

In utero adverse exposures and cardiovascular health in the offspring

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Cardiovascular health can be shaped before birth.
- Maternal conditions, pollutants and unhealthy lifestyle may raise children's future cardiovascular risk.
- Early detection and prevention of adverse exposures is essential to children's cardiovascular health.

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Cardiovascular disease (CVD) remains the leading cause of global mortality, with a concerning trend toward younger onset. This shift highlights the urgent need to advance the window of attention and intervention for cardiovascular health (CVH). The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that adverse intrauterine exposures can program long-term alterations in offspring CVH, underscoring the significance of early-life origins. Maternal health conditions during pregnancy, environmental exposures, and lifestyle factors are consistently associated with adverse cardiovascular outcomes in children, including elevated blood pressure, structural and functional abnormalities, and impaired cardiometabolic profiles. These associations are mediated through pathways involving placental dysfunction, inflammation, oxidative stress, and hormonal imbalance, which collectively reshape fetal cardiovascular development and increase susceptibility to CVD later in life. From a management perspective, adverse intrauterine exposures should be integrated into pediatric CVH risk assessment, and preventive strategies should be shifted to the preconception and prenatal periods. This review highlights intrauterine environment as a critical determinant of intergenerational cardiovascular risk and emphasizes the necessity of implementing precision prevention strategies beginning from the earliest stages of life.

INTRODUCTION

Cardiovascular disease (CVD) remains a major global cause of mortality and disease burden, with its incidence nearly doubling since the late twentieth century, as reported by the Global Burden of Disease (GBD) 2021 study.¹ Although CVDs predominantly manifest in middle and older adulthood,² increasing epidemiological evidence has indicated a worrisome rise in subclinical and clinical cardiovascular abnormalities among younger populations, including adolescents and young adults.³ This shift suggests that strategies aimed solely at delaying CVD until mid- or late adulthood may no longer meet the urgent demands of public health, and that we must move the window for cardiovascular health interventions to much earlier stages of the life course.

However, many CVDs in children and adolescents are often asymptomatic during early stages, presenting primarily in a subclinical state. Consequently, greater emphasis should be placed on pediatric cardiovascular health (CVH), a broader concept encompassing overall cardiovascular well-being. In defining CVH, the American Heart Association (AHA) 2010 writing group recognized health as a much broader, positive state extending beyond the mere absence of disease.⁴ This framework has been updated to "Life's Essential 8", which includes ideal body weight, a balanced diet, regular physical activity, non-smoking status, sleep health, and optimal levels of blood pressure (BP), blood glucose, blood lipids.⁵ Yet, the prevalence of ideal CVH among adolescents remains far from optimal—evidence suggests that early identification and optimization of these metrics are crucial for interrupting pathological progression and for delaying or even preventing adult CVD.⁶ Studies in chil-

dren and adolescents found that only 2 percent of youth met all eight ideal CVH criteria and about 20 percent had high CVH score.^{6,7} Longitudinal study found that childhood CVH status has a long-lasting effect on cardiac structure and function even in early adulthood.⁸ And the International Childhood Cardiovascular Cohort (i3C) Consortium has shown that youth metabolic risk factors—including elevated body mass index, high cholesterol, and hypertension—predict midlife CVD incidence.⁹ Together, these findings underscore the importance of focusing on CVH from the earliest stages of life.

The Developmental Origins of Health and Disease (DOHaD) hypothesis, first proposed by Barker and colleagues in the late twentieth century, emphasizes the long-term programming effects of the in utero and early postnatal environment on adult disease risk in later stages of life.¹⁰ CVD is one of the most critical endpoints studied within the DOHaD framework. A wealth of studies has demonstrated that in utero adverse exposures will reshape embryonic and fetal cardiovascular structure and function via multiple pathways, leading to asymptomatic cardiovascular alterations in offspring during early adulthood and even childhood.¹¹ The intrauterine environment plays an important role on organogenesis and functional maturation, serving as a modifiable determinant of offspring health. Against this backdrop, the concept of *In utero Pediatrics* has emerged,¹² advocating early screening and prevention of developmental origins of diseases during the preconception and prenatal periods, thereby shifting the intervention window forward.

Accordingly, this review summarizes current evidence on how maternal health conditions, environmental exposures, and lifestyle factors during pregnancy shape cardiovascular development and health in offspring, with a focus on underlying mechanisms and early, modifiable windows for prevention. Building on emerging consensus, we seek to identify early determinants of pediatric CVH and propose potential avenues for precision prevention beginning from fetal life.

MATERIALS AND METHODS

Sources and search strategy

We systematically searched PubMed, Web of Science Core Collection, Scopus and Embase using predefined terms capturing (i) prenatal or intrauterine exposures and (ii) offspring cardiovascular outcomes. Search strings combined controlled vocabulary (MeSH/Emtree) and free-text keywords encompassing exposure windows (preconception, early/mid/late gestation), in utero exposures and clinically relevant cardiovascular outcomes.

Reference lists of eligible articles and key narrative reviews were manually scanned for additional records. All retrieved citations were exported to EndNote and deduplicated across sources. Full search key words are provided in the supplement (Table S1).

Eligibility criteria

We included human studies only (prospective birth cohorts, case-control analyses nested within cohorts, cross-sectional follow-ups and randomized

clinical trials) that explicitly evaluated prenatal exposures and offspring cardiovascular outcomes from birth through childhood or adolescence. Eligible outcomes included echocardiographic or cardiac magnetic resonance measures, vascular indices, blood pressure and cardiometabolic biomarkers.

We excluded animal studies, environmental monitoring without health endpoints, genetics-only analyses, commentaries, conference abstracts lacking primary data, and studies that focused on congenital heart defects (CHD).

Study selection and screening

Two reviewers independently screened titles/abstracts and full texts using the predefined criteria. Discrepancies were resolved by consensus or consultation with a third reviewer.

Data extraction

From each eligible study, we extracted: cohort design and setting; sample size; time of recruitment and age at follow-up; exposure type and measurement method; effect estimates (β coefficients, ORs, RRs, or standardized mean differences) with 95% CIs; and study limitations (Table S2). When available, we also recorded sex-stratified or trimester-specific estimates, mediation analyses, and sensitivity analyses addressing residual confounding or selection bias.

Synthesis strategy, effect-size reporting, and clinical interpretation

Given substantial heterogeneity across cohorts in exposure definitions, measurement timing, cardiovascular endpoints, and analytical adjustments, we conducted a narrative synthesis without pooling estimates or ranking exposures by magnitude. Within individual studies, we report effect sizes as provided by the authors. Because no validated cardiovascular biomarker or universal developmental cardiac risk threshold exists for children, interpretation is anchored to study-specific context.

MATERNAL HEALTH CONDITIONS

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy, defined as "any degree of glucose intolerance with onset or first recognition during pregnancy".¹³ A substantial body of evidence indicates that intrauterine hyperglycemia exposure is associated with multiple cardiovascular alterations in offspring during childhood and pre-adolescence, including elevated BP,^{14,15} vascular dysfunction,¹⁶ subclinical cardiac structural remodeling¹⁷ and metabolic impairment.^{18–20}

Abnormal BP has been identified as an early and clearly consequence of GDM on offspring in large population-based cohorts. A large multicenter cohort study in the United States (ECHO cohort, N=12,480) reported that GDM significantly increased the risk of hypertension in offspring aged 2–18 years, even after controlling for maternal BMI and socioeconomic factors.²¹ Similar observations were made in a multinational cohort (N=3,317), where maternal GDM were associated with poorer cardiovascular health scores at age 10–14 years, particularly through elevated BP.¹⁴ Beyond resting BP, GDM has also been shown to affect physiological response to stress. A cohort study conducted in India (N=213) found that adolescents exposed to GDM exhibited significantly higher systolic blood pressure (SBP) and heart rate responses in the face of stress stimuli, suggesting early abnormalities in autonomic regulation and possible predisposition to later cardiovascular disease.²²

Vascular structural alterations and dysfunction in GDM-exposed offspring have also been documented.^{16,23} A prospective cohort study from Singapore (GUSTO cohort, N=479) found that higher maternal fasting glucose levels during pregnancy, even below the threshold for GDM diagnosis, were significantly associated with increased carotid intima-media thickness (cIMT) and accelerated pulse wave velocity (PWV) in offspring at age 6, suggesting the risk of reduced arterial compliance and early vascular aging.¹⁶

Parallel alterations in cardiac morphology have been reported from the Netherlands Generation R cohort (N=1,959), where higher maternal blood glucose levels in early pregnancy correlated with increased left ventricular mass and decreased diastolic function in offspring at the age of 10, suggesting that it may be a long-term basis for the risk of heart failure.¹⁷

In terms of metabolism, the effect of GDM on the homeostasis of glucose

and lipid metabolism in the offspring has been confirmed by multiple long-term follow-up studies. Follow-up analyses from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort consistently demonstrate adverse metabolic profiles in offspring exposed to GDM. In the Hong Kong cohort (N=970), such exposure was associated with higher BMI, greater insulin resistance (HOMA-IR), and unfavorable lipid profiles in the prepubertal period, together with an elevated risk of obesity, hypertension, and abnormal glucose tolerance.²⁰ Broadly, additional and larger HAPO follow-up (N=4,160) further showed that intrauterine hyperglycemia is independently linked to impaired glucose metabolism and reduced insulin sensitivity during later childhood and early adolescence.²⁴ What's more, a prospective study conducted by Shanghai Birth Cohort (N=1,016), found that even in mothers who did not undergo the GDM, higher maternal glucose concentration were associated with higher BP and lower left ventricular ejection fraction (LVEF) in offspring aged 4 years.²⁵

Notably, the harm of GDM is likely to extend to the clinical endpoint of cardiovascular disease. A population-based cohort study in Denmark (Danish National Birth Cohort, N=over 54,000) with 40 years of follow-up found that maternal diabetes during pregnancy significantly increased the risk of ischemic heart disease and stroke in offspring during young and middle adulthood.²³

Overall, evidence relating GDM to offspring cardiovascular phenotypes is highly consistent across diverse cohorts and age stages. Although variations in diagnostic criteria, exposure definitions, and analytical adjustments exist, the convergence of findings still supports intrauterine hyperglycemia as an important risk factor for offspring cardiovascular health.

Gestational hypertension

Gestational hypertension (GH) is a common complication during pregnancy. Its association with cardiovascular health outcomes in offspring—particularly BP regulation, cardiac structure, and glucolipid metabolism—has been widely investigated.

Multiple large-scale cohorts consistently report increased offspring BP following GH exposure. Early evidence from a Swedish investigation published in 1994 (N=53), showed higher systolic BP at age 12.5 among GH-exposed children compared to those born after normotensive pregnancies. Subsequent large-scale cohorts consistently report similar findings.²⁶ A study conducted in British (N=6,619) reported that children born to mothers with GH exhibited a persistent persistently elevated SBP from childhood, with the elevation sustained at least through adolescence.²⁷ Similarly, the Odense Child Cohort study in Denmark (N=2,434) found that offspring BP trajectories from 4 months to 5 years were significantly associated with maternal BP during pregnancy, with notable sex-based differences.²⁸ Collectively, these findings suggest that maternal GH may influence the in utero programming of BP regulation.

Maternal GH has also been linked to adverse alterations in cardiac structure in offspring. A prospective cohort study conducted in Rotterdam (N=2,502) demonstrated that elevated maternal diastolic blood pressure (DBP) was associated with reduced left and right ventricular end-diastolic volumes (LVEDV and RVEDV) and decreased right ventricular ejection fraction (RVEF) in 10-year-old offspring. Notably, the strength of this association between mother-child pairs exceeded that of the father-child pairs, underscoring the intrauterine environment's significant role.²⁹ Another large study conducted in a British cohort (N=1,592) confirmed these structural alterations, finding decreased LVEDV and increased relative wall thickness (RWT) in 17.7-year-old offspring exposed to maternal pre-eclampsia.³⁰

By contrast, the impact of GH on offspring metabolic health, particularly insulin sensitivity and glucose and lipid metabolism, remains inconclusive. Some studies report elevated fasting glucose and insulin levels in children exposed to GH in utero. For instance, a Swedish cohort study (N=52) found higher fasting glucose (5.2 vs. 4.9 mmol/L) and insulin resistance indices (1.5 vs. 1.0) in GH-exposed children compared to controls.³¹ In line with these findings, a Danish national cohort (N=2,448,753) revealed a significantly increased risk of type 2 diabetes and gestational diabetes in GH offspring (HR = 1.57 and 1.37, respectively).³² However, contradictory evidence exists. The Finnish NFBC 1986 cohort study (N=5,573) found elevated total cholesterol but no significant differences in glucose or insulin levels at age 16.³³ A

prospective observational follow-up study (N=979) found no significant changes in glycemic or lipid parameters in GH offsprings aged 5–10 years.³⁴ These inconsistencies may be due to variations in study design, sample size, follow-up duration, or environmental and lifestyle factors.

Taken together, the association between GH and BP regulation and structural cardiac adaptations in offspring is consistently demonstrated across prospective cohorts. By contrast, findings regarding metabolic alterations are more heterogeneous and less well-defined. Future research should devote greater attention to metabolic pathways, long-term metabolic trajectories, and potential modifiers of these outcomes in offspring exposed to GH.

Gestational obesity

Gestational obesity is generally defined as a body mass index (BMI) exceeding 30 kg/m² during pregnancy. A growing body of research has demonstrated that gestational obesity exerts adverse effects on the cardiovascular health of offspring, including higher BP, cardiac structure and function, metabolic abnormalities, and increased long-term cardiovascular disease risk.

Regarding offspring BP, a prospective cohort study conducted in China (N=1,452) found that each 1 kg/m² increase in maternal BMI in early pregnancy was associated with a +0.24% increase in SBP at age 4 to 7 years old.³⁵ Another study in Amsterdam (N=3,074) showed that per unit increment of prenatal BMI was associated with a +0.14 mmHg increase in SBP and +0.11 mmHg in DBP at age 5 to 6 years old.³⁶

As for cardiovascular structure and function, a meta-analysis involving 13 studies confirmed that offspring of obese women exhibited ventricular septal thickening and left ventricular diastolic dysfunction in infancy, while no significant changes were observed in left ventricular mass or end-diastolic volume.³⁷ The RADIEL six-year follow-up study (N=201) showed that children of obese mothers had higher BMI, SBP and cIMT, although arterial dimensions and wall stiffness were not clearly linked to maternal obesity.³⁸ The UPBEAT randomized trial (N=122) in the UK provided complementary evidence, demonstrating at a 3-year follow-up that children of obese mothers exhibited concentric left ventricular remodeling, higher resting heart rate, and early diastolic dysfunction compared with offspring of normal-BMI mothers, while antenatal lifestyle intervention partially mitigated such adverse cardiac phenotypes.³⁹

Gestational obesity is also associated with an increased risk of obesity and CVD in offspring in later life. A longitudinal observational cohort study conducted in Colorado, USA (N=414) showed that maternal gestational obesity increased the risk of childhood overweight or obesity by 1.84-fold.⁴⁰ The Ma'anshan Birth Cohort in China (N=2,603) demonstrates a consistent association between maternal BMI and obesity risk before 6 years of age.⁴¹ Evidence from large national birth cohorts further indicates that maternal obesity confers elevated long-term CVD risk in offspring. A Swedish national cohort (N=2,230,115) showed that higher maternal BMI in early pregnancy was associated with a progressively elevated risk of CVD from childhood to young adulthood, reaching up to a 2.51-fold higher risk for offspring of mothers with obesity grade III.⁴² Consistent with this, an Israeli cohort (N=242,342) showed that maternal obesity was associated with a 1.59-fold higher risk of cardiovascular hospitalizations in offspring up to 18 years.⁴³

Collectively, these findings suggest that maternal obesity during pregnancy was associated with early-life cardiovascular remodeling, adverse cardiometabolic profiles, and increased long-term susceptibility to CVD in offspring. Emerging randomized trial data also indicated that antenatal lifestyle interventions may partially mitigate adverse cardiac remodeling in offspring of obese mothers, raising cautious optimism that maternal obesity-related influences on offspring cardiovascular health could be modifiable. Future studies are wanted to more precisely define optimal targets for gestational weight control, evaluate long-term cardiovascular outcomes in offspring, and develop tailored intervention strategies for obese pregnant women, with the broader goal of informing early prevention and management of cardiovascular disease from a life-course perspective.

Endocrine diseases and autoimmune diseases

Current knowledge regarding the long-term cardiovascular health of offspring born to mothers with autoimmune or endocrine disorders remains

limited, as most existing evidence has focused on congenital heart block or structural cardiac abnormalities rather than later-life cardiovascular function or cardiometabolic profiles.⁴⁴ Emerging data nevertheless suggest that maternal autoimmune conditions and thyroid dysfunction may influence early growth trajectories and markers of cardiovascular health.

In a cohort of children born to mothers with rheumatoid arthritis (N=167), higher maternal disease activity during pregnancy was associated with rapid postnatal catch-up growth, a pattern previously linked to less favorable cardiometabolic profiles in adulthood.⁴⁵ However, an age-matched Korean cohort (N=291) found generally normal growth recovery by two years, indicating mixed evidence.⁴⁶ Likewise, in children born to mothers with thyroid disorders, a long-term follow-up study in Danish (N=965) have found that maternal subclinical hypothyroidism was significantly associated with an increase of 3.6 mmHg in offsprings' SBP at a young age.⁴⁷ And a retrospective study in Boston (N=8,413) found that maternal hypothyroidism was also closely linked to 1.80-fold increased risk of low birthweight, a characteristic related to increased cardiometabolic risk.⁴⁸ In addition, a relatively small study (N=59) suggested that maternal thyroid dysfunction could cause fetal cardiac remodeling and subsequently affect cardiac function.⁴⁹

In terms of glucose and lipid metabolism, the Ma'anshan birth cohort (N=1,130) has demonstrated that elevated maternal free thyroxine (FT4) levels during pregnancy were associated with 0.02 mmol/L increase in fasting blood glucose but a concurrent 13% reduction in hypercholesterolemia risk at ages 4–6, indicating a dual influence of maternal thyroid hormones on metabolic outcomes.⁵⁰

Taken together, these observations point to possible links between maternal autoimmune or thyroid disorders and early alterations in offspring cardiovascular health, but the evidence remains heterogeneous, indirect, and constrained by study design limitations, underscoring the need for large-scale prospective cohorts with standardized cardiovascular endpoints and extended follow-up to clarify whether these early signals translate into clinically meaningful long-term cardiometabolic risk.

ENVIRONMENTAL EXPOSURE

Ambient air pollution

Ambient air pollution has emerged as an important and modifiable risk factor for cardiovascular disease.^{51–53} Prenatal exposure to air pollution, including particulate matter (PM), nitrogen dioxide (NO₂), ozone (O₃), and others, has been shown to be associated with early alterations in children's CVH.⁵⁴ These changes involve BP levels and cardiovascular metabolic dysregulation, such as glucose metabolism and BMI patterns.^{55–58}

Studies investigating prenatal pollutant exposure and children's BP levels have consistently observed positive associations, particularly with fine PM. Studies in USA and Europe have reported that higher exposures to PM with aerodynamic diameters ≤ 2.5µm (PM_{2.5}) and ≤ 10µm (PM₁₀) and black carbon during the late pregnancy were associated with higher BP levels in newborns.^{59,60} Furthermore, results in the Boston Birth Cohort (N=1,293) have demonstrated that per 5µg/m³ increment in third trimester PM_{2.5} exposure was associated with a 3.49 times higher risk of elevated BP in 3- to 9-year-old children.⁵⁵ Complementing these findings, an analysis from the CANDIE (Conditions Affecting Neurocognitive Development and Learning in Early Childhood) cohort (N=822) reported that higher prenatal PM_{2.5} exposure during the second trimester was associated with about a 10-percentile increase in BP levels at preschool-aged with a modification by maternal folate status.⁶¹

Investigations into children's cardiometabolic health have suggested that prenatal air pollution exposures may be associated with disrupted BMI trajectories, glucose regulation, and lipid homeostasis. A Mediterranean birth cohort (N=633) found that higher in utero PM_{2.5} and PM₁₀ exposure was associated with about 1.6 times higher risk of obesity in early childhood,⁶² while a Swedish study (N=5,815) found no significant association between the prenatal exposure to NOx and the risk of children obesity.⁶³ In contrast, long-term BMI trajectories from birth to adolescence often showed no consistent association, reflecting heterogeneity in exposure windows and population susceptibility.^{64–66} Glucose metabolism in children also appeared sensitive to prenatal PM_{2.5} exposure, a study conducted by Moody et al. in Mexico (N=365) have revealed significant associations between gestational

PM_{2.5} exposure and an annual 0.25% increase in HbA1c levels from aged 4–5 years to 6–7 years.⁶⁶ Additionally, analyses from the Healthy Start study (N=578) demonstrated links between prenatal black carbon exposure and 0.25 increase in HOMA-IR and other insulin resistance markers at about 5-year-old.⁶⁶ These findings have suggested that prenatal air pollution may serve as an environmental driver for the development of diabetes in early-life. As for dyslipidemia, evidence in children was limited and inconsistent, with few studies reporting alterations in cholesterol or triglyceride levels in early childhood following prenatal pollution exposure.^{66,67}

Collectively, consistent associations were observed between prenatal PM exposure and elevated BP in urban children, while the results on cardiometabolic parameters remain heterogeneous. Air pollution is a complex mixture of multiple chemical components that often occur as co-exposures and present in both outdoor and indoor environments. Yet, indoor air pollution is more difficult to assess, and exposures from sources such as cooking emissions and volatile compounds from indoor materials may be prolonged and accumulated. These effects are likely underestimated, and current evidence is extremely limited, with few studies to date examining congenital heart defects.^{68,69} Future researches with integrated assessment of pollutant mixtures both in indoor and outdoor environment and improved spatial and temporal resolution will be essential to enhance the effectiveness of findings and to strengthen the evidence base for environmental management policies.

Climate-related exposures

Climate change has led to an increasing frequency of extreme weather events, raising growing concerns about their potential impact on fetal development. Several studies using exposome-wide association study (ExWAS) approaches have identified prenatal exposure to ambient temperature, humidity and extreme weather events as important modifiers of BP trajectories in children.^{70–73}

Temperature. In a multi-center European cohort (N=4,279), higher ambient temperature during pregnancy was reported to correlate with a 1.1 mmHg decrease in BP levels in children aged 4–5 years.⁷⁰ A birth cohort from UK (N=7,454) found a slower increase of SBP (–0.17 mmHg/year, 95% CI: –0.28 to –0.07) with per interquartile range increase in temperature and repeated the observations in 4 independent European cohorts.⁷¹ And a study conducted in China (N=5,971) also demonstrated the identical associations throughout childhood.⁷⁴ These findings align with clinical epidemiological evidence from another study in China (N=6,158), which reported that prenatal exposure to lower temperatures was associated with a higher risk of hypertension in offspring.⁷⁵ However, in the European HELIX cohort (N=1,277), although similar negative associations between prenatal temperature and DBP in children aged 6–11 years were reported, opposite correlations were observed in SBP,⁷² indicating minor heterogeneity.

Humidity. Higher humidity was associated with a faster increase of SBP (0.29 mmHg/year, 95% CI: 0.20–0.39) in the UK cohort (N=7,454) mentioned previously,⁷¹ whereas ambient humidity during gestation was found to exhibit a U-shaped relationship with BP levels (RR=0.83, 95% CIs: 0.78, 0.89, P = 0.028) in the China cohort (N=5,971).⁷⁴

Extreme weather events. Extreme heat exposure has been increasing in frequency and severity due to climate change and its impact on CVH in children is also taken into consideration. A perspective cohort study in China (N=1,100) demonstrated that maternal heat exposure above the 95th percentile was associated with an increased risk of LVH (OR = 1.37, 95% CI 1.26–1.50), and a J-shaped relationship was observed for cardiac structure, with few alterations in BP of 4-year-old children.⁷⁶

Overall, most studies have reported consistent associations between higher ambient temperatures during pregnancy and lower BP levels or slower BP increases in offspring, whereas evidence regarding humidity remains limited and mixed. In contrast, previous research regarding extreme weather events mainly focused on CHD, while the association between that and early CVH in offspring is scarce. Moreover, findings across climate-related studies are difficult to compare because exposure definitions vary widely—some rely on pregnancy-averaged measures, others assess trimester-specific windows, and some consider only conditions at conception or birth. Regional differences in climate patterns may further contribute to variability in observed associations. These issues underscore the need for more harmo-

nized approaches and additional research to clarify the cardiovascular implications of climate-related exposures during pregnancy.

Urban environment

Greenness. Green space has been increasingly recognized as a salutogenic environmental factor that may support cardiovascular health. Evidence from the ENVIRONAGE birth cohort in Limburg, Belgium (N=427) showed that an IQR increment in residential greenness was associated with a 1.2 mmHg lower SBP and DBP in neonatal.⁵⁹ And similar trend was identified in the multi-center European cohort for offspring aged 4–5 years.⁷⁰

Built environment. Opposite to greenness, building density was reported to correlate with higher BP levels. The ENVIRONAGE cohort reported that an IQR increment in percentage industrial area was associated with a 1.0 mmHg higher DBP.⁵⁹ The European cohort reported higher DBP in association with higher building density as well.⁷⁰ In addition, an IQR higher facility density was observed to associate with a 1.7 mmHg reduction of DBP in the HELIX cohort,⁷² indicating the potential protection of accessibility of public services.

Noise. Environmental noise has been identified as a detrimental exposure associated with adverse cardiovascular outcomes. The only evidence from the multi-center European cohort reported the association between noise and higher DBP in offspring.⁷⁰

Current epidemiological evidence has predominantly focused on postnatal periods,^{77–79} with limited evidence addressing prenatal exposure and its long-term cardiovascular consequences. These existing studies are concentrated in a few early European urban cohorts and are limited to blood pressure outcomes. Further research is needed to clarify the cardiovascular impacts of prenatal exposure to urban environment.

Toxicants in food, water and consumer products

Heavy metals and mineral substances. Among various environmental factors, heavy metals are of particular concern due to their detrimental effects on reproductive health. Arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) are ubiquitous environmental contaminants that enter the human body primarily through diet, drinking water, or ambient air.^{80,81} These metals can traverse the placental barrier, exposing the developing fetus. A birth cohort study in China (N=2535, 2680, 2534 relatively in three trimesters) showed that prenatal As exposure was associated with higher BP of children, suggesting that the third trimester may represent a critical window for mitigating the impact of As exposure on childhood BP.⁸² Regarding Cd, cohort studies from diverse regions indicated that gestational exposure was negatively associated with cardiovascular parameters in childhood. A longitudinal study conducted in rural Bangladesh found that each doubling of maternal urinary Cd concentration was associated with a 0.73 mmHg increase in SBP.⁸³ Further research in the USA found (N=565) that the combination of shorter gestation and higher prenatal Pb exposure contributes to an elevated risk of increased SBP at 4–6 years of age, particularly in infants born before 37 weeks' gestation.⁸⁴ Sex-stratified analyses yield mixed results, study from the USA (N=323) suggested a stronger association between prenatal Pb and BP in boys,⁸⁵ whereas another study from Mexico (N=457) reported significant associations with increases in BP specifically in girls.⁸⁶ Mercury (both inorganic and organic forms as methylmercury (MeHg)) crosses the placenta easily. As fetal blood has larger hematocrit and higher concentrations of hemoglobin and plasma albumin, it accumulates 30–70% more MeHg than maternal blood.^{87,88} The potential cardiotoxic effects of prenatal MeHg exposure on child BP and cardiac autonomic function has been investigated in multiple studies across the world.^{89–91} Study from Guadeloupe (N=592) found that higher Hg levels in cord blood were associated with elevated BP and heart rate variability in children.⁹²

Bisphenol A (BPA). Prenatal exposure to BPA has shown consistent associations with altered BP in children. A meta-analysis involving 8 studies across the world (N=4,026) found that maternal exposure to organic pollutants, particularly BPA and pesticides, was significantly associated with a 0.6 increase in the z-score of SBP in offspring aged 2–8 years, especially when exposure occurred in the first trimester.⁹³ In the INMA-Sabadell cohort from Spain (N=1,064), higher maternal urinary concentrations of BPA were linked to sex-specific changes in lower BP in girls but higher BP in boys aged 10 years.⁹⁴ Another study from Korea (N=645) showed that 1 log unit increment

of prenatal urinary BPA concentration was associated with a 7.9 mmHg increase in DBP at age 4.⁹⁵

Phthalates. Similar to BPA, prenatal phthalate exposure has been associated with both BP alterations and cardiometabolic programming. In the INMA-Sabadell cohort mentioned above, phthalate exposure exhibited sex-specific associations with offspring BP that were similar to those observed for BPA.⁹⁴ Another study from the INMA-Sabadell cohort (N = 391) reported that a one log µg/g creatinine increase in prenatal exposure to high-molecular-weight phthalates was associated with a decrease of 0.28 BMI z-scores in boys, but an increase of 0.30 BMI z-scores in girls.⁹⁶ A meta-analysis by Gao et al., including seven studies (N = 5,746), found that higher prenatal exposure to DEHP (Bis(2-ethylhexyl) phthalate) was associated with lower SBP and DBP z-scores (-0.109 and -0.126, respectively), as well as reduced glucose and insulin levels in boys and elevated triglyceride levels.⁹⁷ A narrative review of 54 studies emphasized that phthalates and bisphenols could shape perinatal and postnatal cardiometabolic programming.⁹⁸

Per- and polyfluoroalkyl substances (PFAS). PFAS have been particularly implicated in both BP changes and lipid disturbances. A study from the Shanghai Birth Cohort (N=129) found that maternal plasma levels of PFAS mixture throughout pregnancy were positively associated with offspring DBP, mean arterial pressure (MAP), and the risk of childhood hypertension at age of 4.⁹⁹ Conversely, higher umbilical cord blood concentrations of long-chain PFAS were negatively associated with offspring SBP and DBP.¹⁰⁰ Regarding cardiometabolic indices, prenatal perfluorodecanedioic acid, perfluorononanoic acid, and perfluorooctane sulphonate levels were positively associated with elevated total cholesterol and triglycerides, with consistent results across sex and ethnicity.^{101,102}

Organophosphate. Few studies have reported association between prenatal organophosphate pesticide exposure with offspring CVH. The Generation R study from Netherlands (N=643) revealed that higher maternal urinary concentrations of OPPs metabolites were associated with lower cIMT and carotid distensibility, and higher SBP z-scores in children.¹⁰³

Other persistent organic pollutants. Substances such as polychlorinated biphenyls (PCBs), dichloro-diphenyl-dichloro-ethylene (DDE), hexachlorobenzene (HCB), are long-lasting environmental contaminants that can accumulate in human tissues and have been increasingly studied for their potential impact on offspring cardiometabolic health. In the European HELIX cohort (N=1,277), an interquartile-range increase of maternal PCB-118, DDE and HCB concentrations were associated with a 1.4 mmHg, 1.6 mmHg and 1.5 mmHg decrease in SBP of offsprings aged 6 to 11 years respectively.⁷² In adolescence, an observational cohort study from Dutch (N=101) reported that prenatal PCB exposure was linked to lower high density lipoprotein cholesterol and adiponectin in boys, while polybrominated biphenyl ethers were associated with higher triglycerides in girls.¹⁰⁴ Additionally, the Spanish INMA-Menorca birth cohort study (N=379) found that organochlorines such as HCB were associated with higher BMI, body fat percentage, and adverse lipid profiles by age 14, while PCBs were linked to elevated low density lipoprotein and cardiometabolic risk scores in a sex-dependent manner.¹⁰⁵

Overall, the majority of current studies have reported associations between prenatal exposure to various toxicants and higher BP levels in offspring, whereas evidence regarding cardiac structure, vascular indices, and metabolic disturbances remains much more limited and heterogenic. Considerable heterogeneity exists across studies due to regional and temporal differences in exposure levels, variations in analytical platforms, and the selection of biological specimen. In addition, sex differences have emerged as a recurring theme, with several studies suggesting potential effect modification by child sex. More harmonized exposure assessment strategies, standardized cardiovascular phenotyping, and adequately powered cohorts are needed to improve comparability across studies.

LIFESTYLE

Tobacco and alcohol use

Prenatal exposure to tobacco and alcohol represents significant modifiable risk factors for adverse cardiovascular outcomes in offspring, impacting both cardiac development and long-term cardiovascular function.

Prenatal tobacco exposure (PTE), including both active maternal smoking and secondhand smoke, exerts multi-faceted detrimental effects on offspring

cardiovascular health. Epidemiological studies have consistently linked maternal smoking during pregnancy with elevated BP in offspring. Studies conducted in large-scale European birth cohorts found that Maternal smoking during pregnancy was independently associated with higher SBP in preschool children,^{106,107} with the Rotterdam study specifically documenting higher DBP in exposed offspring.¹⁰⁸ Lower birth weight and increased obesity measures might mediate the adverse effects of PTE on BP in children.¹⁰⁹ Moreover, PTE are associated with significant vascular structural changes detectable from the neonatal period onward. Studies in Europe reported that neonates whose mothers smoked have significantly arterial intima-media thickness (aIMT)¹¹⁰ and atherosclerotic lesions.¹¹¹ Furthermore, a study conducted in Holland found that children with PTE have higher cIMT at 5 years of age.¹¹² Aside from vascular structure and function, evidence from separate studies has demonstrated the cardiovascular consequences of PTE extend to cardiac morphology and autonomic function. PTE is associated with characteristic structural alterations including enlarged left ventricular diameters¹¹³ and dilated aortic root dimensions,¹⁰⁸ along with impaired autonomic regulation evidenced by reduced heart rate variability^{114,115} in early childhood. Notably, while these findings highlight the multi-systemic impact of PTE, the underlying mechanisms remain to be fully elucidated.

Prenatal alcohol exposure during critical developmental windows exerts complex effects on offspring cardiovascular health. Cohort studies suggest that maternal alcohol consumption may elevate BP during pregnancy, potentially contributing to GH,¹¹⁶ which is independently associated with offspring hypertension in later life,¹¹⁷ indicating that prenatal alcohol exposure could indirectly affect offspring BP through maternal GH-mediated pathways. Despite consistent evidence for heavy exposure, the effects of moderate consumption remain controversial, possibly due to residual confounding.¹¹⁸ Current evidence highlights the highest risk during preconception and early pregnancy,¹¹⁹ reinforcing recommendations to avoid alcohol during these critical periods. Future research should focus on elucidating dose-dependent effects and molecular mechanisms underlying these developmental perturbations.

Overall, prenatal tobacco and alcohol exposure significantly impair offspring cardiovascular health. Tobacco exposure elevates blood pressure, alters vascular structure, and disrupts cardiac function. Alcohol exposure contributes to maternal hypertension and programs sex-specific cardiovascular dysfunction, with females more vulnerable. Both exposures exhibit lasting effects, emphasizing the need for avoidance during critical developmental windows. However, mechanisms remain under investigation.

Dietary pattern

The status of maternal diet and nutrition were found highly associated with offspring's cardiovascular health in the future. According to the impact on health, dietary patterns were commonly divided into unhealthy/Western diet and healthy diet, which could be further divided into Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet and plant-based diet.¹²⁰⁻¹²³

Unhealthy/Western diet is characterized by high consumption of processed meats, refined grains, sugary foods/beverages, fried foods, and saturated fats.¹²⁰ In the CANDLE study (N=846), maternal Healthy Eating Index 2010 scores were negatively associated with BP levels of children born to white women independent from pre-pregnancy overweight or obesity, maternal smoking, or breastfeeding.¹²⁴ A relative smaller study (N=121) observed that gestational hypertriglyceridemia correlated with elevated BP and serum leptin levels of children.¹²⁵ Although direct human evidence is limited, maternal unhealthy/Western diet are closely linked to obesity, GDM, and gestational hypertension, which may affect offspring CVH through associated metabolic and inflammatory pathways.

Mediterranean diet is a specific example of a healthy diet, rich in plant-based foods, olive oil, and fish, with moderate dairy and low red meat.¹²¹ One study carried out in Spain (N=657) showed that maternal seafood consumption, which is a main characteristic of Mediterranean diet, was not associated with better cardiovascular health of offspring.¹²⁶ Meanwhile, another study conducted in Spain (N=2,195) found the same results.¹²⁷ However, a study in UK (N=234) demonstrated that maternal oily fish consumption during late pregnancy was associated with decreased PWV, which signified reduced aortic stiffness. Higher oily fish consumption was associated with a 0.084

m/s per portion per week decrease of PWV.¹²⁸

Collectively, maternal diet significantly impacts offspring's future cardiovascular health, with dietary patterns categorized as unhealthy/Western or healthy. The Western diet, high in processed foods and saturated fats, is well-known to be linked to offspring BP levels. But the Mediterranean diet, rich in plant-based foods, olive oil, and fish, showed mixed results. Standardized diet assessment and intervention trials in larger population are desirable to provide better recommendations for pregnancy individuals.

Physical activity and sedentary behavior

Prenatal exercise has been associated with improved fetal outcomes, including decreased fat mass, enhanced stress tolerance, and advanced neurobehavioral development.¹²⁹ Emerging evidence suggests that maternal physical activity during pregnancy may exert beneficial effects on offspring cardiometabolic health, while excessive sedentary behavior may confer potential risks.

The Avon Longitudinal Study of Parents and Children (ALSPAC) from the UK (N=4,665) found that higher levels of self-reported maternal moderate-to-vigorous physical activity (MVPA) at 18 gestational weeks were modestly associated with a -0.013 mmol/L difference in offspring glucose levels at age 15. However, associations with BMI, BP, and lipid profiles were attenuated after adjustment for confounders.¹³⁰ Growing Up Today Study (GUTS) in the US (N=24,289) demonstrated that engaging in at least 150 min/week of MVPA during pregnancy was associated with a 21% decrease of the risk of obesity in offsprings.¹³¹ Another research in a smaller scale (N=43) found that infants born to women who participated in regular aerobic exercise during pregnancy had higher heart rate variability at one month of age.¹³² However, a few systematic reviews indicated that maternal prenatal exercise did not significantly impact offsprings' cardiovascular outcomes.^{133,134}

On the other hand, sedentary behavior has been linked to adverse perinatal outcomes. For example, higher sedentary time in pregnancy was observed among women who delivered macrosomic infants, particularly those with increased newborn abdominal circumference.¹³⁵ Nonetheless, other studies found no significant associations between early pregnancy sedentary time and mean birthweight and other cardiovascular outcomes, nor did replacing sedentary time with light or moderate activity affect birth size.¹³⁶ More standardized longitudinal research with refined cardiovascular endpoints is warranted.

Although increasing physical activity and reducing sedentary time are widely recognized health-promoting behaviors, evidence for their intergenerational benefits remains inconclusive, and recommended activity levels during pregnancy vary substantially depending on maternal health status. Future studies should clarify dose-response relationships, identify sensitive windows of activity, and examine how maternal cardiometabolic conditions modify these associations to better guide individualized prenatal activity recommendations.

Sleep behavior

Increasing evidence suggests that maternal sleep disturbances during pregnancy may contribute to adverse birth outcomes such as small-for-gestational-age (SGA) and preterm delivery, which are recognized to program long-term cardiovascular dysfunction.

Human studies on the effects of short maternal sleep on offspring cardiovascular health show inconsistent findings. Huang et al. reported that ≤ 7 h sleep during the second trimester increased preterm birth risk,¹³⁷ while Macdonald et al. found no significant associations between poor sleep and birth outcomes.¹³⁸ However, animal studies provide stronger evidence: gestational sleep restriction leads to offspring hypertension, higher basal heart rate, impaired baroreflex, and renal alterations.^{139,140}

Night-shift work, a common form of circadian disruption, has also been linked to increased risk of SGA and low birthweight.¹⁴¹ These exposures are further associated with altered offspring cardiometabolic regulation, including elevated HOMA-IR and risk of overweight at age 7 from Taiwan Birth Panel Study (N=407).¹⁴²

Sleep-disordered breathing, particularly obstructive sleep apnea (OSA), though traditionally associated with birthweight alterations,^{143,144} also contributes to long-term cardiovascular risk. Chen et al. found that maternal

OSA during pregnancy has been linked to offspring left ventricular dysfunction, oxidative stress, and sex-specific increases in BP in rats,¹⁴⁵ but few human studies have confirmed the association between maternal OSA and cardiovascular outcomes in the offspring.

Overall, evidence suggests maternal sleep disturbances during pregnancy—including short sleep duration, night-shift work, and sleep-disordered breathing—may increase risks of adverse birth outcomes and program long-term cardiovascular dysfunction in offspring. Human studies remain scarce and show mixed and indirect findings. Further investigation is strongly needed to clarify these relationships and their long-term cardiovascular consequences in offspring.

Mental health

Perinatal mental health has emerged as a potentially important but under-recognized determinant of early-life cardiovascular risk. In September 2022, the World Health Organization (WHO) released the *Guide for integration of perinatal mental health in maternal and child health services*, underscoring that untreated perinatal mental health problems not only increase maternal mortality but can also adversely affect offspring growth and development from the neonatal period through childhood.¹⁴⁶⁻¹⁴⁸

It is well established that perinatal mental health issues can influence both the mental and physical health of children. In a cohort of 4,318 mother-child pairs, depressive symptoms at 18 and 32 weeks of gestation were related to larger brachial artery diameters in offspring, and maternal anxiety at 18 weeks showed similar associations.¹⁴⁹ Another study (N=8,606) shows that depression at 18 weeks of gestation has been associated with higher SBP in offspring at age 18 (1.62 mmHg [0.17, 3.07]), while anxiety at the same gestational period correlates with elevated DBP at age 7 (0.70 mmHg [0.02, 1.38]); this difference persists into age 18 (0.89 mmHg [0.05, 1.73]).¹⁵⁰ These effect sizes are modest (on the order of 1–2 mmHg), but the direction of associations across studies is broadly consistent and suggests that intrauterine psychological distress may have a lasting, albeit small, influence on vascular structure and blood pressure regulation.

Mental health conditions such as depression and anxiety may also affect offspring cardiovascular risk indirectly by promoting maladaptive maternal behaviors, including smoking and alcohol consumption, which cluster with other adverse exposures.¹⁵¹ This behavioral pathway likely mediates part of the observed associations but also makes it difficult to isolate the independent effect of maternal psychological distress.

A core challenge in current research in this field lies in the complexity of confounding factors. Genetic predispositions may interact with perinatal psychological stress via epigenetic mechanisms. At the same time, socioeconomic factors and postnatal lifestyle conditions of the offspring further complicate the ability to isolate the independent effects of maternal psychological exposure on long-term cardiovascular outcomes in children.¹⁵²

Maternal supplementation

Calcium. Maternal calcium status plays a central role in blood pressure regulation, and calcium supplementation during pregnancy is recommended by WHO to reduce the risk of hypertensive disorders and adverse obstetric outcomes.¹⁵³ Evidence for long-term cardiovascular benefits in offspring is, however, mixed. A randomized controlled trial (RCT) conducted in Argentina (N=518) demonstrated that calcium supplementation during pregnancy significantly reduces the risk of high systolic blood pressure (≥ 95 th percentile) in offspring aged 5 to 9 years (RR=0.59, 95% CI: 0.39 to 0.90).¹⁵⁴ Two studies conducted in the United States reported consistent conclusions,^{155,156} with one RCT showing the effect to be age-dependent: no significant difference was found at 3 months ($P > 0.05$), but a notable one emerged at 2 years ($P < 0.05$). In contrast, trials from Australia and The Gambia found no effect of gestational calcium supplementation on mean SBP or DBP between 4 and 10 years of age.¹⁵⁷ Therefore, more high-quality research is needed to clarify how gestational calcium supplementation affects the cardiovascular health of offspring.

Folic acid/Vitamin B12. Maternal folate and vitamin B12, as key cofactors in the methionine–homocysteine cycle, are central to epigenetic programming and have been linked to cardiometabolic risk in offspring.^{158,159} A cohort study in Amsterdam (N=1,950) reported linear associations between

lower maternal folate and vitamin B12 levels at a median of 13 gestational weeks and less favorable cardiometabolic markers in children aged 5-6 years: each 10 nmol/L decrease in maternal folate was associated with a 0.07 kg/m² increase in offspring BMI, and each 100 pg/mL decrease in vitamin B12 correlated with a 0.49 bpm increase in resting heart rate.¹⁶⁰

Another cohort study in Rotterdam, the Netherlands (N=4,449) yielded similar results and showed a positive correlation between higher maternal folic acid/vitamin B12 levels in early pregnancy (average 13 weeks) and better cardiovascular health in offspring at age 10.¹⁶¹ A 1-standard deviation score (SDS) increase in maternal folate was related to lower offspring BMI (0.04 SDS) and SBP (0.06 SDS), and lower risks of overweight/obesity (13% reduction) and clustered cardiovascular risk (21% reduction). For vitamin B12, a 1-SDS increase was associated with lower DBP (0.05 SDS), lower fasting glucose (0.06 SDS), and higher HDL cholesterol (0.04 SDS). When vascular outcomes were examined, continuous folate and vitamin B12 levels were not significantly associated with carotid intima-media thickness (cIMT) or carotid distensibility at age 10, but subgroup analyses showed that low folate (<8 nmol/L) related to decreased carotid distensibility, and low vitamin B12 (<145 pmol/L) to increased cIMT.¹⁶² Notably, self-reported folic acid supplementation in early pregnancy was not associated with carotid outcomes, in contrast to biomarker-based exposures.

Overall, these well-characterized cohorts support a consistent association between higher maternal folate/vitamin B12 levels and a slightly more favorable cardiometabolic profile in offspring. However, effect sizes are small, findings for vascular structure and function are mixed, and all data are observational. The discrepancy between biomarker-based measures and self-reported supplementation suggests that background nutritional status, dose, and bioavailability may be more important than supplement use per se. Thus, while the evidence is coherent in direction and biologically plausible, the causal impact of routine folate/B12 supplementation on offspring cardiovascular health remains uncertain.

Socioeconomic status

Socioeconomic status (SES) has been demonstrated to significantly increase the risk of preterm birth through the cooccurrence of two or more adversities in education, income, marital status, and occupational stability.¹⁶³ Substantial evidence indicates a significant association between lower maternal SES during pregnancy and adverse cardiovascular health outcomes in offspring.

A prospective cohort in the Netherlands (N=5,843), revealed that a lower maternal educational level was linked to higher systolic blood pressure, with a difference of up to 2.80 mm Hg and diastolic blood pressure levels in offspring at age 6. These children also exhibited a higher fractional shortening, which might represent an early cardiac adaptation to higher blood pressure and body mass index.¹⁶⁴ A study of low-income Mexican American dyads (N=322) found prenatal neighborhood economic disadvantage raised kids' adiposity at 4.5, leading to poor cardiometabolic health at 7.5, but family hardship had no such effect.¹⁶⁵

Simultaneously, disadvantaged SES often coexists with multiple established risk factors that can impair offspring cardiovascular health. Lower maternal SES during pregnancy is associated with an elevated risk of developing gestational diabetes mellitus.¹⁶⁶ It is also linked to reduced access to residential green spaces, reflecting poorer living environments.¹⁶⁷ Furthermore, women with lower SES exhibit higher rates of smoking, lower participation in leisure-time physical activity, and greater susceptibility to psychological stress, such as increased depressive symptoms in late pregnancy.¹⁶⁸⁻¹⁷⁰

Consequently, SES should be interpreted primarily as a marker of accumulated structural and behavioral disadvantage rather than a singular causal exposure. The current evidence base, drawn mainly from prospective cohorts, consistently points to worse cardiovascular profiles among children born to socioeconomically disadvantaged mothers, but residual confounding is highly probable and interventional data are lacking (Figure 1).

POTENTIAL MECHANISTIC PATHWAYS

Placental dysfunction

The placenta was once considered a passive barrier, but now it is considered a dynamic regulator of fetal development. It acts as a nutrient trans-

porter, endocrine organ, and immune mediator, adapting to maternal signals while protecting the fetus from harmful exposure. The following is a summary of the mechanisms by which placental mediated intrauterine adverse exposure affects the cardiovascular health of offspring.

First, the placenta is highly sensitive to epigenetic modifications induced by the maternal environment, mainly involving three key mechanisms, including DNA methylation, histone modification, and miRNA derived from the placenta. Maternal hyperglycemia in gestational diabetes (GDM) can change the methylation pattern of placental genes such as LEP (leptin) and PPARG, and affect fetal obesity and vascular function.¹⁷¹ What's more, hypermethylation of promoters such as ANRIL and eNOS in umbilical cord endothelial cells is associated with reduced arterial stiffness and nitric oxide mediated vasodilation.^{172,173} Hypertensive disorders in pregnancy, such as preeclampsia, can upregulate HIF-1 α (hypoxia inducible factor) due to hypoxia, which can alter the chromatin structure of fetal endothelial cells and increase susceptibility to vascular dysfunction.^{174,175} In addition, miRNAs derived from the placenta (miR-210 under hypoxia) can be transferred to fetal tissues and inhibit angiogenesis related genes such as VEGFA, impairing vascular development.¹⁷⁶ These epigenetic changes collectively mediate the long-term effects of maternal conditions on fetal programming.

Second, the placenta plays a crucial role in regulating fetal nutrition supply, and maternal metabolic disorders can disrupt this balance through several key mechanisms such as glucose transport, lipid metabolism, and amino acid transport. Maternal hyperglycemia during pregnancy can upregulate the expression of GLUT1 in the placenta, leading to fetal hyperinsulinemia and myocardial hypertrophy.¹⁷⁷ What's more, Maternal obesity during pregnancy increases the expression of FABP4 (fatty acid binding protein 4) in the placenta, which can enhance fetal lipid uptake and make offspring more susceptible to early atherosclerosis.¹⁷⁸ In addition, maternal malnutrition can lead to disrupted mTOR signaling in the placenta, which limits the supply of essential amino acids and damages fetal heart growth.¹⁷⁹ The changes in placental nutrient transport highlight how maternal metabolic status have a lasting impact on fetal development and long-term health.

Third, the placenta is a crucial endocrine organ that can regulate fetal cardiovascular development through hormone signaling, including leptin and adiponectin, glucocorticoids, sex hormones, etc. Maternal obesity can disrupt placental leptin signaling, leading to fetal high leptin levels and excessive sympathetic nervous system activity, thereby increasing the susceptibility of offspring to hypertension.¹⁸⁰ Circulating cortisol levels are 5-10 times higher in the mother than in the fetus as placental 11 β -HSD2 serves as a barrier to inactivate glucocorticoids from the maternal circulation to avoid fetal overexposure to high cortisol levels.¹⁸¹ Chronic maternal stress can inhibit placental 11 β -Hydroxysteroid dehydrogenase 2 (11 β -HSD2) activity, increase fetal glucocorticoid exposure, and may lead to impaired vascular function in offspring.¹⁸² What's more, Excessive androgen levels in polycystic ovary syndrome (PCOS) can lead to placental mediated masculinization of female fetal blood vessels, thereby increasing the risk of offspring developing hypertension.¹⁸³

In addition, maternal metabolic disorders such as obesity and preeclampsia can trigger a cascade of oxidative stress and inflammation in the placenta, which can have adverse effects on the fetus. Diabetes during pregnancy will increase the production of ROS in the placenta, leading to fetal DNA damage and premature aging of blood vessels.¹⁸⁴ Maternal obesity upregulates the secretion of placental pro-inflammatory factors such as TNF- α and IL-6, which are transferred to the fetal circulation, activating the NF- κ B pathway and impairing endothelial function.¹⁸⁵ And these mechanisms may mediate the association between maternal pathological status and offspring cardiovascular disease risk.

Inflammation and oxidative stress

Diverse adverse intrauterine exposures – including maternal hypertensive disorders, diabetes (both gestational and pre-gestational), and environmental toxicants (such as heavy metals, PFAS) – converge upon two critical, interconnected pathophysiological pathways: chronic low-grade inflammation and oxidative stress.¹⁸⁶ These pathways become aberrantly activated during critical windows of fetal development, disturbing normal developmental programming and exerting profound, long-lasting effects on the structural,



Figure 1. In utero exposures during pregnancy and offspring cardiovascular health Maternal health conditions, lifestyle factors, and environmental exposures jointly shape in utero influences on fetal cardiovascular development, with potential long-term consequences for children's cardiovascular health.

functional, and metabolic set points of the fetal cardiovascular system.^{187,188} This significantly elevates the offspring's lifetime risk of CVD.¹⁸⁹

Exposure of the mother to adverse factors during pregnancy can result in the exacerbation of maternal inflammation. Maternal hypertension, diabetes (especially GDM), and obesity are intrinsically pro-inflammatory conditions.^{190,191} Hyperglycemia, elevated free fatty acids, leptin resistance, and adipose tissue macrophage infiltration drive significantly increased levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6, IL-1 β) in adipose tissue and systemically.¹⁹²⁻¹⁹⁴ Overactivation of the renin-angiotensin system (RAS) in hypertension also exerts potent pro-inflammatory effects.¹⁹⁵ Besides, heavy metals (such as Pb, Cd) and PFAS are recognized immunotoxins, activating maternal immune cells (e.g., macrophages) and inducing cytokine release.¹⁹⁶ High-fat/high-sugar diets promote gut dysbiosis and endotoxin (LPS) translocation into the circulation, can activate Toll-like receptor 4 (TLR4)

signaling and systemic inflammation.¹⁹⁷

Maternal inflammatory mediators, reactive oxygen species (ROS), advanced glycation end products (AGEs), and environmental toxins can cross the placenta or induce localized placental inflammation, resulting robust local production of pro-inflammatory cytokines, chemokines, and prostaglandins within the placenta.¹⁹⁸ Chronic inflammation impairs placental vascular development (disrupted angiogenesis), increases vascular resistance, promotes a pro-thrombotic state, and disrupts trophoblast invasion and spiral artery remodeling (critical in hypertensive disorders). This results in reduced placental perfusion, restricted nutrient/oxygen transport (potentially leading to IUGR), or aberrant selective nutrient transfer. Inflammatory damage weakens the placental barrier, potentially allowing increased passage of maternal inflammatory mediators or toxins into the fetal circulation. Placental inflammation leads to inadequate placental development and

loss of barrier function. Consequently, placental inflammatory monocytes of maternal origin become capable of migration to the embryonic heart.¹⁹⁹ Pro-inflammatory signaling pathways (such as NF- κ B) become abnormally activated in fetal tissues, establishing an "inflammatory memory". PFAS could directly affect offspring by triggering oxidative stress, inflammation, or metabolic pathways,²⁰⁰ causing the release of reactive oxygen species (ROS) and cytochrome C, and resulting in increased apoptosis of embryonic stem cell-derived cardiomyocytes.²⁰¹

Furthermore, many prenatal insults directly generate or impair the clearance of ROS. Exposure to heavy metals like Cd and As can deplete endogenous antioxidants (e.g., glutathione, superoxide dismutase) and/or enhance the activity of pro-oxidant enzymes (e.g., NADPH oxidases).^{196,202} This imbalance leads to oxidative damage of critical cellular components, including lipids, proteins, and DNA in fetal cardiovascular progenitor cells, endothelial cells, and cardiomyocytes.^{203,204} Inflammation and oxidative stress are tightly intertwined.²⁰⁵ Besides, ROS can activate pro-inflammatory pathways, while inflammatory cytokines can further stimulate ROS production, creating a vicious cycle.²⁰⁶ The combined insults of inflammation and oxidative stress during critical windows of development can affect angiogenesis, impair endothelial nitric oxide (NO) bioavailability, promote vascular smooth muscle cell proliferation and migration.²⁰⁷

Epigenetics programming

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA (ncRNA) regulation, can influence gene expression without altering the DNA sequence. In recent decades, these mechanisms have been increasingly recognized as key pathways of these adverse prenatal exposures affecting cardiovascular health in children.^{208,209} This section to explore how such exposures impact children's cardiovascular health via epigenetic modifications.

DNA methylation is the most extensively studied epigenetic mechanism, typically regulating gene silencing or activation in CpG island regions.²⁰⁹ Adverse intrauterine exposures can alter fetal DNA methylation patterns, thereby influencing the expression of cardiovascular-related genes. Gestational diabetes mellitus (GDM) has been associated with differential methylation of genes involved in metabolism and BP regulation (such as *LEP* and *IGF2*) in the placenta and umbilical cord blood of newborns, increasing the offspring's risk of metabolic syndrome and atherosclerosis.²¹⁰⁻²¹² Preeclampsia has also been linked to altered DNA methylation patterns in genes related to vascular development, inflammatory responses, and metabolic regulation.²¹³⁻²¹⁵ Prenatal exposure to air pollution may lead to global hypomethylation in placental tissues,²¹⁶ as well as specific gene methylation changes, including *LINE-1*, *superoxide dismutase 2*, and *LEP*.²¹⁷⁻²¹⁹ Furthermore, studies have shown that prenatal exposure to air pollutants is associated with slowed epigenetic aging at birth, suggesting delayed fetal development or immature cardiovascular systems.²²⁰

Histone acetylation and methylation regulate gene expression by altering chromatin accessibility. A human study involving 609 mother-newborn pairs reported associations between prenatal exposure to PM_{2.5} and black carbon with histone levels in cord blood.²²¹ Animal studies have shown that nicotine exposure can enhance the expression of angiotensin receptor genes in carotid bodies via histone modifications, leading to elevated BP and increased cardiovascular reactivity, laying the groundwork for programmed hypertension.²²² MicroRNAs (miRNAs), a type of non-coding RNA, regulate gene expression by binding to mRNAs to suppress their translation or promote degradation. Air pollution has been found to influence the expression patterns of several miRNAs in the placenta and cord blood, such as *miR-21* and *miR-210*, which are involved in the regulation of cardiac hypertrophy, heart rate, and energy metabolism.²²³

In conclusion, epigenetic mechanisms act in concert to reprogram gene expression networks, thereby influencing BP regulation, cardiac structure, and metabolic function. Identifying epigenetic biomarkers may offer new avenues for early screening and intervention in high-risk individuals.

Neuroendocrine regulation

Adverse conditions within the intrauterine environment have emerged as pivotal drivers of fetal programming processes that predispose offspring to

cardiovascular dysfunction.²²⁴ These long-term effects are considered to be primarily mediated by dysregulation of maternal neuroendocrine stress pathways, including the hypothalamic–pituitary–adrenal (HPA) axis^{225,226} and the sympatho–adrenal–medullary (SAM) system.²²⁷

The HPA axis plays a pivotal role in orchestrating fetal adaptations to intrauterine stress by modulating the production of glucocorticoids (GCs), which are essential for tissue differentiation and cardiovascular maturation.²²⁸ To prevent the detrimental effects of excessive GC exposure, maternal HPA axis activity undergoes physiological adaptations during pregnancy, and the placenta expresses 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which enzymatically inactivates maternal cortisol before it crosses into the fetal circulation.²²⁹ However, this protective mechanism can be compromised by a range of adverse intrauterine exposures, including maternal metabolic disorders,²³⁰ alcohol consumption,²³¹ prenatal stress,²³² air pollution,²³³ endocrine-disrupting chemicals (EDCs),²³⁴ and various xenobiotics.²³⁵ These factors have been associated with decreased placental 11 β -HSD2 expression and dysregulated maternal cortisol rhythms, leading to excessive fetal GC exposure and subsequent disruption of fetal HPA axis programming. This hormonal imbalance has been linked to the developmental programming of cardiovascular dysfunction through multiple interrelated pathways. Experimental studies have demonstrated that prenatal GC overexposure can induce cardiac programming via multiple interrelated mechanisms. Excessive GCs impair dopamine D1 receptor signaling and activate oxidative stress pathways, including the PKC-GRK2 axis, thereby promoting the development of hypertension in later life.²³⁶ Concurrently, cardiac development is disrupted through epigenetic remodeling, most notably via hypermethylation of the *Bmp4* promoter in cardiomyocytes, which suppresses its expression and diminishes HIF-1 α mediated antioxidant responses, ultimately increasing cardiomyocyte apoptosis and vulnerability to ischemic injury.²³⁷⁻²³⁹ In addition, renal programming appears to involve persistent disturbances in arachidonic acid metabolism,²⁴⁰ glomerular structural damage, and sodium retention, all of which may contribute to sustained BP dysregulation even after postnatal restoration of renal mass.²⁴¹ Evidence from human cohort studies further suggests that the relationship between maternal cortisol and offspring BP is both sex- and time-dependent, indicating that the impact of physiological GC levels may vary depending on the timing, magnitude, and context of fetal exposure.²⁴²

Distinct from the endocrine-mediated programming of the HPA axis, the SAM system primarily influences cardiovascular development through alterations in autonomic function. Evidence from animal studies indicates that prenatal challenges, including maternal protein restriction, intermittent hypoxia, and glucocorticoid excess, may program the fetal sympathetic system toward exaggerated postnatal autonomic reactivity.^{243,244} In particular, prenatal cold exposure has been shown to elevate offspring BP by enhancing both central and peripheral sympathetic activity, a process associated with overactivation of the hypothalamic paraventricular nucleus and angiotensin II type 1 receptor signaling.²⁴⁵

Additionally, maternal obesity has been linked to early-life sympathetic hyperactivity and impaired cardiopulmonary function in offspring, increasing susceptibility to metabolic and hypertensive disorders later in life.²⁴⁶ Together, these findings highlight prenatal sympathetic overactivation as a key contributor to later cardiovascular risk.

Among these interrelated pathways, as the bridge between mother and offspring, placental dysfunction may appear to be the most proximal and direct mechanism. Leon et al. emphasized that the placenta and fetal heart develop in close synchrony, suggesting the strong connection between placental development and cardiogenesis.²⁴⁷ Epigenetic modification, inflammation and oxidative stress, endocrinal regulation, as well as malnutrition and hemodynamic dysfunction within the placenta may program the fetal cardiovascular system and act as the core mechanistic link between adverse intrauterine exposures and cardiovascular risk later in life (Figure 2).

EARLY DETECTION AND PREVENTION

Clinical risk assessment framework

Recognizing that the intrauterine environment can program long-term cardiovascular risk necessitates proactive strategies for identifying susceptible individuals early in life. Effective screening can facilitate timely interventions aimed at mitigating these programmed risks.

Existing clinical guidelines, such as those from the Expert Panel on Inte-

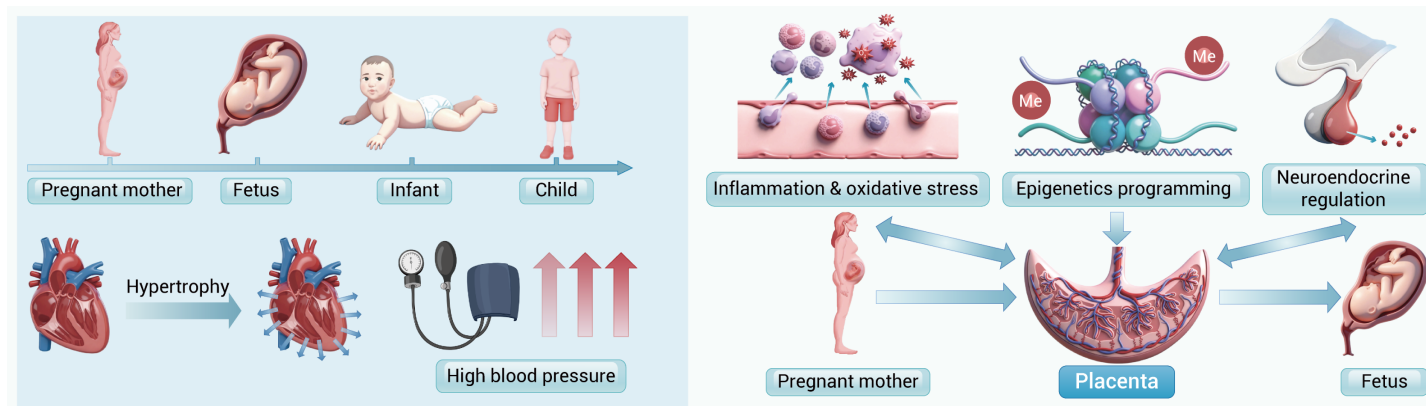


Figure 2. Potential mechanisms linking in utero factors to offspring cardiovascular risk Maternal, placental, and fetal interactions contribute to inflammation and oxidative stress, epigenetic programming, and neuroendocrine regulation. These processes promote fetal cardiac development and predispose offspring to impaired cardiovascular health in childhood.

grated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, provide a framework for assessing cardiovascular risk factors from infancy through young adulthood.²⁴⁸ A cornerstone of this assessment is obtaining a detailed family history of early atherosclerotic CVD. This involves inquiring about parents, grandparents, aunts, or uncles who experienced conditions like myocardial infarction, angina, stroke, coronary artery bypass grafting (CABG), stenting, angioplasty, or sudden cardiac death before the age of 55 years for male relatives and 65 years for female relatives. Such family history should be evaluated at specific pediatric encounters, for example, around age 3 years, again between 9–11 years, and at 18 years, with updates at non-urgent health encounters.²⁴⁸ If a positive family history of early CVD is identified, guidelines recommend a more intensive evaluation of the child for other established cardiovascular risk factors. These include dyslipidemia, hypertension, obesity, diabetes mellitus, exposure to tobacco smoke, and a sedentary lifestyle.²⁴⁸

Furthermore, current guidelines emphasize age-specific recommendations for promoting cardiovascular health through nutrition (e.g., advocating for breastfeeding, transitioning to healthy dietary patterns), encouraging regular physical activity, and counseling on tobacco exposure avoidance from birth.²⁴⁸ While these guidelines are valuable, a critical consideration is that they predominantly focus on postnatal risk factors and general family history. There is an evident gap in systematically incorporating and weighting specific adverse intrauterine exposures into a formal risk score for offspring, which could enable a more nuanced and individualized risk assessment from birth. Such a “DOHaD-informed risk score” remains an important unmet need.

Biomarker-based stratification

To enhance early detection and risk stratification beyond traditional clinical factors, research is actively exploring novel biomarkers. There are various potential biomarkers for identifying long-term cardiovascular risks in offspring exposed to adverse intrauterine environments (AIEs). Placental biomarkers, such as the sFlt-1 to PlGF ratio, reflect placental health and may predict offspring vascular health. Epigenetic markers, particularly DNA methylation patterns in cord blood or peripheral blood cells, can indicate in utero stress and future CVD susceptibility. Metabolic and inflammatory markers, identified through lipidomics, metabolomics and cytokine analysis, may reveal early signs of metabolic and vascular dysregulation. Other potential biomarkers related to endothelial function and oxidative stress are also being explored. However, the predictive accuracy of some biomarkers used in isolation may be limited, suggesting a combination with biophysical parameters and maternal characteristics could be more effective. Additionally, biomarkers like NT-proBNP may behave differently in postpartum screening. The interconnectedness of cardiac, neural, and metabolic systems implies that screening for cardiovascular risk in exposed offspring should be integrated with surveillance for neurodevelopmental delays and metabolic dysfunction.^{249,250}

Preconception and prenatal health optimization

Addressing the long-term cardiovascular consequences of adverse intrauterine exposures requires robust public health strategies that span the life course, from preconception through adulthood. These strategies must aim to prevent AIEs where possible, mitigate their impact when they occur, and address the broader social determinants that contribute to these risks.

A fundamental tenet of public health action in this domain is the adoption of a life-course perspective. This acknowledges that the foundations for adult cardiovascular health and disease are established very early in life, even before birth.²⁵¹ Efforts should therefore prioritize primordial prevention—actions taken to prevent the development of risk factors (like maternal obesity or GDM) in the first place—and primary prevention—managing existing risk factors in mothers or young children to prevent the onset of disease processes.^{252,253} This approach shifts the focus from late-stage interventions to proactive, early-life investments in health.

A significant opportunity for prevention lies in optimizing the health of women *before* they conceive.²⁵⁴ Public health initiatives should vigorously promote preconception health, encouraging healthy nutrition, maintenance of a healthy weight, effective management of any pre-existing chronic conditions (e.g., diabetes, hypertension), and access to mental health support for women of reproductive age.

Once pregnancy occurs, ensuring universal access to high-quality, comprehensive prenatal care is paramount. This includes timely screening and effective management of pregnancy-specific conditions like GDM and preeclampsia, which are known AIEs. Early identification of these conditions through routine prenatal visits, glucose tolerance testing, and BP monitoring enables timely intervention to minimize maternal and fetal risks. Moreover, individualized care plans, nutritional counseling, and close follow-up for high-risk pregnancies can further reduce the likelihood of long-term cardiometabolic consequences in the offspring.

Perinatal conditions involving maternal bacterial or viral infection, chorioamnionitis, and premature rupture of membranes also require timely monitoring, intervention, and treatment. Although evidence on postnatal cardiovascular outcomes is scarce, limited studies have reported associations between maternal infection and fetal cardiac alterations.^{255–257} Given that these conditions may have important implications for offspring cardiovascular health, appropriate maternal screening for TORCH and GBS (*Streptococcus agalactiae*), and the timely use of antibiotics or vaccines should be ensured.

Furthermore, public health messaging must continue to emphasize the critical importance of the avoidance of harmful exposures such as tobacco smoke, alcohol, and environmental toxins throughout gestation. These factors are modifiable and have well-documented associations with poor birth outcomes.^{258–260} The public health authorities should strengthen efforts toward environmental regulation and the safe management of organic pollutants to reduce maternal and fetal exposure risks. Policies aimed at monitoring and controlling the use of industrial chemicals, pesticides, and persistent organic pollutants are essential. Implementing stricter environmental standards, promoting green alternatives, and improving community-level expo-

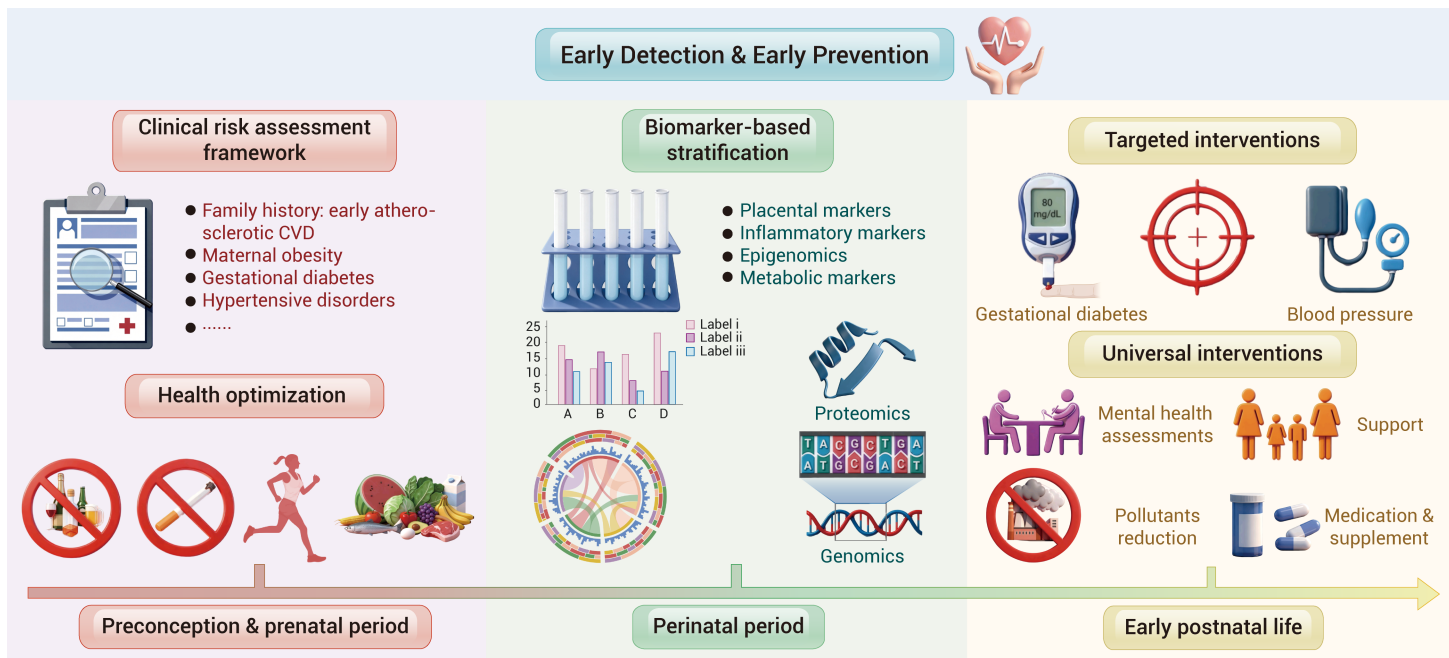


Figure 3. An integrated framework for early detection and prevention of in utero adverse exposures to safeguard offspring cardiovascular health.

sure surveillance can collectively contribute to healthier environments for women of reproductive age and their children.

Mental health must also be central to prenatal care. Pregnancy is a sensitive period when a woman's psychological state can directly affect both her own and her child's long-term health.²⁶¹⁻²⁶³ Promoting emotional well-being through supportive services and physical activity—which has been associated with reduced stress, anxiety, and depression symptoms—is essential.¹⁴⁶ Strengthening family awareness and involvement in maternal mental health is equally important, as emotional support from partners and close relatives can buffer stress and promote resilience. Public health systems should also work to expand the accessibility and integration of perinatal mental health services, ensuring that all women—regardless of socioeconomic status—can receive timely screening, counseling, and referral when needed.

Digital health tools offer scalable means to support healthy behaviors. Programs like Text4baby and Quit4baby provide accessible, evidence-based guidance through mobile messaging.^{264,265} These tools demonstrate the potential for low-cost, personalized lifestyle interventions to enhance prenatal health literacy and engagement.

The understanding that maternal health before and during pregnancy directly translates into the "health capital" of the next generation provides a powerful rationale for prioritizing maternal health services. Investing in the well-being of women of reproductive age through lifestyle support, mental health care, and accessible prenatal service is a direct investment in the long-term health of the population and a key strategy to break intergenerational cycles of chronic disease.

Universal and targeted early-life interventions for individuals

Personal health management during pregnancy also plays a crucial role in reducing adverse intrauterine exposures and promoting long-term cardiovascular health in the offspring.

During pregnancy, women should aim to maintain appropriate weight gain according to their pre-pregnancy BMI by following a balanced diet and engaging in regular physical activity. Meals should include adequate amounts of vegetables, fruits, whole grains, lean proteins, calcium, iron, and folate, while minimizing intake of processed foods, added sugars, and trans fats. In the absence of medical contraindications, at least 150 minutes of moderate-intensity exercise per week—such as walking, swimming, or prenatal yoga—is recommended.^{262,263}

Chronic conditions like hypertension and diabetes should be well controlled before and throughout pregnancy. Pregnant women should attend regular prenatal check-ups to ensure timely screening and appropriate management

of gestational diabetes and hypertensive disorders. For those diagnosed, individualized treatment plans including dietary guidance and medication, if necessary, should be followed under professional supervision. High-risk pregnancies may require closer monitoring through multidisciplinary care.

Avoiding harmful exposures is equally important. Women should completely abstain from smoking and alcohol, and avoid secondhand smoke. Efforts should be made to reduce contact with environmental pollutants, including air pollution, pesticides, and household chemicals. Choosing fresh produce with low pesticide residues, using indoor ventilation, and staying away from heavily polluted areas can help minimize exposure risks.

Mental health support should be an integral part of prenatal care. Women are encouraged to participate in regular mental health assessments and seek timely support if experiencing stress, anxiety, or depressive symptoms. Maintaining daily routines, ensuring quality sleep, and engaging in light physical activity can promote emotional well-being. Support from partners and family members also plays a vital role and should be actively encouraged.

Optimal use of supplementation needs to be recommended to each pregnancy woman. Folic acid should be initiated before conception and continued through early pregnancy at recommended doses to meet increased demand. Calcium supplements are often needed when dietary intake is insufficient, particularly for women with low dairy consumption or higher risk of hypertensive disorders. Vitamin B12 status should be assessed in women with vegetarian or low-animal-product diets, with supplementation provided as needed to prevent deficiency. Regular prenatal check-ups, nutritional screening, and adherence to national or clinical guidelines are essential for tailoring supplementation to individual needs and ensuring these micronutrients are used safely and effectively (Figure 3).

EMERGING TRANSLATIONAL THERAPEUTIC PERSPECTIVES

In addition to early identification and preventive strategies, experimental and translational efforts of potential therapeutic approaches aiming to maternal-fetal interface have been emerged. Nanomedicine is a novel therapeutic platform to deliver bioactive molecules directly to the placenta or fetal circulation with high precision. Gene therapies through nanoparticles including lipid conjugate, polymeric nanoparticles, lipid nanoparticles and liposomes are currently at the preclinical stage.²⁶⁶ For instance, plasmid DNA-FuGENE administrated intravenously in pregnant mice exhibited potential of gene editing therapy in CHD.²⁶⁷ Furthermore, a non-viral, polymer nanoparticle-mediated IGF-1 gene delivery strategy demonstrated the ability to impact placental function and correct fetal growth restriction in a guinea pig model.²⁶⁸ Placenta-targeted ionizable lipid nanoparticles encapsulating VEGF

mRNA were also reported to ameliorate pre-eclampsia and improve fetal growth in a murine model.^{269,270}

These emerging researches suggest that targeted maternal-fetal therapeutics, especially those leveraging nanomedicine for placental delivery, may provide a future avenue to mitigate cardiovascular risk programmed by adverse intrauterine environments. Nonetheless, existing studies have primarily assessed prenatal and perinatal outcomes, whereas data on long-term cardiovascular health in the offspring remain scarce. In addition, translation to clinical practice will require rigorous safety evaluation, ethical consideration, and long-term follow-up in human studies. The establishment and implementation of a rigorous research framework encompassing design, experimental, manufacturing, preclinical, clinical, regulatory and business considerations for nanomedicine are essential to ensure ethical responsibility, safety, and successful clinical translation.^{271,272}

CONCLUSION

Adverse in utero exposures—including maternal health conditions, environmental exposure, and unhealthy lifestyles—are increasingly recognized as early determinants of cardiovascular risk in offspring. Evidence from birth cohorts has substantially advanced our understanding of these developmental origins; however, most studies remain constrained by a narrow focus on BP and metabolic traits. Long-term, high-resolution assessments of cardiac structure and function in children are strikingly scarce, and the absence of standardized frameworks for pediatric cardiovascular phenotyping continues to limit cross-study comparability and translational relevance.

The advent of multi-omics technologies offers unprecedented opportunities to bridge this knowledge gap. Projects such as HELIX, INMA, COCOA, and C-MACH have begun to delineate molecular signatures linking prenatal exposures to cardiovascular health across genomic, epigenomic, transcriptomic, metabolomic, and exposomic layers.²⁷³⁻²⁷⁷ Yet, the field faces persistent challenges: high-dimensional data with modest sample sizes, inconsistent analytical pipelines, and limited causal inference. Additionally, longitudinal and transgenerational cohort studies provide essential insight into the lasting and heritable effects of prenatal exposures. While studies like ALSPAC and Framingham have illuminated early-life determinants of adult cardiovascular risk, longer follow-up and more detailed exposure profiling are still needed.^{278,279} Integrating multi-omics into multigenerational designs will be critical for disentangling genetic, epigenetic, and environmental contributions. Moving forward, embedding robust multi-omics integration and causal modeling into large-scale, longitudinal and intergenerational cohorts will be essential to unravel the interplay of genetic, epigenetic, and environmental factors driving early cardiovascular programming.

What is urgently needed now is a global, coordinated effort to harmonize exposure assessment and cardiovascular phenotyping, supported by open data sharing and cross-disciplinary collaboration. Such integration will not only refine risk stratification but also accelerate the discovery of actionable biomarkers and mechanistic targets, laying the foundation for precision prevention strategies. Ultimately, translating these insights into early-life screening and tailored interventions has the potential to reshape cardiovascular disease prevention across the life course.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

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