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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Sex Differences in Cardiovascular Disease and Unique Pregnancy-Associated Risk Factors in Women

Anna C. OKelly, MD, MPhil[1]
Michael C. Honigberg, MD, MPP[1,2,*]

Address
[1]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[*,2]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 185 Cambridge Street, CPZN 3.187, Boston, MA, 02114, USA
Email: mhonigberg@mgh.harvard.edu

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Abstract

Purpose of review Cardiovascular disease is the leading cause of mortality in women. Beyond conventional cardiovascular risk factors, women additionally face sex-specific cardiovascular disease risk factors, which include a history of adverse pregnancy outcomes. Adverse pregnancy outcomes include the hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm delivery, and small-for-gestational age delivery. Here, we review sex differences in cardiovascular disease with an emphasis on pregnancy-associated risk factors and discuss implications for the prevention and treatment of cardiovascular disease in women.
Recent findings Adverse pregnancy outcomes, especially the hypertensive disorders of pregnancy, have been linked to diverse cardiovascular conditions, accelerated cardiovascular aging, and multimorbidity. Chronic hypertension appears to be a key mediator of accelerated cardiovascular disease risk in women with hypertensive disorders of pregnancy. Recent genetic analyses suggest a shared genetic predisposition between adverse cardiometabolic traits and development of hypertension in pregnancy. Mechanisms linking gestational diabetes, preterm delivery, small-for-gestational age delivery, and infertility to cardiovascular disease are less well understood.

Summary The mechanisms linking adverse pregnancy outcomes to future cardiovascular disease remain incompletely understood. Further research is needed to better understand this relationship and the implications of adverse pregnancy outcomes for cardiovascular disease prevention.

Introduction

Cardiovascular disease is the leading cause of death in both men and women worldwide [1, 2••, 3–5]. By 2030, annual deaths from cardiovascular disease will exceed 22 million according to World Health Organization estimates [6, 7]. Despite its considerable burden in both sexes, cardiovascular disease in women is often under-recognized and under-treated [8–16]. Women are less likely to receive guideline-directed prevention and treatment [14, 17], reach recommended cardiovascular risk factor targets [12, 18], or be included in cardiovascular disease research studies and clinical trials [17, 19, 20]. These increasingly recognized disparities have spurred efforts to raise awareness of women's heart health, including advocacy initiatives and guidelines focused on cardiovascular disease in women [10, 21, 22].

In addition to conventional cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia [23], women face unique sex-specific risk factors. In particular, adverse pregnancy outcomes (APOs), including the hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus, small-for-gestational-age (SGA), and preterm delivery, as well as premature menopause, are increasingly recognized as harbingers of elevated future cardiovascular disease risk [24••]. Professional societies, including the American Heart Association, European Society of Cardiology, and American College of Obstetricians and Gynecologists, now recommend that clinicians elicit an obstetric and gynecologic history when assessing a woman's cardiovascular risk [2, 21–23, 25]. Here, we review sex differences in cardiovascular disease with an emphasis on pregnancy-associated risk factors and discuss implications for the prevention and treatment of cardiovascular disease in women.

Sex differences in conventional cardiovascular risk factors

Common lifestyle and behavioral factors influence the development of cardiovascular disease in sex-specific ways. Smoking, though more common in men, disproportionately increases cardiovascular disease risk in women [1, 26]. The sex-specific relative risk attributable to smoking is higher in women than in men by 25% for coronary artery disease (CAD) [27, 28], by 50% for myocardial infarction (MI) [27], and is equal or higher for stroke [29]. Similarly, meta-analyses indicate that diabetes increases the risk of CAD and stroke to a greater extent in women [1, 17, 23, 30–35]. Obesity is associated with greater relative risk of hypertension [26] and CAD [36] in women. Among individuals with established cardiovascular disease, women tend to present to care later, are more likely to minimize their symptoms, and are less likely to take prescribed medications [10–13, 18, 37, 38].

Sex differences also exist with respect to relative risk factor control. Women are less likely to meet physical activity recommendations and more likely to be obese [18, 33, 39–42]. This trend appears to begin in childhood and continues through adulthood, possibly attributable to gender differences in perceived safety exercising in public and to challenges in balancing professional and

familial responsibilities which disproportionately fall on women [18, 33, 39–42]. Women are also less likely to reach target glucose and HbA1c levels than men and have worse dyslipidemia control [12, 18, 37]. Sex differences in risk factor control also extend to women who develop acute coronary syndrome (ACS) [43–46]. These sex differences are especially pronounced at older ages, which disproportionately affects women given their greater longevity [11, 12, 37, 40, 47].

Sex differences in cardiovascular diseases

Atherosclerotic cardiovascular disease

Though CAD is more common in men [7, 30], it is the leading cause of death in both sexes [10, 30, 45, 48]. CAD prevalence in women has been rising steadily over time [10, 30, 35, 48], and among individuals > 75 years old, those who experience ACS are more likely to be female [47]. Although younger individuals who experience ACS are more likely to be male, ACS in younger women still occurs [47]. In an international registry of 1182 patients ≤ 45 years old with ACS between 2010 and 2016, 187 (15.8%) were women [49]. In a French study examining demographics of patients hospitalized with ACS, 20.4% of those < 65 years of age were women [50]. Young women with ACS are more likely than other individuals to experience ACS caused by non-atherothrombotic mechanisms, such as spontaneous coronary artery dissection (SCAD) and vasospasm [51–53]. Women additionally present with a broader range of symptoms, although "typical" chest pain remains the most common presenting complaint in ACS across age and sex demographics [43, 51, 54, 55]. Both of these factors may influence why ACS in young women is more likely to be missed and underdiagnosed [47, 56–58], and why the mortality rate from MI in this demographic is as much as twice that of men [47, 56–58]. Even when appropriately diagnosed, women who present with ACS are less likely to undergo percutaneous coronary intervention (PCI) or receive appropriate guideline-directed therapy [14, 59, 60]. Women with ACS are more likely to experience recurrent major adverse cardiovascular events (MACE) even after receiving appropriate therapy [10, 11, 43–46, 51, 54, 57, 61, 62]; this finding may be partially attributable to older average age and a higher average burden of underlying comorbidities among women versus men with ACS [45].

Heart failure

Women represent approximately half of the US population with heart failure (HF), and the incidence of HF in women is rising [15, 63]. Women are more likely than men to have HF with preserved ejection fraction (HFpEF), possibly due to their greater predilection to develop elevated arterial stiffness, concentric LV hypertrophy, and diastolic dysfunction [47, 64–66]. Women's unique distribution of comorbitidies, including higher rates of obesity and the metabolic syndrome, microvascular dysfunction [47, 63–65, 67–70], and increased longevity likely contribute as well.

HF is associated with sex differences in quality of life and mortality. Women tend to be more symptomatic from HF than men with similarly severe HF [47, 64–66], and data suggest that both HFpEF and HF with reduced ejection fraction (HFrEF) more negatively affect women's quality of life [64, 65, 71].

Somewhat paradoxically, data also show that outcomes, including mortality, are better in women with HF overall [64, 71–74]. However, women with very advanced HF are less likely than men to be referred for ventricular assist devices or transplants, and those who are listed have worse waitlist outcomes and are less likely to undergo transplantation [47, 75, 76].

Valvular heart disease

In both sexes, the two most common causes of valvular heart disease are aortic stenosis and mitral regurgitation [77, 78]. Aortic stenosis is most commonly age-related, which affects women disproportionately given their greater longevity. Aortic stenosis presents with similar symptoms in men and women, though women tend to be more symptomatic [47, 77, 79]. Transcatheter aortic valve replacement (TAVR) is associated with greater short- and mid-term survival at 1 month [80, 81], 1 year [80–82], and 5 years [82] in women, though is also associated with a higher rate of peri-procedural and procedural complications [47, 80–85].

Mitral regurgitation is more common in women [47]. As with aortic stenosis, women with mitral regurgitation tend to be more symptomatic from their disease [77, 86–88]. They are also less likely than men to undergo mitral valve surgery [77, 86–88] and tend to have worse post-procedural outcomes and survival when they do [47, 86, 89, 90]. Worse preoperative risk profiles in women are thought to underpin these sex differences [86, 89, 90].

Pregnancy-related cardiovascular risk factors

Adverse pregnancy outcomes include the hypertensive disorders of pregnancy (e.g., gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome), gestational diabetes mellitus, preterm delivery, and delivery of a small-for-gestational-age infant. Given that these APOs are associated with a 50–300% increased risk of future cardiovascular disease [8, 11, 17, 93, 94••, 95], they are increasingly recognized as important cardiovascular risk signals in women. As noted earlier, professional societies now recommend that an obstetrical history be taken as part of a woman's cardiovascular history [2••, 21–23, 25]. These questions should focus on number of pregnancies and their outcomes, maternal complications and APOs during pregnancy, and any overt residual cardiovascular risk factors that persist after delivery (Table 1).

A history of HDP (e.g., preeclampsia, gestational hypertension), gestational diabetes, SGA, and/or preterm delivery is now incorporated as a "risk-enhancing factor" in multi-society guidelines for the management of cholesterol and primary cardiovascular prevention [2••, 24••]; specifically, per guidelines, a history of ≥ 1 APO among women at intermediate (7.5–20%) 10-year risk of atherosclerotic cardiovascular disease should prompt initiation of primary prevention statin therapy. APOs thus signal an early opportunity to examine modifiable cardiovascular disease risk factors in middle-aged women, a group whose cardiovascular disease risk may be particularly underestimated and undertreated [3, 12]. The following sections review specific APOs and their links to future cardiovascular disease (Fig. 1).

Table 1. Screening guideline for asking about pregnancy and cardiovascular disease risk

How many pregnancies have you had?
How many miscarriages have you had? • Do you know why the miscarriage occurred?
Were any of your babies born prematurely? • Do you know why they were born prematurely? • Did you go into spontaneous labor early or were you induced? • How many weeks before your due date were they born?
How much did your babies weigh at birth?
Did you have preeclampsia in any pregnancies?
Did you have high blood pressure in any pregnancies?
Did you have new diabetes in any pregnancies?
Did you gain significant weight during pregnancy? • Did you return to your pre-pregnancy weight after delivery?
Have you had high blood pressure since your last pregnancy?

Adapted from Hauspurg et al., 2018 [8]; Seely et al., 2015 [91]; Roberts and Catov, 2012 [92]

Hypertensive disorders of pregnancy

The association between HDP and future cardiovascular disease is now well established. Though most data on cardiovascular risk focus on preeclampsia, associations are also well described for gestational hypertension. Cardiovascular risks likely extend to HELLP syndrome and eclampsia as well, although data are sparse for these much rarer conditions. The public health repercussions of HDP and preeclampsia are significant, with a recent US study reporting that 15% of US women experience some form of HDP, and 7.5% experience preeclampsia, at least once [96••].

HDP have now been associated with the future development of diverse cardiovascular diseases. The most widely reported cardiovascular disease association with HDP is CAD [97, 98••, 99–102]. Women with prior HDP develop both subclinical/non-obstructive atherosclerosis as well as clinically significant

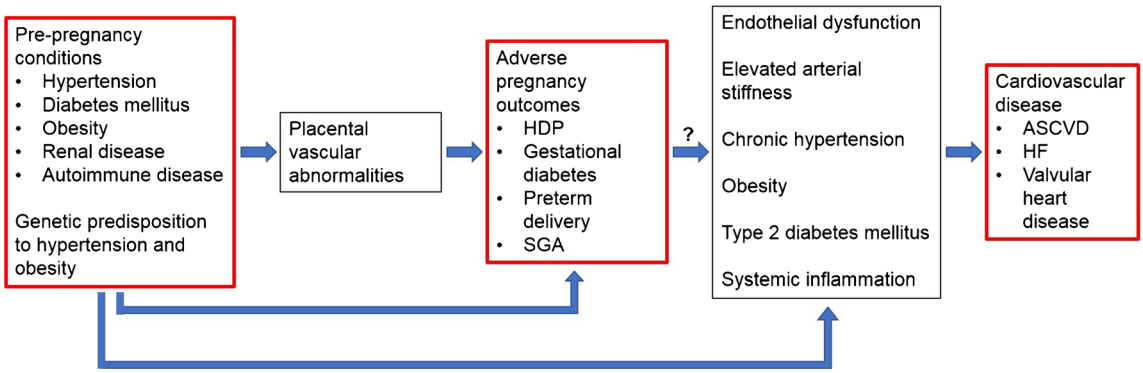

Fig. 1. Proposed mechanisms linking pre-pregnancy risk factors to adverse prengnacy outcomes and subsequent cardiovascular disease.

adverse cardiovascular events (e.g., myocardial infarction and stroke) at accelerated rates compared with unaffected women [97, 98••, 99, 100, 102].

HDP are also associated with higher incidence of heart failure. Specifically, HDP are associated with peripartum cardiomyopathy, a form of cardiomyopathy with reduced ejection fraction that develops toward the end of of pregnancy or first five postpartum months [21, 103–105]; with dilated cardiomyopathy arising beyond the typical window for peripartum cardiomyopathy [106, 107]; and possibly with future HFpEF over the longer term [108–114], though evidence for an association with HFpEF has been largely speculative to date. Studies have also demonstated increased risks of valvular disease including aortic stenosis and mitral regurgitation [98••], as well as atrial fibrillation [115], and venous thromboembolism [101] following HDP. HDP are associated with increased lifetime mortality, with more severe HDP associated with even higher risk of subsequent cardiovascular disease and mortality [108, 116, 117]. Garovic et al. recently demonstrated that women with a history of HDP accumulate multimorbidity over the long term more rapidly than unaffected women, consistent with a syndrome of accelerated cardiovascular aging [96••, 118].

Multiple mechanisms linking HDP to future cardiovascular disease have been proposed, including inflammation [119], endothelial dysfunction [120], and increased arterial stiffness [65, 121]. Adverse cardiometabolic risk factors also likely mediate, at least in part, the relationship between HDP and future cardiovascular disease. HDP are strongly associated with future risk of metabolic syndrome [97, 122–124], including dyslipidemia [91, 98••, 125••], type 2 diabetes mellitus [98••, 125••, 126], and weight gain and being overweight or obese [127, 128]. Women with HDP are at particularly elevated risk of developing chronic hypertension [98••, 99–101, 108, 123, 125••]. Chronic hypertension appears to be a key mediator linking HDP to subsequent cardiovascular disease, accounting for 50–80% of the excess risk for future cardiovascular disease in women with history HDP in studies employing causal mediation analysis to test mediation effects [98••, 106, 129]. The strong epidemiological association between HDP and chronic hypertension and other cardiometabolic risk factors begs the question of whether HDP are merely a signal of latent cardiometabolic risk, are causal for development of cardiometabolic risk factors and cardiovascular disease, or both [8, 91] .

In the "risk signal" framework, pregnancy serves as a "stress test" that unmasks vulnerable cardiometabolic and cardiovascular substrate [8, 130–133]. In support of this hypothesis, Honigberg et al. recently found that genetic predisposition to hypertension and elevated body-mass index (BMI) were associated with the development of HDP using a Mendelian randomization approach [134]. This finding implies both that elevated blood pressure and BMI are causal for HDP and that HDP signal an increased underlying genetic risk for these cardiometabolic traits. Although HDP are also epidemiologically linked to type 2 diabetes, there was no genetic association between type 2 diabetes and HDP identified.

Alternatively, preeclampsia may be an inciting event that triggers the development of cardiovascular disease [91, 135] or accelerates the natural age-related development of cardiovascular disease [98••]. This causal relationship is supported by its dose-responsive nature, whereby more severe or preterm HDP as well as recurrent HDP are associated with higher future cardiovascular disease

burden [120, 136]. Honigberg et al. also observed that polygenic risk of HDP was associated with a small but significant increase in blood pressure in middle age, suggesting that causality between elevated blood pressure and HDP may be bidirectional [134].

Gestational diabetes mellitus

Gestational diabetes is associated with twofold future risk of cardiovascular disease [8, 137, 138]. Though subsequent development of type 2 diabetes may partially mediate the association between gestational diabetes and cardiovascular disease, gestational diabetes has also been independently associated with future cardiovascular disease even without interim development of type 2 diabetes [8, 137–141]. Though the relationship—like other APOs and future cardiovascular disease—is incompletely understood, potential mechanisms include elevated systemic inflammation [141–143] and endothelial dysfunction [144, 145], leading to both microvascular disease and macrovascular atherosclerosis [138, 146]. Gestational diabetes, like HDP, may also constitute a risk signal for latent cardiometabolic risk [138, 147].

Preterm delivery and small-for-gestational age delivery

Preterm delivery and SGA delivery are also associated with increased future maternal cardiovascular disease [1, 23, 133, 148]. Preterm delivery is associated with up to threefold increased risk of future coronary artery disease and cardiovascular mortality [149] independent of other pregnancy complications and other cardiovascular disease risk factors [148–154]. Both preterm and SGA delivery are related to future cardiovascular disease risk in a dose-dependent fashion, with more severe pregnancy complications associated with more severe future cardiovascular disease [150, 151, 155].

The proposed mechanisms linking both preterm delivery and fetal growth disorders to future cardiovascular disease are similar and overlapping with those relating HDP and gestational diabetes to cardiovascular disease. These include demographic factors such as smoking and minority race [149, 156, 157], traditional cardiovascular risk factors [149, 156, 157], and increased inflammation [148, 149, 152••], endothelial dysfunction [149, 158•], and elevated arterial stiffness [149]. Placental growth factor (PIGF) is a specific maternal vascular factor that has been implicated, with low PIGF in pregnancy associated with SGA infants, abnormal cardiovascular remodeling, and increased risk of postpartum cardiovascular disease [101, 159–161]. Future research is needed to clarify whether additional unique mechanisms link SGA and preterm delivery to future cardiovascular disease.

Infertility and parity

Maternal reproductive characteristics have been shown to influence future cardiovascular disease risk. A history of both miscarriage or stillbirth, as well as significant multiparity, are associated with increased future cardiovascular disease risk, including CAD [162–165]. Though the exact mechanism linking infertility and cardiovascular disease remains somewhat unclear, both infertility and future cardiovascular disease may be attributed to shared comorbidities including obesity [166], polycystic ovarian syndrome (PCOS) [93, 167, 168], thrombophilia [169], and poor overall health [170].

The relationship between parity and cardiovascular risk appears to be J-shaped, with both nulliparity and significant multiparity associated with increased cardiovascular risk [171–176]. Though the precise nadir varies across studies, the lowest risk is generally seen around 2–4 births, and more than 5–6 pregnancies are consistently associated with elevated future cardiovascular risk [93, 168, 173, 177–179]. Significant multiparity (> 5 births) may be associated with cardiovascular disease because of lasting physiologic effects of multiple pregnancies: normal pregnancy is associated with increased insulin resistance, activation of the renin-angiotensin-aldosterone system, and changes in endothelial function, and these adaptations may exert enduring cardiovascular effects [168, 173, 177, 179–181]. Multiparity is also associated with more weight gain and higher BMI [171, 173, 182], dyslipidemia [173, 183], type 2 diabetes [184, 185], and subclinical atherosclerosis [186]. Socioeconomic factors also contribute substantially—if not more—to the observed J-shaped relationship. Low socioeconomic status and related health behaviors are associated with both increased parity and cardiovascular disease burden [177, 187, 188]. Higher parity is also associated with higher levels of emotional and financial stress, which may further contribute to cardiovascular disease development [171, 179, 188–190].

Implications of adverse pregnancy outcomes for cardiovascular disease prevention

As discussed above, adverse pregnancy outcomes serve as a risk signal for elevated future cardiovascular disease risk. Three time points present themselves as potential windows for preventive care: prior to pregnancy, during pregnancy, and after pregnancy. Ensuring that women have access to routine preventive healthcare pre-conception optimizes their chances of uncomplicated pregnancy. Given that approximately one in five women will have at least one APO associated with increased risk of incident cardiovascular disease, close monitoring of at-risk women throughout pregnancy allows early detection of any complications that may arise [133, 191]. For women identified to be high risk for preeclampsia based on clinical risk factors, low-dose aspirin has been shown to decrease preclampsia risk by 10–24% [192, 193]. Furthermore, ensuring preconception and postpartum adherence to primary prevention guidelines including screening lipids and weight management is especially important. Maintaining normal weight and blood pressure after pregnancy complicated by HDP has been associated with reduced risk of postpartum chronic hypertension, which may in turn reduce the risk of future cardiovascular disease, although prospective, randomized weight loss-focused studies in this population are lacking [98••, 134, 194]. Given elevated genetic risks of hypertension and obesity associated with HDP, aggressive lifestyle modification for primordial and primary prevention of cardiovascular risk factors seems prudent; research to identify targeted risk-reduction strategies and therapeutics is needed. Ongoing follow-up after pregnancy ensures that cardiovascular risk factors are properly identified and managed.

No evidence-based guidelines exist to guide postpartum follow-up after pregnancy complicated by APO. Current expert recommendation is that

follow-up should occur within 3–6 months after delivery [133, 195]. In the USA, efforts to ensure follow-up may be hindered among women who lack of health insurance [196, 197]. Furthermore, it may be logistically challenging for new mothers to attend frequent clinic appointments while caring for a new infant, and it is unclear how to best provide follow-up [191, 195, 198]. Smith et al. established a postpartum clinic with standardized follow-up at 6 months [191], a time-point deemed to be soon enough after delivery to provide an opportunity to discuss lifestyle interventions and prevent risk factors from becoming entrenched, and coinciding with society guidelines regarding follow-up for women whose pregnancies were complicated by gestational diabetes [191, 199]. Relying on subspecialty clinics, however, may be inefficient and unrealistic [198]. As such, efforts to bolster education for all providers—primary care physicians, obstetricians, cardiologists, and others—who are involved in the care of postpartum patients will help to ensure a history of APO is appropriately identified and followed [198].

Future directions

Numerous unanswered questions about optimizing postpartum care for women with APOs remain (Table 2) [8, 91]. Better defining the optimal follow-up schedule and risk reduction strategies after APOs will help ensure identified risk factors and health needs are properly addressed. More collaborative multidisciplinary and cross-specialty work is needed to develop best practices to ensure enhanced longitudinal follow-up [25, 133]. Mechanistic understanding of causal pathways is currently lacking but may ultimately enable the development of novel and targeted preventive therapies [91]. Overall, pregnancy provides a unique opportunity for early identification of women at increased cardiovascular disease risk to implement preventive care and improve long-term health outcomes.

Table 2. Key knowledge gaps and areas for future research regarding adverse pregnancy outcomes, infertility, and future cardiovascular disease

Are adverse pregnancy outcomes causal for future cardiovascular disease, are they a signal of shared upstream risk, or both?
How do cardiometabolic implications differ among the hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, and small-for-gestational age delivery?
Are hypertensive disorders of pregnancy associated with heart failure with reduced ejection fraction, heart failure with preserved ejection, or both?
Why are hypertensive disorders of pregnancy associated with valvular heart disease? What is the mechanism of mitral regurgitation in this population?
Why are women with infertility predisposed to develop cardiovascular disease?
How can providers most effectively optimize women's overall health and reduce cardiovascular risk following adverse pregnancy outcomes?
How can mechanistic understanding between adverse pregnancy outcomes and cardiovascular disease ultimately lead to novel preventive strategies and therapies?

Compliance with Ethical Standards

Conflict of Interest

Michael C. Honigberg reports grants from U.S. NHLBI (T32HL094301-07) during the conduct of the study. Anna C. O'Kelly declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent Statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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This study of parous women in the UK Biobank found that women with a history of hypertensive disorders of pregnancy had elevated arterial stiffness decade postpartum compared to unaffected women, and that these women developed coronary artery disease, heart failure, aortic stenosis, and mitral regurgitatoin at accelerated rates. This constellation of findings generated the hypothesis that hypertensive disorders of pregnancy are associated with a syndrome of accelerated cardiovascular aging. The study additionally identified subsequent development of chronic hypertension as a key mediator between hypertensive disorders of pregnancy and future cardiovascular disease risk.

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