.* Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. *Hypertension* **63**, 683-691 (2014).

53 Santos, S. *et al.* Maternal body mass index, gestational weight gain, and childhood abdominal, pericardial, and liver fat assessed by magnetic resonance imaging. *Int J Obes (Lond)* **43**, 581-593 (2019).

54 Ay, L. *et al.* Maternal anthropometrics are associated with fetal size in different periods of pregnancy and at birth. The Generation R Study. *BJOG* **116**, 953-963 (2009).

55 Geurtsen, M. L. *et al.* High maternal early-pregnancy blood glucose levels are associated with altered fetal growth and increased risk of adverse birth outcomes. *Diabetologia* **62**, 1880-1890 (2019).

56 Geurtsen, M. L. *et al* . Maternal Early-Pregnancy Glucose Concentrations and Liver Fat Among School-Age Children. *Hepatology* **74** (2021).

57 Wahab, R. J., *et al*. Associations of Maternal Glycemia in the First Half of Pregnancy With Alterations in Cardiac Structure and Function in Childhood. *Diabetes Care* **43**, 2272-2280 (2020).

58 Wahab, R. J. *et al.* Maternal Glucose Concentrations in Early Pregnancy and Cardiometabolic Risk Factors in Childhood. *Obesity (Silver Spring)* **28**, 985-993(2020).

59 Miliku, K. *et al.* Associations of Maternal and Paternal Blood Pressure Patterns and Hypertensive Disorders during Pregnancy with Childhood Blood Pressure. *J Am Heart Assoc* **5** (2016).

60 Yesil, G. D. *et al.* Influence of Maternal Gestational Hypertensive Disorders on Microvasculature in School-Age Children: The Generation R Study. *Am J Epidemiol* **184**, 605-615 (2016).

61 Josefson, J. L. *et al.* The Joint Associations of Maternal BMI and Glycemia with Childhood Adiposity. *J Clin Endocrinol Metab* **105** (2020).

62 Scholtens, D. M. *et al.* Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism. *Diabetes Care* **42**, 381-392 (2019).

63 Taylor, K. *et al.* Effect of Maternal Prepregnancy/Early-Pregnancy Body Mass Index and Pregnancy Smoking and Alcohol on Congenital Heart Diseases: A Parental Negative Control Study. *J Am Heart Assoc* **10**, e020051 (2021).

64 Rutkowski, R. E., *et al*. Proportion of critical congenital heart defects attributable to unhealthy prepregnancy body mass index among women with live births in Florida, 2005-2016. *Birth Defects Res* **113**, 1285-1298, (2021).

65 Helle, E. I. T. *et al.* First Trimester Plasma Glucose Values in Women without Diabetes are Associated with Risk for Congenital Heart Disease in Offspring. *J Pediatr* **195**, 275-278, (2018).

66 Priest, J. R., *et al*. Maternal Midpregnancy Glucose Levels and Risk of Congenital Heart Disease in Offspring. *JAMA Pediatr* **169**, 1112-1116 (2015).

67 Andraweera, P. H. *et al.* Mechanisms linking exposure to preeclampsia in utero and the risk for cardiovascular disease. *J Dev Orig Health Dis* **11**, 235-242 (2020).

68 Burton, G. J., *et al*. Placental Origins of Chronic Disease. *Physiol Rev* **96**, 1509-1565 (2016).

69 Smith, G. D. & Ebrahim, S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* **33**, 30-42 (2004).

70 Tyrrell, J. *et al.* Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight. *JAMA* **315**, 1129-1140 (2016).

71 Warrington, N. M. *et al.* Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet* **51**, 804-814 (2019).

72 Wang, G. *et al.* Investigating a Potential Causal Relationship Between Maternal Blood Pressure During Pregnancy and Future Offspring Cardiometabolic Health. *Hypertension* **79**, 170-177 (2022).

73 Bond, T. A. *et al.* Exploring the causal effect of maternal pregnancy adiposity on offspring adiposity: Mendelian randomisation using polygenic risk scores. *BMC Med* **20**, 34 (2022).

74 Frisell, T., *et al*. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* **23**, 713-720 (2012).

75 Kral, J. G. *et al.* Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics* **118**, e1644-1649 (2006).

76 Lawlor, D. A., *et al*. Does maternal weight gain in pregnancy have long-term effects on offspring adiposity? A sibling study in a prospective cohort of 146,894 men from 136,050 families. *Am J Clin Nutr* **94**, 142-148 (2011).

77 Ludwig, D. S., *et al*. Pregnancy weight gain and childhood body weight: a within-family comparison. *PLoS Med* **10**, e1001521 (2013).

78 Smith, J. *et al.* Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J Clin Endocrinol Metab* **94**, 4275-4283 (2009).

79 Razaz, N., *et al*. Maternal obesity and risk of cardiovascular diseases in offspring: a population-based cohort and sibling-controlled study. *Lancet Diabetes Endocrinol* **8**, 572-581 (2020).

80 Patro, B. *et al.* Maternal and paternal body mass index and offspring obesity: a systematic review. *Ann Nutr Metab* **63**, 32-41 (2013).

81 Gaillard, R., *et al*. Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review. *J Dev Orig Health Dis* **10**, 314-321 (2019).

82 Landon, M. B. *et al.* Mild gestational diabetes mellitus and long-term child health. *Diabetes Care* **38**, 445-452 (2015).

83 Louise, J. *et al.* The effects of dietary and lifestyle interventions among pregnant women with overweight or obesity on early childhood outcomes: an individual participant data meta-analysis from randomised trials. *BMC Med* **19**, 128 (2021).

84 Heijmans, B. T. *et al.* Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* **105**, 17046-17049 (2008).

85 Roseboom, T. J., *et al*. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. *Maturitas* **70**, 141-145 (2011).

86 Gaillard, R., *et al*. Maternal weight gain in different periods of pregnancy and childhood cardio-metabolic outcomes. The Generation R Study. *Int J Obes (Lond)* **39**, 677-685 (2015).

87 Fraser, A. *et al.* Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation* **121**, 2557-2564 (2010).

88 Karachaliou, M. *et al.* Association of trimester-specific gestational weight gain with fetal growth, offspring obesity, and cardiometabolic traits in early childhood. *Am J Obstet Gynecol* **212**, 502 e501-514 (2015).

89 Vidakovic, A. J. *et al.* Maternal plasma PUFA concentrations during pregnancy and childhood adiposity: the Generation R Study. *Am J Clin Nutr* **103**, 1017-1025 (2016).

90 Stephenson, J. *et al.* Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet* **391**, 1830-1841 (2018).

91 Fleming, T. P. *et al.* Origins of lifetime health around the time of conception: causes and consequences. *Lancet* **391**, 1842-1852 (2018).

92 Black, R. E. *et al.* Health and development from preconception to 20 years of age and human capital. *Lancet* **399**, 1730-1740 (2022).

93 Vogelezang, S. *et al.* Associations of Fetal and Infant Weight Change With General, Visceral, and Organ Adiposity at School Age. *JAMA Netw Open* **2**, e192843 (2019).

94 Leunissen, R. W., *et al*. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA* **301**, 2234-2242 (2009).

95 Jaddoe, V. W. *et al.* First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. *BMJ* **348**, g14 (2014).

96 Bedzhov, I., *et al*. Developmental plasticity, cell fate specification and morphogenesis in the early mouse embryo. *Philos Trans R Soc Lond B Biol Sci* **369** (2014).

97 Li, L., Lu, X. & Dean, J. The maternal to zygotic transition in mammals. *Mol Aspects Med* **34**, 919-938 (2013).

98 Nicholas, L. M. *et al.* The early origins of obesity and insulin resistance: timing, programming and mechanisms. *Int J Obes (Lond)* **40**, 229-238 (2016).

99 Fleming, T. P. *et al.* Do little embryos make big decisions? How maternal dietary protein restriction can permanently change an embryo's potential, affecting adult health. *Reprod Fertil Dev* **27**, 684-692 (2015).

100 Wyman, A., *et al*. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring. *Endocrinology* **149**, 466-469 (2008).

101 Ruebel, M. L. *et al.* Obesity Modulates Inflammation and Lipid Metabolism Oocyte Gene Expression: A Single-Cell Transcriptome Perspective. *J Clin Endocrinol Metab* **102**, 2029-2038 (2017).

102 Leary, C., *et al*. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. *Hum Reprod* **30**, 122-132 (2015).

103 Mook-Kanamori, D. O. *et al.* Risk factors and outcomes associated with first-trimester fetal growth restriction. *JAMA* **303**, 527-534 (2010).

104 Martyn C.N, *et al*. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet* **350**(9082):953-5 (1997)

105 Gaillard, R., *et al*. Placental vascular dysfunction, fetal and childhood growth, and cardiovascular development: the generation R study. *Circulation* **128**, 2202-2210 (2013).

106 Verburg, B. O. *et al.* Fetal hemodynamic adaptive changes related to intrauterine growth: the Generation R Study. *Circulation* **117**, 649-659 (2008).

107 Llurba, E. *et al.* Maternal and foetal angiogenic imbalance in congenital heart defects. *Eur Heart J* **35**, 701-707 (2014).

108 Llurba, E. *et al.* Maternal serum placental growth factor at 11-13 weeks' gestation and fetal cardiac defects. *Ultrasound Obstet Gynecol* **42**, 169-174 (2013).

109 Bongers-Karmaoui, M. N., *et al*. Associations of maternal angiogenic factors during pregnancy with childhood carotid intima-media thickness and blood pressure. *Atherosclerosis* **338**, 46-54 (2021).

110 Bongers-Karmaoui, M. N. *et al.* Associations of maternal angiogenic factors during pregnancy with alterations in cardiac development in childhood at 10 years of age. *Am Heart J* **247**, 100-111 (2022).

111 Gishti, O. *et al.* Influence of maternal angiogenic factors during pregnancy on microvascular structure in school-age children. *Hypertension* **65**, 722-728 (2015).

112 Gishti O, *et al.* Fetal and infant growth patterns associated with total and abdominal fat distribution in school-age children. *J Clin Endocrinol Metab* **99**, 2557-66 (2014).

113 Hanson, M. A., *et al*. DOHaD - the challenge of translating the science to policy. *J Dev Orig Health Dis* **10**, 263-267 (2019).

114 Sermondade N, *et al*. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update* **19**:221-31. (2013)

115 Guo D, *et al*. The impact of BMI on sperm parameters and the metabolite changes of seminal plasma concomitantly. *Oncotarget* **8**:48619-48634. (2017)

116 Raad G, *et al.* Paternal obesity: how bad is it for sperm quality and progeny health? *Basic Clin Androl* **27**:20 (2017)

117 Bakos HW, *et al*. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. *Fertil Steril* **95,** 1700-4 (2017)

118 Bromfield JJ, *et al.* Maternal tract factors contribute to paternal seminal fluid impact on metabolic phenotype in offspring. *Proc Natl Acad Sci USA* **111**, 2200-5 (2021)

119 Jaddoe, V. W. V. *et al.* The LifeCycle Project-EU Child Cohort Network: a federated analysis infrastructure and harmonized data of more than 250,000 children and parents. *Eur J Epidemiol* **35**, 709-724 (2020).

120 Wiertsema CJ, *et al.* First trimester fetal proportion volumetric measurements using a Virtual Reality approach. *Prenat Diagn* **41**, 868-876 (2021)

121 Wiertsema CJ, *et al.* Innovative approach for first-trimester fetal organ volume measurements using a Virtual Reality system: The Generation R Next Study. *J Obstet Gynaecol Res* **48**, 599-609 (2022)

122 Reus AD, *et al*. Early pregnancy placental bed and fetal vascular volume measurements using 3-D virtual reality. *Ultrasound Med Biol* **40**, 1796-803 (2014)

123 Felix, J. F. *et al.* Cohort Profile: Pregnancy And Childhood Epigenetics (PACE) Consortium. *Int J Epidemiol* **47**, 22-23u (2018).

124 Drury S, *et al*. Cell-Free Fetal DNA Testing for Prenatal Diagnosis. *Adv Clin Chem* **76**, 1-35. (2016)

125 Steinberger, *et al*. Cardiovascular Health Promotion in Children: Challenges and Opportunities for 2020 and Beyond: A Scientific Statement From the American Heart Association. *Circulation* **134,** e236-55 (2016)

126 https://www.who.int/health-topics/obesity/

127 Tranquilli, A. L. *et al.* The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens* **4**, 97-104 (2014).

128 https://srhr.org/rhl/article/who-recommendation-on-the-diagnosis-of-gestational-diabetes-in-pregnancy

129 Zhou, T. *et al.* Prevalence and Trends in Gestational Diabetes Mellitus Among Women in the United States, 2006-2017: A Population-Based Study. *Front Endocrinol (Lausanne)* **13**, 868094 (2022).

130 https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3236

Acknowledgments

R.G. received funding from the Dutch Diabetes Foundation (grant number 2017.81.002), the Netherlands Organization for Health Research and Development (NWO, ZonMW 543003109, NWO, ZonMw 09150172110034, EU Horizon 2020 research and innovation programme under the ERA-NET Cofund action (no 727565), EndObesity, ZonMW no. 529051026) V.J. received a grant from the Netherlands Organization for Health Research and Development (NWO, ZonMw 05430052110007) and a European Research Council Consolidator Grant (ERC-2014-CoG-648916).

Competing interests

No competing interests.

Key points

- Obesity, hypertension, type 2 diabetes and dyslipidaemia are highly prevalent among women of reproductive age and complicate over 30% of pregnancies in Western countries.
- Maternal cardiovascular disorders before and during pregnancy, seem to lead to embryonic and fetal cardiovascular developmental adaptations, which predispose to an increased risk of cardiovascular dysfunction and disease in the offspring throughout the life course. Especially, the preconception period, early pregnancy and infancy seem to specific critical periods in early life related to future cardiovascular disease risk. Future research urgently needs to focus on identifying optimal levels of cardiovascular-related exposures in both women and men from preconception onwards that are associated with cardiovascular health and disease in offspring, and the mechanisms underlying these associations. Use of innovative imaging techniques to study cardiovascular development from embryonic life onwards, novel "omics" approaches to identify functional adaptations and strong collaborations between cohorts studies worldwide offer opportunities to address these research issues.
- Novel prevention strategies focused on improving cardiovascular health in men and women from preconception onwards may offer great opportunities for better cardiovascular health in future

903 generations and stop the intergenerational cycle of cardiovascular diseases transmission.

904

905

906

Figure 1. Major cardiovascular adaptations to pregnancy

Box 1. Major cardiovascular adaptations to pregnancy

[bH1] Gestational weight gain

[bH2] Early pregnancy

- Maternal fat accumulation
- Increase in breast tissue
- Growth of uterus
- Expansion of blood volume

[bH2] Late pregnancy

- Growth of fetus, placenta and uterus
- Expansion of amniotic fluid
- Increase in blood volume and extracellular fluid

[bH1] Haemodynamic adaptations

- Increase in heart rate, stroke volume and cardiac output
- Cardiac hypertrophy
- Increase in plasma volume
- Decrease in arterial and peripheral vascular resistance
- Decrease in blood pressure levels

[bH1] Metabolic adaptations

[bH2] Early pregnancy

- Increase in insulin sensitivity
- Increase in glycogen content and lipid deposition

[bH2] Late pregnancy

- Increased insulin resistance
- Increased gluconeogenesis
- Increase in circulating levels of glucose, free fatty acids and amino acids

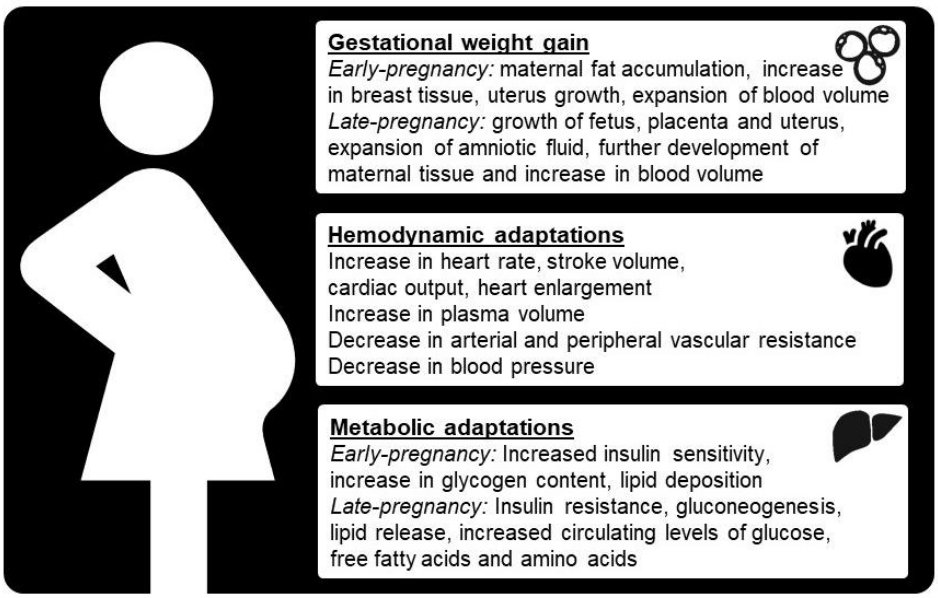


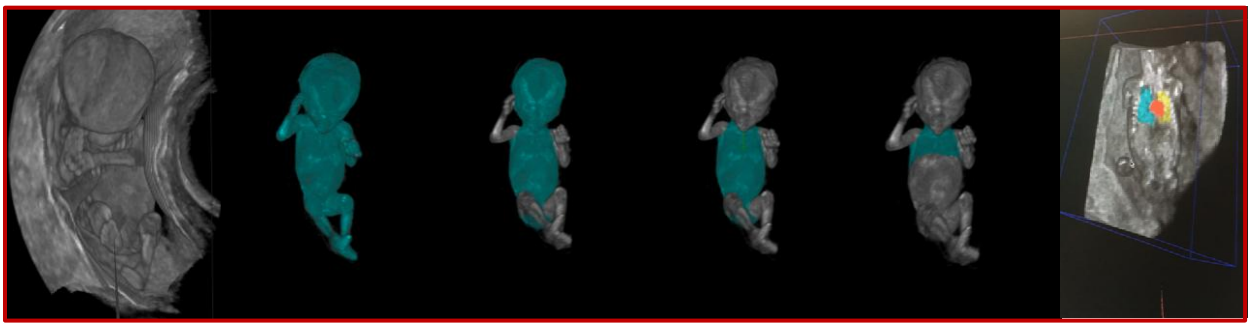
Fig. 1 | Cardiovascular development and disease from the preconception period onwards. Cardiovascular health in women and men before conceiving a child can affect the quality of their oocytes and sperm cells, thus affecting embryonic development. The first 8 weeks of life (the embryonic stage) is characterized by rapid development of the cardiovascular system. Additional structural cardiac and vascular remodelling occurs in the fetus during the second and third trimesters of pregnancy. In the developing embryo and fetus, developmental adaptations that occur in response to maternal cardiovascular disorders can lead to programming of cardiovascular organs, which might have consequences for cardiovascular health in later life. These adaptations can influence growth and development from infancy into adulthood, and predispose individuals to cardiovascular diseases and premature death in later life. Cohort studies most commonly use questionnaires, medical records and repeated research centre visits to collect clinical, imaging and laboratory data, which are used to assess the cardiovascular risk profile of the offspring.

Fig. 2 | Potential mechanisms involved in how impaired maternal cardiovascular health before and during pregnancy can result in cardiovascular dysfunction and disease in the offspring.

Conceptual model for potential underlying mechanisms leading from impaired cardiovascular health in women before and during pregnancy to cardiovascular dysfunction and diseases in the offspring.

Impaired maternal cardiovascular health is a complex trait, which reflects multiple components including fat accumulation, higher blood pressure, insulin resistance and dyslipidemia, which leads to a pro-inflammatory environment and higher circulating levels of glucose, free fatty acids and amino acids. This adverse maternal environment from preconception onwards may negatively affect gametogenesis and endometrial quality and lead to placental, embryonic and fetal structural and functional developmental adaptations. These developmental adaptations predispose to increased risks of adverse birth outcomes, cardiovascular dysfunction in childhood and cardiovascular diseases and premature mortality in adulthood. This leads to the intergenerational continuation of the cardiovascular disease epidemic.

Fig. 3 | 3D ultrasonography and virtual reality approaches to assess embryonic development



Combining 3D ultrasonography traces with virtual reality technology can facilitate the assessment of embryonic development, as show in this image of an embryo aged 9 weeks[120,121] Virtual reality technology allows in-depth perception and interaction with the projected images, enabling the stepwise assessment of growth and development of different embryonic body proportions, such as the thorax in this image, and organ structures[120,121]. The image on the right depicts the cardiac and lung areas.

Table 1. Prevalence of cardiovascular disorders before pregnancy in women

Risk factor	Ideal range[a]	Condition or disease	Prevalence (%)	Refs
Cardiovascular-related disorders diagnosed before pregnancy				
BMI	<25.0 kg/m^2	Underweight (BMI<18.5 kg/m^2)	2	9, 126
		Overweight (BMI ≥25.0–29.9 kg/m^2)	28	9, 126
		Obesity (BMI ≥30.0 kg/m^2)	40	9, 126
BP levels	≤120/80 mmHg	Chronic hypertension before pregnancy or before20 weeks gestation: SBP ≥140 mmHg and/or DBP ≥90 mmHg	5	10, 127
Glucose levels	Fasting blood glucose levels <5.5 mmol/l	Type 1 or 2 diabetes diagnosed before pregnancy: fasting plasma glucose ≥7.0 mmol/l; 2 h post-load venous plasma glucose ≥11.1 mmol/l; 2 h post-load capillary plasma glucose ≥12.2 mmol/l ; random plasma glucose ≥11.1 mmol/; and HbA1c ≥ 6.5% or 48 mmol/mol	2	128, 129
Cholesterol levels	Total cholesterol <5.1 mmol/l	Hypercholesterolaemia: total cholesterol ≥ 5.0 mmol/l	8	,130
Cardiovascular-related disorders diagnosed during pregnancy				
BMI	<25.0 kg/m^2	Inadequate gestational weight gain: <12.5 kg for BMI <18.5 kg/m^2; <11.5 kg for BMI ≥18.5–24.9 kg/m^2; <7 kg for BMI ≥25.0–29.9 kg/m^2 and <5 kg for BMI ≥30.0 kg/m^2	20	8, 25
		Excessive gestational weight gain: >18 kg for BMI <18.5 kg/m^2; >16 kg for BMI ≥18.5–24.9 kg/m^2; >11.5 kg for BMI ≥25.0–29.9 kg/m^2 and > 9 kg for BMI ≥30.0 kg/m^2	50	8, 25
BP levels	≤120/80 mmHg	Gestational hypertension: de novo SBP ≥140 mmHg and/or DBP ≥90 mmHg at or after 20 weeks gestation in the absence of features of pre-eclampsia	10	10, 127
		Pre-eclampsia, defined as gestational hypertension accompanied by more than one of the following new-onset conditions at or after 20 weeks gestation: proteinuria and other maternal organ dysfunction including AKI, liver involvement, neurological complications, haematological complications and uteroplacental dysfunction	3	10, 127
		Pre-eclampsia superimposed on chronic hypertension: chronic essential hypertension and development of maternal organ dysfunction consistent with pre-eclampsia	25 of women with chronic hypertension	10, 127
Glucose levels	Fasting blood glucose levels <5.5 mmol/l	Diabetes during pregnancy, diagnosed at any time in pregnancy if one or more of the following criteria are met in women who have not been previously diagnosed with diabetes: fasting plasma glucose ≥7.0 mmol/l ; 2 h plasma glucose ≥11.1 mmol/l after a 75g oral glucose load; random plasma glucose ≥11.1 mmol/l together with symptoms	Not reported	NA

		Gestational diabetes, diagnosed at any time in pregnancy if one or more of the following criteria are met in women who were not previously diagnosed with diabetes: fasting plasma glucose 5.1–6.9 mmol/l; 1 h plasma glucose ≥10.0 mmol/l after a 75g oral glucose load; 2 h plasma glucose 8.5–11.0 mmol/l after a 75g oral glucose load	8	128, 129
Cholesterol levels	Total cholesterol <5.1 mmol/l	No official pregnancy recommendations	NA	NA

[a]Ideal range for optimal cardiovascular health in women of reproductive age as defined by the AHA. The disease definitions described are derived from leading worldwide health-care institutions and societies, which are commonly used in contemporary population-based cohort studies, but specific cut-off values and definitions may vary across Western countries. Prevalences based on estimates from large Western population studies, but may vary across Western countries, partly due to countryspecific cut-off values and definitions.

Table 2. Overview of the associations between maternal and offspring cardiovascular health

Maternal risk factor	Cardiovascular disorder	Cardiovascular risk profile in offspring[a]	
		Childhood (birth to 18 years)	Adulthood
BMI	Maternal prepregnancy obesity	Increased risk of macrosomia, cardiac congenital anomalies obesity and high blood pressure. Increased risk of suboptimal lipid profile, impaired glucose metabolism and cardiac and vascular changes are related to high concurrent childhood BMI	Increased risk of obesity, type 2 diabetes and cardiovascular and cerebrovascular disease; increased risk of hospital admission for cardiovascular disease; increase risk of premature all-cause death
	Excessive gestational weight gain	Increased risk of macrosomia and obesity. Increased risk of high blood pressure and impaired glucose metabolism are related to concurrent childhood BMI	Increased risk of obesity
Blood pressure	Chronic prepregnancy hypertension	Increased risk of cardiac congenital anomalies and high blood pressure	Increased risk of cardiovascular disease
	Gestational hypertension	Increased risk of low birth weight and high blood pressure	Increased risk of cardiovascular disease
	Pre-eclampsia	Increased risk of low birth weight, cardiac congenital anomalies and high blood pressure	Increased risk of cardiovascular and cerebrovascular disease
Glucose	Pregestational diabetes	Increased risk of low birth weight, macrosomia, cardiac congenital anomalies, high BMI, high blood pressure and impaired glucose tolerance	Increased risk of cardiovascular and cerebrovascular disease
	Gestational diabetes	Increased risk of macrosomia, cardiac congenital anomalies, high blood pressure and impaired glucose tolerance	Increased risk of cardiovascular and cerebrovascular disease
Cholesterol	Hypercholesterolaemia	No large-scale studies available	No large-scale studies available

[a]The childhood outcomes described in the Table have been derived from contemporary observational studies summarized in meta-analyses and systematic reviews for childhood outcomes, whereas the adulthood outcomes were based on findings from large-scale population studies with follow-up until adulthood.

1