Current Problems in Cardiology 49 (2024) 102695

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Invited Review Article

Maternal-fetal dyad beyond the phenomenology of pregnancy: from primordial cardiovascular prevention on out, do not miss this boat!

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ARTICLE INFO

Keywords:
Adverse pregnancy outcomes
Cardiovascular prevention
Gender medicine
Maternal fetal dyad
Perinatal medicine
Pregnancy

ABSTRACT

Pregnancy represents a stress test for every woman's cardiovascular (CV) system, and a pre-existing maternal unfavorable cardio-metabolic phenotype can uncover both adverse pregnancy outcomes and the subsequent development of cardiovascular disease (CVD) risk factors during and after pregnancy. Moreover, the maternal cardiac and extracardiac environment can affect offspring's cardiovascular health through a complex mechanism called developmental programming, in which fetal growth can be influenced by maternal conditions. This interaction continues later in life, as adverse developmental programming, along with lifestyle risk factors and genetic predisposition, can exacerbate and accelerate the development of CV risk factors and

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https://doi.org/10.1016/j.cpcardiol.2024.102695

Available online 7 June 2024

CVD in childhood and adolescence. The aim of this narrative review is to summarize the latest evidences regarding maternal-fetal dyad and its role on primordial, primary and secondary CV prevention.

Introduction

Pregnancy presents a significant challenge for young women, marked by various psychophysical changes. While studies have extensively explored the physical aspects of pregnancy, attention to the psychological changes affecting the body's responses has only recently gained momentum.[1–4] The American Heart Association (AHA) has proposed a consensus document regarding preconceptional cardiovascular (CV) health in young women. This period is crucial for interventions aimed at identifying and managing CV risk factors in individuals planning to conceive, as they can mitigate adverse pregnancy outcomes (APOs), reducing the risk of maternal and offspring's subsequent CVD.[1,2] Pregnancy itself is a critical period often burdened by high levels of stress.[3–5] According to the AHA consensus, the evaluation of Life's Simple 7 or Life's Essential 8 is crucial to assess lifestyle factors and their impact of CV health.[1,2] Originally comprising seven key health factors, including diet, physical activity, smoking status, body mass index, blood pressure, lipids, and blood sugar, this framework offers a comprehensive approach to assessing and promoting CV health. In a recent update, sleep health was included as an eighth factor, forming the Life's Essential 8 (LE8) framework.[1,2,6] By implementing these factors, individuals can strive for optimal CV health and reduce their CVD risk.[7,8] Additionally, the consensus highlights the importance of the three pillars: stress/resilience, social determinants, and structural policies. These determinants encompass mental well-being, socio-economic factors, and access to healthcare and resources, which affect an individual's overall health. Perinatal stress, anxiety, and depression can negatively impact fetal development and increase the risk of mental issues in the offspring. Moreover, stressors such as unplanned pregnancies, low economic status and inadequate sociomedical support can influence a mother's relationship with food, potentially affecting the fetus, and contribute to the risk of APOs.[9–11]

Stratification of cardiovascular risk in pregnancy: why it is so important

An appropriate assessment of CV risk in women starts from the enclosure of sex and gender-specific risk factors in the evaluation of global CV risk.[12] Alongside traditional CV risk factors, e.g. chronic hypertension, diabetes, hypercholesterolemia, overweight and obesity, physical inactivity, it has been established that specific sex and gender CV risk factors should be included. Some of these are closely connected to the perinatal time.[13] Several conditions during a woman's reproductive history can influence or reveal short- and long-term cardiometabolic conditions. Early and late menarche, polycystic ovarian syndrome, infertility, APOs (e.g., hypertensive disorders of pregnancy, HDPs; gestational diabetes, GDM; preterm delivery, PD; intrauterine growth retardation, IUGR), and lack of breastfeeding are all associated with an increased future CVD risk. HDPs, including chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension, are increasingly frequent clinical conditions.[14] This trend is probably due to the increase in traditional CV risk factors in women, even at a young age (physical inactivity and overweight/obesity in particular), together with conditions such as polycystic ovary syndrome, which are related to insulin resistance (IR) and unfavorable cardiometabolic profiles.[15] Moreover, an increase in the pregnancy onset age leaves CVD time to produce its detrimental effects. The onset of pregnancy in these patients often unveils conditions of CV frailty, which manifest precisely with HDPs. The pathophysiological basis of this condition should be ascribed to the pathological development of the placenta. Early preeclampsia pathophysiology includes abnormal trophoblast invasion of the endometrium, which leads to incomplete spiral artery remodeling and, ultimately, placental ischemia, although it seems that the diverse presentations of preeclampsia likely reflect a spectrum of pathophysiology.[13,16] HDPs constitute significant sex-specific risk factors for short and long-term maternal CVD. During the peripartum period, the odds of stroke,[17,18] myocardial infarction[19] cardiomyopathy[20] and spontaneous coronary artery dissection[21] are significantly increased for women who have suffered from HDPs. Moreover, such CVD risk extends well into later life. On the other hand, a genetic predisposition has been found and described, so the unfavorable postpartum CV risk profile has to be related to preexisting genetic conditions.[22]

How to follow up the woman at risk during pregnancy and post-pregnancy: The cardiologist's point of view

As previously discussed, a pre-existing maternal unfavorable cardiometabolic phenotype can uncover both APOs and the subsequent development of CVD risk factors during and after pregnancy.[23] Additionally, the maternal environment can affect offspring CV health through a complex mechanism called "developmental programming", in which fetal growth can be influenced by three significant maternal conditions: pregnancy-related CV disorders (e.g., HDPs, peripartum cardiomyopathy); maternal CV risk factors (e.g., diabetes, physical inactivity, hypercholesterolemia, smoking, obesity); extracardiac disorders (e.g., malnutrition and severe protein deficiency, corticosteroid therapy, abnormal placentation). This interaction continues later in life, as adverse developmental programming, along with lifestyle risk factors and genetic predisposition, can accelerate the development of CV risk factors and CVD in childhood and adolescence.[24] Moreover, CV micro- and macrovascular risk factors track from mother to child, regardless of the course of pregnancy.[25] These considerations highlight the need to prevent primordial and primary CV risk in complicated pregnancies and in mothers with suboptimal CV risk profile to ameliorate short and long-term CV health in both mothers and children.[25] According to the American College of Obstetricians and Gynecologists task force on pregnancy and heart disease, there are nine risk factors for maternal

CVD: older age (more than 40 years), obesity, non-hispanic black race, HDPs, chronic disease (e.g., chronic arterial hypertension, pregestational diabetes mellitus), obstructive sleep apnea, PD, strong family history of CVD and exposure to cardiotoxic drugs. The same task force created a simple flowchart to differentiate common signs and symptoms of normal pregnancy versus abnormal signs suggestive of underlying CVD and requiring prompt evaluation by pregnancy heart team.[26] Furthermore, in 2021, the AHA published a consensus regarding managing perinatal CVD risk factors, focusing on lifestyle modification, healthy dietary patterns, adequate physical activity, and pharmacological therapy.[14]

The role of nutrition before, during, and after pregnancy

Nutrition plays a major role in maternal-fetal well-being, as a healthy maternal dietary pattern, along with adequate cardiometabolic status and placental nutrient supply, ensures positive short and long-term effects on perinatal outcomes and CV risk, both for mothers and offspring.[27] Every woman of childbearing age should be counseled regarding the importance of perinatal maternal nutrition and should be encouraged to adopt a healthy weight before conceiving, and a balanced healthy diet. It has been demonstrated that maternal nutrition in the 12 months before pregnancy greatly influences fetal and neonatal outcomes regarding fetal growth and development, and infant birth weight.[28] Moreover, healthy maternal nutrition up to 3 years before pregnancy is considerably associated with lower risk of APOs.[29] Among all dietary patterns, the DASH (Dietary Approaches to Stop Hypertension) diet is associated with better maternal and fetal outcomes in terms of more favorable blood pressure trend in uncomplicated pregnancy, decreased risk of PD and better metabolic status in mothers with GDM, as compared with other dietary patterns. Moreover, a diet rich in fat and sugar is associated with a higher risk of PD.[28,30,31] However, there is no evidence supporting the universal adoption of the DASH diet compared to other dietary patterns, and more studies are needed to confirm its efficacy. Furthermore, the role of specific dietary patterns in preventing the development of CVD risk factors after an APOs is under study.[6,14,32]

The role of physical activity before, during, and after pregnancy

Physical activity (PA) is a key player in the improvement of cardiometabolic and psychological health before, after, and during pregnancy, as well as of short- and long-term perinatal outcomes and cardiometabolic offspring's status. PA can prevent and reverse all the clinical and subclinical risk factors associated with preeclampsia, determining positive vascular remodeling and angiogenesis, improved endothelial function, reduced oxidative stress and inflammatory status.[33] In this regard, a greater amount of leisure-time PA in the first trimester of pregnancy is related to a lower risk of APOs and pregnant women who exercise as recommended experience a 30% lower risk of developing HDPs and a better CV profile in perimenopause.[34–36] Additionally, PA leads to a significant reduction in gestational weight gain and post-pregnancy overweight, which are, in turn, associated with higher CV risk, especially in women with a history of APOs, and may influence neonatal fat mass, which represents a risk factor for childhood obesity.[37,38] Moderate-intensity PA, alone or associated with diet, determines a 24% and 39% reduction in GDM.[39] Likewise, regular PA can ensure good maternal mental health in terms of stress, quality of life, and prenatal depression, the latter being associated with increased CV risk within 24 months postpartum, leading to lower oxidative stress burden and better long-term metabolic offspring's milieu.[40–42] International guidelines recommend at least 150 minutes of moderate-intensity aerobic PA a week, including muscle-strengthening activities, in uncomplicated pregnancy and during postpartum.[43] Nevertheless, the current levels of PA in these stages of women's lives are still very far from the international recommendations, ranging from 15 to 27.3% during pregnancy, with sedentary time being correlated with increased risk of APOs.[44,45] The prevalence of postpartum PA is low, too, even if there is growing evidence supporting its role in terms of improvement of maternal short and long-term mental and cardiometabolic health.[46–49] The most critical issues are that some women do not return to their pre-pregnancy PA levels and that there is still poor data regarding timing and nature of transitioning to PA following delivery. This strengthens the need for adequate lifestyle and PA counseling throughout the perinatal period.[50]

The role of pharmacotherapy

To date, low-dose aspirin represents the most effective pharmacological therapy for reducing the risk of preeclampsia, and its use is advocated for women at high risk of preeclampsia.[51] A recent systematic meta-analysis including a total of 20,133 patients confirmed that starting aspirin, 75 mg/day, at 12-16 weeks of pregnancy reduces the incidence of preeclampsia by 38% in women at high risk for this complication.[52] Additionally, statins can reverse the condition of increased oxidative stress, chronic inflammation, and endothelial dysfunction underlying the development of preeclampsia. Many ongoing randomized clinical trials are going to confirm the preliminary data regarding the role of pravastatin in reversing.[53–55]

Follow-up during and after pregnancy

As about 90% of women have at least one CV risk factor and the best prevention strategies start decades before CVD manifestations, close cooperation with obstetricians and gynecologists, the so called "healthcare team for women", is decisive in ensuring prompt identification and management of CV risk factors.[56] Patient education and awareness about their CV risk, as well as healthcare providers understanding and knowledge about adequate lifestyle counseling and the importance of a careful assessment of traditional and nontraditional CV risk factors, must be pursued. The latest AHA scientific statement about APOs and CVD risk suggests that, in the postpartum period, a detailed follow-up plan should be arranged, with scheduled clinical evaluations (comprehensive of CV risk factors assessment and couseling about the role of a healthy lifestyle to enhance cardiometabolic and mental health) at 6 weeks, 8-12

weeks, 6 months, and 12 months after delivery.[1457] Special attention should be given to the fourth trimester, as interventions that occur in this period can significantly improve short and long-term CV health.[58] Clinicians' evaluation should be focused on three points: 1) assessment of CV risk factors, medication adherence, mental health, family and social care, lactation support; 2) counseling about the importance of adherence to LE8 and lactation, stress and mental issues coping, short and long-term risk of APOs; 3) treatment of cardiometabolic and mental disorders.[59] CV risk screening should include the assessment of 1) medical history: smoking habit; PA; past medical history or first-degree family history of CVD, diabetes, hypertension; lactation; 2) physical check of cardiometabolic profile: body mass index, waist circumference, resting heart rate and blood pressure; 3) laboratory testing for lipid and glycemic profile.[60] General practitioners should play the most relevant role in long-term CV risk prevention and screen all patients for APOs within 1 year postpartum. Annual CVD risk assessment should be offered to women experiencing any APOs. Women experiencing HDPs should be strictly monitored for resolution of hypertension for 12 weeks postpartum and should be counseled about their increased risk for hypertension and CVD. Women experiencing GDM should be screened for inadequate glycemic control at 4-12 weeks postpartum and counseled about their increased risk of diabetes.[61] PA, family support, adequate quality of life and mental health, and breastfeeding should be encouraged in every woman, the latter being associated with reduced maternal risk of CVD outcomes.[61] However, few interventions have been evaluated to lower CVD risk in women with APOs, and many studies are ongoing regarding the use of pharmacological and non-pharmacological approaches in this clinical scenario. In particular, the incidence of type 2 diabetes (T2D) in women with a history of GDM seems to be reduced by statin therapy, whereas the role of metformin for women with a history of preeclampsia is still under study.[62] It is mandatory to develop interventions that are personalized according to the individual social scenario and incorporated within health care systems, to identify the barriers to interventions and to standardize the postpartum follow-up, to ensure that each healthcare provider's role is clearly outlined to effectively prevent and manage CVD, not only in maternal population but also in the offspring.[1,58,63]

How to follow-up the woman at risk during pregnancy and post-pregnancy: The diabetologist's point of view

Hyperglycemia

Hyperglycemia complicates one in six (16.7%) pregnancies worldwide, either occurring before (preexisting diabetes) or during pregnancy - GDM or diabetes first detected in pregnancy.[64] GDM is responsible for ~80% of cases and is currently defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes[65]; ~90% of cases occurs in low- and middle-income countries. The main pathophysiological mechanisms underlying GDM are basically those sustaining T2D: IR and β-cell dysfunction. Briefly, insulin sensitivity declines in the third trimester of pregnancy as an adaptive physiological response to favor the increase in free fatty acid and glucose blood levels to be used as an energy source by the fetus.[66] In normal pregnancy, the pancreatic β-cells are able to compensate by increasing the release of insulin, whereas dysfunctional β-cells show impaired response to IR, leading to the occurrence of GDM.[67] GDM is associated with a greater risk of short-term acute pregnancy and delivery compcations, but also to long-term offspring and maternal cardiometabolic risk. The continuous and independent association between neonatal adiposity (large for gestational age, LGA) and maternal glycemia was demonstrated by the cornerstone The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study across the full range of maternal glucose levels, even below the threshold for overt diabetes.[68] Longitudinal studies subsequently confirmed that offspring exposed to GDM *in utero* have higher adiposity and a worse metabolic profile across the life course than their unexposed counterparts.[69–71] Importantly, the treatment of GDM, including dietary advice, blood glucose monitoring, and insulin therapy when needed, reduces the rate of serious perinatal outcomes.[72] Thus, it is key to identify women who are planning pregnancy with undiagnosed prediabetes or diabetes and with BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian American individuals and or age ≥35 years who have one or more of the risk factors for GDM, as reported in Table 1. According to the criteria of the American Diabetes Association (ADA), women should be screened before 15 weeks of gestation for abnormal glucose metabolism in terms of fasting plasma glucose (FPG) levels ≥110–125 mg/dL (6.1–6.9 mmol/L) or glycated hemoglobin ($HbA1_C$) 5.9–6.4% (41–47 mmol/mol) or by performing a 75g glucose tolerance test (OGTT).[65] Mothers at high risk (Table 1) not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy should be screened at 24–28 weeks for GDM by performing a 75-g OGTT with different and stringent glucose cut-off values that were associated with adverse outcomes in the HAPO trial (FPG ≥ 92 mg/dL (≥ 5.1 mmol/L); 1-hour ≥ 180 mg/dL (≥ 10.0 mmol/L); 2hours ≥ 153 mg/dL (≥ 8.5 mmol/L).[73] The test is interpreted as positive for GDM if one or more values exceed their corresponding thresholds. Glucose targets to be achieved in pregnancies complicated by GDM are very stringent to minimize acute and long-term fetal complications. Glucose targets suggested by the ADA are FPG<95 mg/dL (<5.3 mmol/L; one-hour postprandial glucose <140 mg/dL (<7.8 mmol/L) or two-hour postprandial glucose <120 mg/dL (<6.7

Table 1
Main risk factors for GDM.[65]

Family history (first-degree relative) for diabetes and/or cardiovascular disease
High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Hypertension (≥130/80 mmHg or on therapy for hypertension)
High-densily lipoprotein (HDL) cholesterol level <35 mg/dL (<0.9 mmol/L) and/or a triglyceride level >250 mg/dL (>2.8 mmol/L)
Prediabetes ($HbA1_C$ ≥5.7% [≥39 mmol/mol], IGT, or IFG) or previous history of GDM
Polycystic ovary syndrome
Human immunodeficiency virus (HIV), exposure to high-risk medicines, history of pancreatitis

mmol/L). Of note, approximately one-third of women who have suffered from GDM will develop T2D later in life[74] as a result of the β-cell defect, explaining the impaired compensation for the increased IR of late pregnancy (resulting in GDM) and the progressive deterioration of glucose tolerance outside of pregnancy.[75,76] As women with previous GDM display a high risk of developing diabetes in life, it is recommended that they undergo a 75-g OGTT at 4–12 weeks postpartum and have lifelong screening for the development of prediabetes or diabetes at least every three years.[77] A large pooled analysis of nine studies yielded data from 5,390,591 women (101, 424 CV events) demonstrating that women with previous GDM display a twofold higher risk of future CVD compared with their peers within the first decade postpartum.[77] After the exclusion of T2D, GDM was associated with more than a 1.5-fold higher risk of CVD.[77] The Nurses' Health Study II cohort study, including US female nurses aged 25 to 42 years who reported at least one pregnancy ($\geq$ six months) at 18 years or older across their reproductive life span followed for 30 years (1989-2019), showed that previous GDM was directly associated with the risk of CVD mortality (HR, 1.59; 95% CI, 1.03-2.47).[78] Indeed, GDM patients display endothelial dysfunction as shown by decreased flow-mediated dilation parameters and serum nitric oxide (NO) levels with an increase in serum endothelin-1 secretion in comparison with normal glucose tolerance group, which may represent a shared alteration underlying preeclampsia.[79] It is possible that the pregnancy related stress may unmask pre-existing CVD predispositions linking GDM to future risk of CVD. GDM severity, maternal obesity, self-identified race/ethnicity, poor diet, and low PA levels predict postpartum T2D and CVD in women.[80] For these reasons, it is mandatory that women with previous GDM receive long-term advice on weight management and lifestyle behavior changes.[65]

Preterm delivery and weight of newborn at delivery

Due to the advances in genetics and epigenetics, innovative insight into the pathophysiology of GDM has been highlighted; moreover, novel approaches to identify women at high risk for progression to postpartum cardiometabolic disease are now available.[76] The association of epigenetic changes, including DNA methylation and circulating microRNAs, with GDM has also been examined. MicroRNAs have proven efficacious in predicting both the development of GDM and its long-term cardiometabolic complications, and they have been associated with PD.[81,82] The relationship between PD and the future CV maternal health has been previously established.[82] The pathophysiological changes underlying PD are strictly related to placental failure, which is frequently linked to HDPs. HDPs, especially preeclampsia, could cause up to a quarter of the association between PD and future maternal CV hospitalization.[83] On the other hand, some infections, specifically related to vessel inflammation, could be associated to PD. During the SARS-CoV2 pandemic, it has been widely demonstrated that specific alteration in endothelium and microvessels (and the related damage to placental trophoblast syncytialization with vascular injuries) could explain PD among infected mothers.[84,85] Moreover, the fetus' weight at birth should be carefully considered when a woman's CV risk profile is evaluated, as fetal micro- and macrosomia are both strictly related to an unfavorable maternal CV risk profile. IUGR is frequently linked to uteroplacental insufficiency due to poor implantation of the spiral arteries and subsequent increased placental vascular resistance, which has similarities to the early pathophysiology of preeclampsia, and could lead to PD.[69] Instead, fetal macrosomia is frequently associated with GDM and high HbA1c levels.[86] This aspect has detrimental effects on the maternal and offspring's CV systems. In fact, intrauterine hyperglycemia exposure has long-term adverse effects on the offspring's CV health. Moreover, infants of diabetic mothers have higher carotid artery intima-media thickness at birth.[18,87] Otherwise, in a recent study, authors found that birth weight percentiles do not explain the predisposition to CV complications in the offspring of hypertensive mothers.[88] Body composition estimation may explain this increased risk. Furthermore, it has been demonstrated that the preconceptional CV condition, specifically pre-pregnancy total cholesterol, is negatively associated with gestational age, and bidirectional associations were found between own birthweight, childhood body mass index (BMI), pre-pregnancy BMI, and child's birth weight.[89] Notwithstanding, some protective factors should be included in the evaluation. Breastfeeding is associated with a lower risk of later-life cardiometabolic and CVD independent of socioeconomic and lifestyle factors.[90] A meta-analysis of 8 studies involving more than one million women highlighted that lifetime breastfeeding duration is progressively associated with CVD risk reduction.[91] Furthermore, the maternal age at the last spontaneously arising pregnancy with regular delivery of a vital baby must be considered. The later the pregnancy naturally occurs, the better the woman's underlying CV condition is.[92]

Future strategies

The exploration of perinatal CV health opens avenues for future research and clinical practice aimed at improving outcomes for both mothers and offspring. While current research emphasizes the physical aspects of pregnancy, further investigations into the interplay between mental and CV health are warranted. Understanding how perinatal stress, anxiety, and depression influence maternal and fetal CV outcomes could inform targeted interventions. As our understanding of CV risk factors expands, there is a need for comprehensive risk assessment models tailored to pregnant women. Integrating traditional risk factors with sex and gender-specific variables, reproductive history, and genetic predispositions could refine risk stratification and enable personalized preventive strategies.[14] Implementing structured perinatal follow-up plans allows for continuous monitoring of CV risk factors and early detection of complications. Longitudinal studies tracking long-term maternal and offspring health can provide insights into the long-term impact of pregnancy-related conditions on CV outcomes. Promoting perinatal healthy lifestyle behaviors, including nutrition and PA, remains mandatory. Future interventions may leverage digital health platforms, remote monitoring technologies, and behavioral interventions to enhance adherence and engagement among pregnant women.[93] Investigating the efficacy and safety of pharmacological interventions in reducing the risk of pregnancy-related complications and subsequent CVD represents a promising avenue. Rigorous clinical trials are needed to establish evidence-based guidelines for medication use in this population. Fostering interdisciplinary

collaboration among obstetricians, gynecologists, cardiologists, and general practitioners is essential for delivering comprehensive care to pregnant women and optimizing CV outcomes.[94] Integrated care pathways and shared decision-making frameworks can enhance coordination and communication among healthcare professionals.[13] Addressing disparities in access to care and healthcare outcomes among pregnant women from diverse socioeconomic and racial/ethnic backgrounds is critical.[95] Future initiatives should prioritize equitable access to preventive services, prenatal care, and CV risk management interventions to mitigate disparities and improve maternal and offspring health outcomes. Finally, encouraging women with knowledge about perinatal CV health empowers them to make informed decisions and actively participate in their care. Culturally sensitive educational materials, support groups, and community-based interventions can promote health literacy and self-management skills among pregnant women.[96,97] By embracing these future perspectives and advancing research in perinatal CV health, and beyond, we can strive to improve the well-being of mothers and offspring and reduce the burden of CVD across generations.[1]

Conclusions

Pregnancy and the reproductive age are a valuable source of information on women's and offspring's CV health, risk factors, and predisposing conditions to CVD. It is therefore very useful to consider this information in the anamnestic phase for a correct and accurate maternal and offspring's CV risk stratification.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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