News in December 2024

1. Gender disparity in morbidity and mortality among patients with ST-elevation myocardial infarction due to spontaneous coronary artery dissection complicated by cardiogenic shock

Background

There is limited data on gender differences among patients with spontaneous coronary artery dissection (SCAD) who present as ST-elevation myocardial infarction (STEMI) and develop cardiogenic shock (CS).

Objectives

To describe outcomes of SCAD patients presenting with STEMI and CS and outline the differences between men and women.

Methods

We queried the US Nationwide Readmissions Database (NRD) from January 2016 to December 2020 to identify patients with SCAD presenting with STEMI who developed CS. We compared the characteristics, trends, and outcomes between men and women in this cohort.

Results

Out of 582,633 hospitalizations with STEMI, 0.2 % (1176 patients) had SCAD, of which 346 (29.4 %) had CS. There was no difference in median age between men and women (64 years (IQR 57–71) vs. 63 years (IQR 49–72), p = 0.181). Men had a higher prevalence of prior myocardial infarction (MI) (14.2 % vs. 6.2 %, p = 0.021). The overall mortality rate of SCAD patients with AMI-CS was 28.2 %, with no difference between men and women. Patients with SCAD who had CS and underwent CABG had a mortality of 20.3 %. ECMO was used in 6.1 % of SCAD patients presenting with STEMI and CS, with a survival rate of 49.9 %.

Conclusion

There were no differences in the baseline characteristics, rates of revascularization, or in-hospital mortality between men and women who had SCAD complicated by CS (SCAD-CS). Patients with SCAD-CS patients who underwent CABG had around 80 % in-hospital survival. CABG should be considered as a method of revascularization in this patient cohort.

2. High BMI in Pregnancy Could Increase Offspring Risk for Insomnia

Although insomnia is highly prevalent and affects up to 1 in 4 adults, the causes of insomnia have not been elucidated. Some research has found that genetics, reproductive hormones, and medical comorbidities may affect insomnia risk. However, the teratogenic effects of maternal BMI on offspring insomnia risk have been unexplored.

To address this knowledge gap, investigators from University of Michigan School of Public Health conducted a nationwide cohort study using data from the Swedish Medical Birth Register (SMBR) and linked national data. Individuals (n=3,281,803) born between 1983 and 2015 were evaluated for insomnia from 2 to 25 years of age on the basis of maternal BMI before 14 weeks' gestation. The investigators also performed a sibling analysis with 1,724,473 full siblings from 771,024 families to test for unmeasured family cofounders for insomnia risk.

During a median (interquartile range [IQR]) follow-up of 17.9 (9.2-26.3) years, 7154 individuals were diagnosed with insomnia at a median (IQR) age of 17.1 (14.0-22.4) years, and 3210 siblings were diagnosed with insomnia at 16.0 (12.7-19.1) years of age.

By 25 years of age, the risk for insomnia was 1.10% among offspring to a mother with an early pregnancy BMI of 35.0 kg/m2 or greater, 0.73% for 30.0 to 34.9 kg/m2, 0.47% for 25.0 to 29.9 kg/m2, 0.31% for 18.5 to 24.9 kg/m2, and 0.27% for less than 18.5 kg/m2.

By 25 years of age, the risk for insomnia was 0.27% among offspring to a mother with a an early pregnancy BMI of less than 18.5 kg/m^2, 0.31% for

18.5 to 24.9 kg/m², 0.47% for 25.0 to 29.9 kg/m², 0.73% for 30.0 to 34.9 kg/m², and 1.10% for a BMI of 35.0 kg/m² or greater.

In the sibling cohort, insomnia risk was similarly associated with maternal BMI in a dose-dependent manner, in which risk was lowest among offspring with the lowest maternal BMI (0.25%) and highest for those whose mothers had a high BMI in pregnancy (0.95%).

Relative to 18.5 to 24.9 kg/m2, offspring insomnia risk was significantly elevated with maternal BMIs of 35.0 kg/m2 or greater (adjusted hazard ratio [aHR], 2.11; 95% CI, 1.83-2.45), 30.0 to 34.9 kg/m2 (aHR, 1.60; 95% CI, 1.45-1.77), and 25.0 to 29.9 kg/m2 (aHR, 1.22; 95% CI, 1.14-1.30).

The investigators also found that additional significant predictors of offspring insomnia included pregnancy and birth outcomes of congenital malformations (HR, 3.71; 95% CI, 3.09-4.45), maternal infection (HR, 3.35; 95% CI, 2.56-4.39), chorioamnionitis (HR, 2.58; 95% CI, 1.17-5.70), prolonged labor (HR, 2.53; 95% CI, 1.69-3.78), pregestational diabetes (HR, 1.48; 95% CI, 1.03-2.13), gestational diabetes (HR, 1.45; 95% CI, 1.12-1.87), placental abruption (HR, 1.49; 95% CI, 1.12-1.96), maternal sleep disorder (HR, 1.70; 95% CI, 1.51-1.92), and smoking during pregnancy (HR, 1.44; 95% CI, 1.36-1.52).

Offspring insomnia risk was also higher with medically indicated extremely preterm birth compared with term or post-term birth (HR, 2.31; 95% CI, 1.42-3.77), birth before 32 weeks' (HR, 1.44; 95% CI, 1.11-1.87) and birth at 32 to 36 weeks' (HR, 1.16; 95% CI, 1.04-1.29) compared with 37 weeks' or after, and elective (HR, 1.37; 95% CI, 1.23-1.52) or emergency (HR, 1.25; 95% CI, 1.12-1.39) cesarean section compared with non-instrumental vaginal birth.

Further, the investigators found the following demographic variables to be significantly associated with offspring insomnia risk: maternal birth in a non-Nordic country, paternal age, maternal age, maternal education, mother not cohabitating with the father-to-be, and parity.

These study results demonstrated that maternal BMI was associated with offspring insomnia risk in a dose-response manner that was not fully explained by factors shared within families. “This novel finding gives evidence to the pre- and perinatal origins of insomnia and suggests potentially new biological mechanisms for insomnia development,” the investigators concluded. “Furthermore, it may be useful in identification of individuals at higher risk of insomnia, allowing for earlier treatment of insomnia and better downstream outcomes.

3. Small Amounts of Vigorous Activity Beneficial for Nonexercising Women

Small amounts of vigorous intermittent lifestyle physical activity (VILPA) are associated with significant reductions in the risk for major adverse cardiovascular events (MACE) among nonexercising women, according to a study published online Dec. 3 in the British Journal of Sports Medicine.

Emmanuel Stamatakis, Ph.D., from the University of Sydney, and colleagues examined sex differences in the dose-response association of VILPA with MACE and its subtypes among individuals self-reporting no leisure-time exercise and no more than one recreational walk per week in the U.K. Biobank. Analyses were also conducted among those self-reporting participation in leisure-time exercise and/or recreational walking more than once a week.

The researchers identified 331 and 488 MACE among 13,018 women and 9,350 men, respectively, during a 7.9-year follow-up. There was a near-linear dose-response association seen for daily VILPA duration with all MACE, myocardial infarction, and heart failure. Dose-response curves were less clear in men, with less evidence of statistical significance. Women's median daily VILPA duration of 3.4 minutes was associated with hazard ratios of 0.55 and 0.33 for all MACE and heart failure, respectively, compared with those with no VILPA. Hazard ratios of 0.70, 0.67, and 0.60 were seen for all MACE, myocardial infarction, and heart failure, respectively, in association with women's minimum doses of 1.2 to 1.6 minutes of VILPA per day.

"Although these findings are observational, they suggest that VILPA may be a promising physical activity target for cardiovascular disease prevention among nonexercising women," the authors write.

4. Tibolone, Oral Estrogen-Progestin Therapy Linked to Risk for Heart Disease

Use of tibolone or oral estrogen-progestin therapy is associated with an increased risk for specific cardiovascular diseases, according to a study published online Nov. 27 in The BMJ.

Therese Johansson, from Uppsala University in Sweden, and colleagues examined the effect of contemporary menopausal hormone therapy on the risk for cardiovascular disease according to the route of administration. The nationwide emulated target trial involved 919,614 women aged 50 to 58 years between 2007 and 2020 without hormone therapy use in the previous two years. Women were assigned to one of eight treatment groups.

Overall, 77,512 women were initiators of any menopausal hormone therapy and 842,102 women were noninitiators. The researchers found that tibolone was associated with an increased risk for cardiovascular disease compared with noninitiation (hazard ratio, 1.52) in intention-to-treat analyses. The risk for ischemic heart disease was increased for initiators of tibolone or oral estrogen-progestin therapy (hazard ratios, 1.46 and 1.21, respectively). The risk for venous thromboembolism was increased in association with oral continuous estrogen-progestin therapy, sequential therapy, and estrogen-only therapy (hazard ratios, 1.61, 2.00, and 1.57, respectively). In per-protocol analyses, tibolone was associated with a higher risk for cerebral infarction and myocardial infarction (hazard ratios, 1.97 and 1.94, respectively).

5. Hypertensive Disorders of Pregnancy Increase the Risk for Myocardial Infarction

BACKGROUND

Angiographic evidence of the anatomy of coronary arteries and the type of coronary artery lesions in women with a history of hypertensive disorders of pregnancy (HDP) are poorly documented.

OBJECTIVES

This study sought to determine the role of a history of HDP as a unique risk factor for early coronary artery disease (CAD) and type of acute coronary syndrome (ACS) (ie, atherosclerotic vs myocardial infarction with nonobstructive coronary arteries [MINOCA]) in women who underwent coronary angiography.

METHODS

This study used a population-based cohort of parous female patients with incident CAD who underwent coronary angiography and age-matched control subjects. The SYNTAX (Synergy between PCI [percutaneous coronary intervention] with TAXUS [Boston Scientific] and Cardiac Surgery) score was assessed to determine the complexity and degree of CAD; MINOCA was diagnosed in the presence of clinical acute myocardial infarction in the absence of obstructive coronary disease.

RESULTS

A total of 506 parous female Olmsted County, Minnesota (USA) residents had incident CAD and angiographic data from November 7, 2002 to December 31, 2016. Women with HDP were younger than normotensive women at the time of the event (median: 64.8 years vs 71.8 years; P = 0.030). There was a strong association between HDP and ACS (unadjusted P = 0.018). Women with HDP compared with women with normotensive pregnancies were more likely to have a higher SYNTAX score (OR: 2.28; 95% CI: 1.02-5.12; P = 0.046), and MINOCA (OR: 2.08; 95% CI: 1.02-4.25; P = 0.044).

CONCLUSIONS

A history of HDP is associated with CAD earlier in life and with a future risk for myocardial infarction with both obstructive and nonobstructive coronary arteries. This study underscores the need for timely detection and treatment of nonobstructive disease, in addition to traditional risk factors.

6. Sex Differences in FFR-Guided PCI vs. CABG in the FAME 3 Trial

Study Questions:

Do outcomes differ by sex after fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) using current-generation drug-eluting stents (DES) compared with coronary artery bypass grafting (CABG)?

Methods:

Data from FAME 3 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 3), an investigator-initiated, multicenter, randomized controlled trial, were used for the present analysis. This trial compared FFR-guided PCI with current-generation DES versus CABG among patients with three-vessel coronary artery disease (CAD) (≥50% diameter stenosis based on visual estimation) and deemed amenable to both FFR-guided PCI and CABG through clinical judgment. Patients with involvement of the left main coronary artery were not included. This prespecified subgroup analysis compared the incidence of major adverse cardiac and cerebrovascular events (MACCE) according to sex, defined as the composite of all-cause death, myocardial infarction (MI), stroke, or repeat revascularization at 3 years.

Results:

A total of 1,500 patients were randomized to either FFR-guided PCI (n = 757) or to CABG (n = 743), of which 17.7% (n = 265) were women. Women participants were older and more likely to have hypertension and a family history of CAD, while men were more likely to be smokers. Women had fewer lesions and less complex CAD (via anatomical SYNTAX score) compared to

men. Women had a significantly higher risk of MACCE at 3 years compared with men after CABG (18.1% vs. 11.7%; adjusted hazard ratio [aHR], 2.07; 95% confidence interval [CI], 1.19-3.60). For PCI, women had a similar risk of MACCE at 3 years compared with men (18.2% vs. 19.1%; aHR, 1.27; 95% CI, 0.79-2.03). Women undergoing PCI had a similar risk of MACCE at 3 years compared with CABG (aHR, 1.15; 95% CI, 0.62-2.11). By contrast, men undergoing PCI had a higher risk of MACCE at 3 years compared with CABG (aHR, 1.68; 95% CI, 1.25-2.25; p for interaction = 0.142), which was mainly driven by a higher risk of MI (aHR, 2.11; 95% CI, 1.26-3.56; p for interaction = 0.102) and repeat revascularization (aHR, 2.26; 95% CI, 1.47-3.47; p for interaction = 0.071).

Conclusions:

The authors conclude that in the FAME 3 trial, at 3 years, women have similar outcomes with FFR-guided PCI compared with CABG, whereas men have improved outcomes with CABG.

Perspective:

These data may assist clinicians in revascularization management of CAD (i.e., PCI vs. CABG); however, it should be noted that the number of women included was relatively small and the study population was predominantly White race. Furthermore, as noted by the investigators, longer-term outcomes may assist in more nuanced understanding of gender differences in revascularization management.

7. Cardiovascular Disease Among Women and Birthing Individuals After Delivering a Child With Congenital Heart Disease

Background

Individuals have a higher risk of cardiovascular disease later in life if they give birth to a child with congenital heart disease (CHD). The mechanism of this association has not been well documented.

Objectives

The authors aimed to describe the prevalence of cardiovascular disease and risk factors in women and birthing individuals 18 to 23 years after delivery of a child with CHD compared to normative data.

Methods

A cross-sectional survey was distributed to mothers whose infants with CHD had undergone cardiac surgery in 1998 to 2003 and previously enrolled in a prospective observational study. We compared rates of cardiovascular disease and risk factors to age- and sex-matched parous women and birthing individuals from National Health and Nutrition Examination Survey.

Results

An attempt was made to contact 533 mothers; 222 (42%) completed the survey. The mean age was 52 years, 86% were White, and 69% completed college. Common cardiovascular risk factors were high cholesterol (32%), hypertension (27%), preterm delivery (32%), and hypertensive disorder of pregnancy (13%). Overall, 15.3% reported presence of cardiovascular disease as defined by atherosclerotic cardiovascular disease, heart failure, valvular disease, or arrhythmia. A higher severity of child's CHD was significantly associated with self-reported maternal cardiovascular disease ($P = 0.03$). Compared to National Health and Nutrition Examination Survey participants, rates of atherosclerotic cardiovascular disease and cardiovascular risk factors were similar.

Conclusions

Women and birthing individuals whose children had CHD had similar rates of cardiovascular risk factors and disease at 18 to 23 years after delivery, compared to age- and sex-matched parous controls. Higher severity of child's CHD was associated with increased risk of maternal cardiovascular disease, an association that should be evaluated in future studies.

8. Female-Specific Factors Don't Enhance Common Risk Calculators

Known risk factors for CVD among women, when added to commonly used risk calculators, don't improve the tools' ability to tease out which female patients need to start an antihypertensive or lipid-lowering medication, according to new data from the UK Biobank.

The study, published online recently in Circulation: Cardiovascular Quality and Outcomes, considered a slew of potential contributors—both together and individually—to CV risk: early menarche, preeclampsia, and endometriosis, among others. Yet none further honed the calibration and discrimination of the Pooled Cohort Equation - Atherosclerotic Cardiovascular Disease (PCE-ASCVD), QRISK2, and PREDICT models.

Lead author Jenny Doust, PhD (The University of Queensland, Herston, Australia), told TCTMD that this was a bit unexpected given the long history of research showing a link between these risk factors and subsequent disease.

"Several studies have shown that women who have a history of the female-specific risk factors considered in our study are at increased risk of CVD," she wrote in an email. But because these studies didn't include clinical values for blood pressure and cholesterol, they can't be used as evidence to guide treatment.

While women with a history of these female-specific conditions "are at an increased risk of CVD relative to other women," what their own findings

suggest is that “having these risk factors doesn’t add to your estimate of risk in the next 5-10 years if you are using a risk calculator such as the PCE-ASCVD,” said Doust.

She emphasized that risk factors unique to female patients should still “absolutely” be considered in clinical settings. “It should be routine for clinicians to specifically ask women about their reproductive history [and] use the presence of these risk factors as an early warning of the risk of later potential risk of CVD and a marker of overall risk of CVD,” Doust advised.

Notably, the current study did not include an evaluation of PREVENT, a calculator released in late 2023 that creates sex-specific estimates of 10- and 30-year CVD risk in patients as young as 30 years, an age when the many pregnancy-related risk factors may be at play; however, PREVENT does not include these female-specific risk factors.

UK Biobank Data

Doust and colleagues turned to the UK Biobank to identify 135,142 women ages 45 to 69 years (mean 57.5 years) who were free from CVD at baseline (2006-2010) and followed through the end of 2019.

The researchers first created Cox proportional hazards models based on the risk factors already included in three contemporary calculators, the PCE-ASCVD, developed in 2013, as well as the 2008 QRISK2, and the 2018 PREDICT.

They then added various female-specific risk factors to the calculations: early menarche (< 11 years); endometriosis; excessive, frequent, or irregular menstruation; miscarriage; number of miscarriages; number of stillbirths; infertility; preeclampsia or eclampsia; gestational diabetes (without subsequent type 2 diabetes); premature menopause (<40 years); early menopause (<45 years); and natural or surgical early menopause (menopause <45 years or timing of menopause reported as unknown and oophorectomy reported at age <45).

During follow-up, the incidence of CVD was 5.3 cases per 1,000 person-years with PCE-ASCVD and PREDICT and 5.2 cases per 1,000 person-years with QRISK.

At the outset, the c-indices for the PCE-ASCVD, QRISK2, and PREDICT models were 0.710, 0.713, and 0.718, respectively. When adding all the female-specific risk factors together to the models, the c-indices were 0.712, 0.715, and 0.720, respectively.

> **It should be routine for clinicians to specifically ask women about their reproductive history [and] use the presence of these risk factors as an early warning of the risk of later potential risk of CVD and a marker of overall risk of CVD.**Jenny Doust

Considered individually, the female-specific risk factors failed to make a difference in c-index, net reclassification index, integrated discrimination index, slope of the regression line for predicted versus observed events, or Brier score for any of the calculators.

“It seems that the female-specific risk factors are early markers of the risk of developing more intermediate risk factors for cardiovascular disease: higher blood pressure, cholesterol, and glucose levels,” said Doust. “Once you include these in the risk prediction, the female-specific risk factors do not add to our ability to predict who will and won’t develop overt CVD.”

An editorial by Setareh Salehi Omran, MD, and Michelle Leppert, MD (both from University of Colorado Anschutz Medical Campus, Aurora), like Doust, also cautions against dismissing female-specific risk factors in clinical practice or in the creation of future scores.

While the characteristics “may not improve CVD risk calculators, these risk factors still play an important role in comprehensive cardiovascular risk stratification in women,” they point out. “Many of these risk factors occur earlier in life and upstream of the causal pathway leading to traditional risk

factors and then CVD, which represents a valuable opportunity for earlier intervention in women." Premature menarche has been tied to later development of hypertension, hypercholesterolemia, and diabetes, for instance, as have adverse pregnancy outcomes.

Moreover, the relationship between these risk factors and CVD may be influenced by more-traditional risk factors, Omran and Leppert explain. "Because these mediators are already included in the risk model, the upstream effects of the exposure may be masked. However, this does not mean that female-specific risk factors do not ultimately affect CVD occurrence."

Instead of abandoning these female-specific factors, it makes more sense to see them as an early chance to identify and prevent the traditional risk factors before they occur, they suggest, adding closer monitoring and lifestyle changes could be protective. "Clinicians should continue to obtain a comprehensive obstetric and gynecological history when assessing CVD risk in women," the editorialists urge.

Doust said she agrees with these takeaways. "These risk factors [need] to be considered as early markers of CVD," she noted. Also, "women with a history of these conditions [need] to be closely monitored for the development of later hypertension, hypercholesterolemia, and diabetes."

9. Potential Sex Differences Seen for FFR-Guided PCI vs CABG in FAME 3

mong patients with three-vessel coronary disease, the outcomes of PCI guided by fractional flow reserve versus CABG may differ between men and women, a prespecified subanalysis of FAME 3 indicates.

Through 3 years, women did just as well with either FFR-guided PCI or CABG in the trial, whereas men had significantly lower rates of MACCE (all-

cause death, MI, stroke, or repeat revascularization) when they underwent surgery, researchers led by Kuniaki Takahashi, MD, PhD, and Hisao Otsuki, MD, PhD (both from Stanford University, CA), report.

“These sorts of studies are really important, because women and men behave differently with respect to their response to our therapies. It’s critical to look at sex differences in cardiovascular medicine trials,” senior author William Fearon, MD (Stanford University and VA Palo Alto Health Care, Palo Alto, CA).

He acknowledged, however, that FAME 3 had a low proportion of women, who made up just 17.7% of the trial population. “Clearly, we need more data. This is just a start,” said Fearon. “But I do believe it provides important, clinically useful information.”

The findings were published online recently in JACC: Cardiovascular Interventions.

Revascularization Outcomes by Sex

Prior research has shown that cardiovascular outcomes often differ between women and men, but there is limited contemporary evidence in the area of coronary revascularization, Fearon said, noting that much of the existing data come from older studies like the SYNTAX trial. In SYNTAX, women had lower 5-year mortality after CABG versus PCI, a difference that was not seen in men and disappeared by 10 years.

To get a more up-to-date look at potential sex differences in an era with improved revascularization techniques and medical therapy, he and his colleagues performed a prespecified subgroup analysis of FAME 3, which compared fractional flow reserve (FFR)-guided PCI using current-generation DES and CABG in patients with three-vessel CAD who were eligible for either procedure. PCI was not shown to be noninferior to CABG at 1 year, with no significant difference between procedures in terms of death, MI, or stroke at 3 years.

Of the 1,500 patients in the trial, only 265 were women, who were older (mean age 67.4 vs 64.6 years), more frequently had hypertension and a family history of CAD, and were less likely to be smokers compared with men. The complexity of CAD was less in women versus men.

During PCI, female patients received fewer stents and had a shorter total stent length per patient. For CABG, women received fewer arterial grafts and were less likely to receive a left internal mammary artery (LIMA) graft and multiple arterial grafts.

MACCE incidence through 3 years of follow-up was higher in women versus men irrespective of revascularization type (18.1% vs 15.4%; adjusted HR 1.43; 95% CI 1.01-2.03). This was driven by women having a greater risk compared with men in the CABG arm (18.1% vs 11.7%; adjusted HR 2.07; 95% CI 1.19-3.60), with no difference between the sexes in the PCI arm (18.2% vs 19.1%; adjusted HR 1.27; 95% CI 0.79-2.03).

Because women tend to be at higher risk due to their older age and greater comorbidity burden, “it may not be that surprising that the outcomes after bypass surgery in women were worse than they were compared with men,” Fearon said.

The impact of the two revascularization strategies appeared to differ between women and men, although none of the P values for the interactions were statistically significant. Among female patients, MACCE risk was similar when comparing FFR-guided PCI to CABG (adjusted HR 1.15; 95% CI 0.62-2.11). But for men, PCI was associated with a greater 3-year risk of MACCE versus CABG (adjusted HR 1.68; 95% CI 1.25-2.25), attributed mostly to higher risks of MI and repeat revascularization.

The lack of a difference between revascularization strategies in women is “partly because women are at higher risk for CABG because of their age and comorbidities, their smaller arteries, things like that,” Fearon proposed. “But also, they may gain more benefit from FFR guidance because they have more negative lesions that don’t need PCI, so their PCIs were less complex.

They had shorter stents and fewer stents. So I think it's a combination of things that led to the similar outcomes."

These results may differ from what was seen in the SYNTAX trial "because FAME 3 mandated FFR-guided PCI, which may be even more beneficial in women compared with men," Fearon speculated.

As for the better outcomes with CABG for men, he said, "the sort of simplistic way of looking at it is men are able to tolerate CABG better and they don't incur the early risk, but they do gain the long-term benefit."

A Call for More Research in Women

Commenting for TCTMD, cardiothoracic surgeon Jennifer Lawton, MD (Johns Hopkins Medicine, Baltimore, MD), said she wasn't surprised by the findings since the subgroup analysis in the paper reporting the 1-year results indicated that men did better with CABG, with no difference between strategies in women.

She added, however, that it's difficult to draw any firm conclusions due to the low number of women in the trial, which points to a larger issue.

"Women are not enrolled in clinical trials as much and in many of the original trials, the data are based on results in men," Lawton said. She noted that "we're all looking forward to the [ROMA:Women] trial," which is enrolling only female patients, and said it's important to have more women serve as principal investigators for trials. That has been shown to lead to better representation of female participants.

When it comes to personalizing revascularization choices by sex, "I don't think we're quite there yet," Lawton said. "I have an algorithm that I use when I go and see any patient, and no matter what the patient looks like or the sex of the patient, I try to do all arterial grafting in all patients. I try not to be biased from the beginning walking into the room."

While awaiting much-needed additional data in women, this analysis of FAME 3 does not support a change in practice, she said. “But it does tell us that in terms of FFR-guided decisions, at least in the short term, which is 1- and now 3-year data, CABG is better for men for three-vessel disease.”

In an accompanying editorial, Enrico Fabris, MD, PhD (University of Trieste, Italy), and Roxana Mehran, MD (Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY), note that “there are still many unknowns regarding potential differences in outcomes between men and women that may translate in personalized approaches for coronary revascularization. Therefore, it is crucial to reassess strategies for treating women and address the significant gap in understanding whether sex should influence the choice between PCI and CABG. These knowledge gaps must be addressed.”

10. Women Report Less Poststroke Medication Adherence Than Men

Poststroke medication nonadherence is more prevalent among U.S. women than men, according to a study published online Dec. 4 in the Journal of the American Heart Association.

Chen Chen, M.P.H., from the University of Michigan School of Public Health in Ann Arbor, and colleagues examined sex differences in poststroke medication adherence, overall and by drug class. The analysis included 1,324 patients with first-ever ischemic stroke with self-reported medication adherence evaluated at 90 days after stroke.

The researchers found that women were more likely to report nonadherence to cholesterol-lowering drugs (prevalence ratio [PR], 1.80; 95 percent confidence interval [CI], 1.14 to 2.84) and antiplatelets (PR, 1.53; 95 percent CI, 1.003 to 2.34). Results were attenuated when adjusting for obesity, whereas adjusting for age, marital status, access to care, smoking, and alcohol consumption accentuated sex differences. The sex difference for nonadherence to cholesterol-lowering drugs was modified by race and

ethnicity, with a larger sex difference in Mexican American individuals (PR, 3.00; 95 percent CI, 1.65 to 5.48) versus non-Hispanic White individuals (PR, 1.30; 95 percent CI, 0.52 to 3.27). There were no significant sex differences for nonadherence to antihypertensives and overall nonadherence.

"More specifically designed studies among U.S. populations are needed to replicate our findings and understand the unique pattern of sex differences in nonadherence to different secondary stroke prevention drugs," the authors write.

11. Risk of MI After Pregnancy With Hypertension

Study Questions:

What is the anatomy of coronary arteries and the type of coronary artery lesions in women with a history of hypertensive disorders of pregnancy (HDP)?

Methods:

This study used a population-based cohort of parous female patients with incident coronary artery disease (CAD) who underwent coronary angiography and age-matched control subjects. The SYNTAX (Synergy between PCI [percutaneous coronary intervention] with TAXUS [Boston Scientific] and Cardiac Surgery) score was assessed to determine the complexity and degree of CAD; myocardial infarction with nonobstructive coronary arteries (MINOCA) was diagnosed in the presence of clinical acute myocardial infarction (MI) in the absence of obstructive coronary disease. Acute coronary syndrome (ACS) was defined as patients with MI or those with PCI or coronary artery bypass grafting with ST-segment elevation MI, non–ST-segment elevation MI, or unstable angina, on clinical chart review. Multivariable models were adjusted for the following risk factors for CAD unless otherwise specified: age, body mass index, smoking history, hyperlipidemia, diabetes, and hypertension.

Results:

A total of 506 parous female Olmsted County, Minnesota (USA) residents had incident CAD and angiographic data from November 7, 2002–December 31, 2016. Women with HDP were younger than normotensive women at the time of the event (median: 64.8 years vs. 71.8 years; p = 0.030). There was a strong association between HDP and ACS (unadjusted p = 0.018). In unadjusted models, the odds of overall HDP were significantly higher in ACS cases compared with control subjects (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.07-2.05; p = 0.018), and results remained significant after independent adjustment of covariates. Women with HDP compared with women with normotensive pregnancies were more likely to have a higher SYNTAX score (OR, 2.28; 95% CI, 1.02-5.12; p = 0.046) and MINOCA (OR, 2.08; 95% CI, 1.02-4.25; p = 0.044).

Conclusions:

The present study reports several novel findings regarding HDP and the future risk for CAD by using a population-based cohort. First, women with a history of HDP on average experience CAD events 7 years earlier than women with a history of normotensive pregnancies. Second, there is a strong association between HDP and ACS that remained significant after controlling for demographic variables and comorbidities. Third, among ACS cases, women with a history of HDP compared with women with normotensive pregnancies were more likely to have a higher atherosclerotic burden, as demonstrated by the SYNTAX score, and a diagnosis of MINOCA.

Perspective:

Given the substantial evidence, a history of HDP is included as a nontraditional, sex-specific cardiovascular disease (CVD) risk factor in recent guidelines. Such inclusion is important because the increased risk in women cannot be fully accounted for by the prevalence of traditional risk factors. Whether HDP facilitate subsequent CVD because of shared traditional risk factors and pathophysiological pathways or whether distinct

mechanisms independent of conventional risk factors are playing a role is essentially unaddressed in the literature. These data demonstrate that nonatherosclerotic disease could play a significant role in the origin of ACS in 18% (i.e., one in five) of women with a history of HDP.

In this study, although most women with ACS and a history of HDP had clear evidence of MINOCA, one-third developed MI because of medical conditions leading to a mismatch in myocardial oxygen supply and demand, as in type 2 MI. Although the exact pathophysiology by which HDP promote ACS remains to be determined, recognition of a history of HDP as an independent risk factor for ACS, particularly MINOCA, may help stratify women who would benefit from risk reduction strategies and provide a novel therapeutic target for improving prognosis in women with ACS.

12. Tackling change: menopause as a cardiovascular disease risk factor and the path to health equity

Introduction

Prevention as a way to decrease cardiovascular disease morbidity and mortality has long been promoted. Cardiovascular societies and organizations have argued that an ounce of prevention is worth a pound of cure, producing significant reductions in cardiovascular disease mortality and prolonging lives.

Initiatives to decrease risk through nutrition, exercise, and healthy life choices have reaped benefits, but some cardiovascular risks are inescapable, particularly for women. For example, cardiovascular disease is a leading cause of mortality associated with pregnancy,1 and while pregnancy is typically—but not universally—a choice, many of the cardiovascular risks of pregnancy are inescapable. Poverty increases cardiovascular disease morbidity and mortality,2 and women are disproportionately impoverished. There are strong arguments that some of the risks faced by women are not

biologically based and that entrenched sociological inequities have powerful roles in driving cardiovascular disease.3

One of the most significant risk factors for cardiovascular disease in women is unavoidable: menopause. Women who live beyond their reproductive phase experience menopause, whether it is following a gradual, decade-long disruption in ovarian function, or the abrupt loss of functional ovaries through oophorectomy or other events that cause a sudden loss of ovarian function. Despite the virtual certainty of menopause, the mechanisms by which menopause shapes cardiovascular risk remain largely unknown, presenting a substantial obstacle to the development of interventions that mitigate risk and improve women's health.

2. Obstacles to health

Why is there such a significant knowledge gap with menopause? Surprisingly, the connection between menopause and cardiovascular health was unknown until a 1976 report from the Framingham study identified a connection.4 Interestingly, comments from a journal editor immediately following the study harshly and dismissively criticized the proposed link.

While the relationship between menopause and cardiovascular disease is confirmed, little headway in understanding the mechanisms beyond the decline of oestrogens has occurred. This embarrassing lack of progress derives in large part from under-investment in women's health research: globally only 4% of research and development budgets are directed to women's health issues, of which the vast majority goes to cancer and reproductive research. In North America, Canadian and US federal health funding agencies dedicate 7 and 11% of their budgets to women's health, respectively. It is clear why our knowledge of women's health generally—and cardiovascular health specifically—is indigent when systems generating information are starved for resources.

A second factor inhibiting advances in understanding the health effects of menopause has been the lack of an animal model for fundamental scientific research. Ovariectomized animals have traditionally been used to investigate physiological changes and pathological risks of menopause, but this model does not include the transitional phase of perimenopause, and it removes androgen-producing elements of the ovaries that remain intact after menopause. Lab animals like mice do not experience menopause, which precludes aging animals as a model.

Ground-breaking work by Dr Patricia Hoyer's group at the University of Arizona led to the development of an animal model of menopause in which the injection of 4-vinylcyclohexene diepoxide (VCD) induces a gradual disruption in ovarian function that closely mimics the human condition.5 The ability to study the complex physiological changes of menopause in lab animals represents a significant advance in the ability to investigate not only the impact of menopause on cardiovascular disease but also a host of alterations that arise postmenopause.

3. Foundational research

The development of the physiologically relevant VCD model of menopause creates an unprecedented opportunity to advance our understanding of women's heart health through fundamental research. The model has been used to investigate the impact of menopause on atherosclerosis,6 blood pressure regulation,7 and ischaemic injury,8 identifying molecular changes and mechanisms of increased cardiovascular disease risk.

One of the most powerful elements of the VCD-induced model of menopause is the ability to study perimenopause and its impact on health for the first time in animal models. We showed that cardiac myofilaments are dynamically affected during perimenopause,9 as is calcium removal by SERCA2a.10 These studies allowed the temporal characterization of molecular alterations in the cardiovascular system that occur in conjunction with perimenopausal changes in ovarian hormone synthesis.

The exploration of the chronological development of menopause is critical for the creation of rationally designed therapies that specifically target maladaptive changes in a time-sensitive manner. Clinical trials examining the effectiveness of oestrogen replacement therapy revealed that the timing of treatment onset was critical for maximum benefits, with interventions starting within 10 years of menopause being the most effective. We reported that the cardiac response to oestrogen receptor agonists varies across perimenopause,9 an effect that could explain discrepant findings concerning oestrogen replacement therapy and the role of timing. Our data on perimenopause suggest that the window of therapeutic opportunity might be earlier than the onset of menopause and that perimenopausal interventions should be considered to mitigate cardiovascular changes that underlie postmenopausal risk.

4. Path forward

The creation of an animal model of menopause that faithfully recapitulates the complex hormonal changes in a temporally relevant manner represents a critical step in understanding how menopause acts as a powerful risk factor for cardiovascular disease. This model also offers the opportunity to discover the molecular changes underlying risk and creates the opportunity to design mitigating interventions.

While basic science research is vital to understand the effects of menopause and improve women's cardiovascular health, there remain significant obstacles on the path towards gender equity: social barriers, including the disproportionate number of girls and women who are impoverished, permit and promote poor health. Unequal access to care in the form of economic barriers and systematic discrimination cause women to receive less guideline-driven care. Finally, the underinvestment in research focused on women's health perpetuates the knowledge gap that bolsters health inequality.

Some movement to erase gender-based health discrepancies have started, with global leading efforts by the Canadian Institutes of Health Research to ensure a greater inclusion of females in health research, and a plan by the US National Institutes of Health to invest $12 billion in new funding for women's health research. True equity requires broader societal change, including in health, research, and academic organizations, and demands stable financial support. The payoff from these investments will be substantial: a 2024 report by the McKinsey Group estimates that closing the knowledge gap in women's health will erase 75 million years of life lost due to poor health or early death each year and boost the global economy by $1 trillion annually, far outweighing the financial costs of equality.

Without these changes, unavoidable risk factors like menopause will continue to exert needless and negative impacts on women's health, which costs us all.

13. CORSWO Model Stratifies Women According to Coronary Risk

The Coronary Risk Score in Women (CORSWO) can predict the risk of major adverse cardiovascular events (MACE), according to a study published online Dec. 5 in Radiology: Cardiothoracic Imaging.

Guillermo Romero-Farina, M.D., Ph.D., from Vall d'Hebron University Hospital in Barcelona, Spain, and colleagues conducted a retrospective analysis including 2,226 women from a cohort of 25,943 consecutive patients referred for clinical gated single-photon emission computed tomography myocardial perfusion imaging. The occurrence of MACE was assessed during a mean follow-up of 4 ± 2.7 years.

The researchers found that 148 of 1,460 women in the training group had MACE (2.6 percent per year). The best model to predict MACE in women had an area under the receiver operating characteristic curve (AUC) of 0.80 and included age older than 69 years, diabetes mellitus, pharmacologic test, ST-segment depression (≥1 mm), myocardial ischemia >5 percent, perfusion

defect at rest >9 percent, perfusion defect at stress >6 percent, and end-systolic volume index >15 mL. The model achieved moderate performance during validation in 766 women (AUC, 0.78). CORSWO allowed for stratification into four risk levels: low, moderate, high, and very high. In women, the high and very-high risk levels predicted MACE, with excellent performance (AUC, 0.78).

"CORSWO is an effective tool to stratify the risk for MACE into four risk levels, including high and very-high risk, with good accuracy, although requiring multiple imaging variables," the authors write.

14. Cardiovascular Disease Among Women and Birthing Individuals After Delivering a Child With Congenital Heart Disease

Background

Individuals have a higher risk of cardiovascular disease later in life if they give birth to a child with congenital heart disease (CHD). The mechanism of this association has not been well documented.

Objectives

The authors aimed to describe the prevalence of cardiovascular disease and risk factors in women and birthing individuals 18 to 23 years after delivery of a child with CHD compared to normative data.

Methods

A cross-sectional survey was distributed to mothers whose infants with CHD had undergone cardiac surgery in 1998 to 2003 and previously enrolled in a prospective observational study. We compared rates of cardiovascular disease and risk factors to age- and sex-matched parous women and birthing individuals from National Health and Nutrition Examination Survey.

Results

An attempt was made to contact 533 mothers; 222 (42%) completed the survey. The mean age was 52 years, 86% were White, and 69% completed college. Common cardiovascular risk factors were high cholesterol (32%), hypertension (27%), preterm delivery (32%), and hypertensive disorder of pregnancy (13%). Overall, 15.3% reported presence of cardiovascular disease as defined by atherosclerotic cardiovascular disease, heart failure, valvular disease, or arrhythmia. A higher severity of child's CHD was significantly associated with self-reported maternal cardiovascular disease (P = 0.03). Compared to National Health and Nutrition Examination Survey participants, rates of atherosclerotic cardiovascular disease and cardiovascular risk factors were similar.

Conclusions

Women and birthing individuals whose children had CHD had similar rates of cardiovascular risk factors and disease at 18 to 23 years after delivery, compared to age- and sex-matched parous controls. Higher severity of child's CHD was associated with increased risk of maternal cardiovascular disease, an association that should be evaluated in future studies.

Introduction

Cardiovascular disease is the leading cause of death among women.**1** Hypertension continues to be the leading cardiovascular risk factor in women; however, sex-specific risk factors have been increasingly reported in the literature.**1** Women and birthing individuals who give birth to an infant with congenital heart disease (CHD) have been shown to have a higher risk of developing cardiovascular disease later in life, as well as a higher risk of all-cause and cardiovascular disease-specific mortality.**2**,**3** This association persists after controlling for traditional cardiovascular risk factors and preeclampsia, an adverse pregnancy outcome that occurs more commonly among women and birthing

individuals who deliver an infant with CHD compared to those whose infants do not have CHD.**4**,**5**

The mechanisms linking infant CHD with maternal acquired cardiovascular disease are not well understood. One proposed mechanism is angiogenic imbalance, which occurs when antiangiogenic factors in the maternal circulation lead to vascular damage. Other potential mechanisms include shared risk factors (such as hypertension or diabetes), genetic risk, increased psychosocial and financial stress of caring for a medically complex child, or a combination of multiple factors.**6-8**

The purpose of this study is to estimate the prevalence of cardiovascular disease and risk factors among a cohort of mothers who gave birth to an infant with CHD requiring surgical repair and to compare rates of cardiovascular disease to age-matched parous women and birthing individuals from a national sample. A unique feature of this study is access to details of the child's medical history and CHD; we were therefore particularly interested to see if there was an association between features of the infant's medical history, including severity of the infant's CHD, and later development of maternal cardiovascular disease.

Methods

Study population

We recruited mothers of children enrolled in a prospective study of neurodevelopmental who required surgical repair of CHD as neonates or infants between 1998 and 2003. Surgical interventions involved cardiopulmonary bypass, with or without deep hypothermic circulatory arrest. Exclusion criteria included: 1) multiple congenital abnormalities; 2) recognizable genetic/phenotypic syndrome other than chromosome 22q11.2 microdeletion syndrome; and 3) language other than English spoken in the home.**9** The participants in this cohort are contacted annually to complete surveys on medical, behavioral, and developmental outcomes, which have informed multiple studies investigating growth and neurodevelopmental

outcomes in this patient population.**9-12** Ours is the first study from this cohort to focus primarily on a nonpatient member of these families. The participants in this study will be referred to as the Maternal-Children's Hospital of Philadelphia (CHOP) (M-CHOP) cohort. The protocol for our study was approved by the Institutional Review Board at the CHOP. Written informed consent was obtained from all of the participants. Individual requests for access to deidentified data will be considered and require a data use agreement.

Survey development and administration

We developed a multifaceted survey designed to gather information regarding mothers' personal medical and pregnancy history, including pregnancy complications (eg, gestational hypertension, preeclampsia, gestational diabetes), cardiovascular risk factors (eg, hypertension, diabetes, high cholesterol, smoking history, and obesity), cardiovascular diagnoses (eg, coronary artery disease, stroke, heart failure or cardiomyopathy, valvular disease and arrhythmia), and family history of atherosclerotic cardiovascular disease (ASCVD) in first-degree relatives. Questions pertained to all pregnancies and were not limited to the pregnancy of the child with CHD. Survey questions were modeled after the Centers for Disease Control and Prevention (CDC)'s National Health and Nutrition Examination Survey (NHANES). NHANES is an annual survey of approximately 5,000 persons in the United States that requests information regarding demographic, socioeconomic, and health-related information.**13**

The mothers of 533 children enrolled in the original study were contacted via mail and email with information on enrolling in the study. There were 21 individuals who were not contacted for various reasons: the family withdrew from the original study (n = 5), the mothers were deceased (n = 11), the child was adopted as a newborn (n = 2), and there was no parent information available, or the parent/family specifically requested not to be contacted (n = 3). Potential participants with deceased children were contacted via mail and email to inquire initially about interest in participating in our study. If

participants responded affirmatively, they were then given the information to enroll in the study. All participants received a link to a REDCAP questionnaire that allowed their survey responses to be entered directly into a REDCAP database. Participants with incomplete responses were contacted by one of the study coordinators via phone or email to obtain complete and accurate data.

Covariates

Socioeconomic data were collected and participants' responses scored using the Hollingshead Four-Factor Index, which provides a family's composite socioeconomic status score incorporating education, occupation, sex, and marital status.**14** Hollingshead raw scores range from 8 to 66, with higher scores for higher levels of education and occupational prestige. The severity of CHD in the child was classified using previously described categories shown to predict perioperative mortality: class I, 2 ventricles with no aortic arch obstruction; class II, 2 ventricles with aortic arch obstruction; class III, single ventricle without arch obstruction; and class IV, single ventricle with arch obstruction.**15** D-transposition of the great arteries or tetralogy of Fallot are generally in class I, whereas hypoplastic left heart syndrome is class IV. CHD severity was also coded using a STAT score (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) of operative mortality, ranging from level 1 (lowest) to level 5 (highest).**16**

Outcomes

The primary outcomes were rates of self-reported cardiovascular disease and risk factors. Cardiovascular disease included ASCVD, structural heart disease, and arrhythmia. ASCVD was comprised of myocardial infarction, coronary artery disease, stroke, transient ischemic attack, or peripheral artery disease. Structural heart disease included valvular heart disease, cardiomyopathy, or heart failure. Lastly, arrhythmia was defined as supraventricular tachycardia, atrial fibrillation or flutter, ventricular tachycardia or fibrillation. The primary outcome differed according to the

primary and secondary analysis. The primary analysis was conducted exclusively in the M-CHOP cohort, among mothers who gave birth to an infant with CHD. In this analysis, we examined the association of infant CHD and maternal cardiovascular risk factors with maternal cardiovascular disease, as defined as a composite of ASCVD or structural heart disease. These conditions were combined, given shared risk factors.**17** Self-reported arrhythmia may include patients with palpitations or benign arrhythmias, and therefore was excluded from the primary outcome. The secondary analysis focused on comparing self-reported cardiovascular disease among participants in the M-CHOP to NHANES cohorts. In this analysis, cardiovascular disease included only ASCVD due to missing comparable variables for structural heart disease and arrhythmia in the NHANES data.

Analysis

Baseline characteristics and rates of self-reported cardiovascular risk factors and disease among participants who completed the survey were summarized using counts and percentages for categorical variables and means (or medians) and standard deviations (or 25th and 75th percentiles) for continuous variables. Baseline characteristics of participants who completed the survey were compared to the characteristics of participants in the original cohort who did not respond to the survey.

Fisher exact tests were used to test the associations between maternal cardiovascular risk factors and child's CHD class with self-reported maternal cardiovascular disease. Given the small sample size of participants with this outcome (n = 18), a limited number of traditional risk factors was identified a priori and tested using a Fisher exact test. These variables included high cholesterol, hypertension, diabetes, prediabetes, family history of ASCVD, smoking history, and elevated body mass index. The severity of the child's class of heart disease (class 1-4), as well as the associated mortality of the CHD surgical repair (STAT levels 1-5) were also examined. We also examined sex-specific risk factors including hypertensive disorders of pregnancy and gestational diabetes.

We then examined the relationship between our participants who completed the survey with nationally representative data from NHANES survey database. To make the cohorts comparable, we selected participants from NHANES data that had previously given birth, and then matched participants who completed the survey with NHANES participants 1:1 based on age (± 5 years), race (exact), and education (exact) using the Greedy algorithm. Descriptive statistics of each group after matching were examined along with any from the survey cohort that were unmatched. Fisher exact tests were used to compare the matched cohorts for prevalence of cardiovascular disease and risk factors. The criterion for statistical significance for all analyses was set at the nominal $\alpha = 0.05$ level and all data were analyzed using SAS version 9.4 (SAS Institute Inc).

Results

M-CHOP cohort survey results

Of the 533 mothers invited to participate, 226 (42%) completed the survey (**Figure 1**). A total of 4 of these 226 participants were excluded due to personal history of maternal CHD, leaving 222 participants who completed surveys and whose data were analyzed. Differences between responders and nonresponders are presented in **Supplemental Table 1**. Survey responders were more likely to be White, to have children with less severe CHD, and to have children who were less likely to be deceased.

Baseline characteristics of study participants and their children with CHD are presented in **Table 1**. Participants were predominantly White (n = 189, 85.5%) and married (n = 164, 74.2%) with a college degree (n = 152, 68.8%). The mean Hollingshead score was 49 ± 12, suggesting high socioeconomic status. Regarding pregnancy characteristics, a total of 70 (32.1%) participants reported preterm delivery, 16 (7.2%) had gestational hypertension, and 21 (9.5%) had preeclampsia. The most commonly reported cardiovascular risk factors were high cholesterol (n = 71, 32%) and hypertension (n = 59, 26.6%). A minority of participants (n = 64, 29%)

reported any smoking history, with 5% (n = 11) reporting current cigarette use. The most common type of infant CHD was class I (2 ventricles with no obstruction) in 129 (58.1%) children. Class IV CHD (1 ventricle with obstruction) was the second most common in 60 (27.3%) children. A secondary analysis of CHD severity found that a higher STAT score correlated with more complex class of CHD (P < 0.001). Ten (4.5%) children were deceased.

Table 1Baseline Characteristics of Participants in the M-CHOP Cohort (N = 222)

Maternal characteristics	
Age, y	52.2 ± 5.8
Race	
White, non-Hispanic	189 (85.5)
Black, non-Hispanic	21 (9.5)
Other	11 (5.0)
Hispanic ethnicity	11 (5.0)
Married/domestic partner	164 (74.2)
Highest attained education	
<High school	2 (0.9)
High school or some college	67 (30.3)
College graduate or higher	152 (68.8)
Income	
<$25 K	6 (2.7)
$25-49.9 K	22 (10.0)
$50-99.9 K	53 (24.0)
>$100 K	120 (54.3)

Prefer no answer	20 (9.0)
Hollingshead score	49 ± 12
Hollingshead score, range	11-66
Insurance	
Private	199 (89.6)
Medicaid/Medicare	18 (8.1)
Uninsured	4 (1.8)
CV risk factors	
High cholesterol	71 (32.0)
HTN	59 (26.6)
Diabetes	26 (11.7)
Prediabetes (n = 196)	23 (11.7)
Family history of ASCVD (n = 221)	108 (48.6)
Family history of premature ASCVD (n = 107)	46 (42.6)
Smoking history (n = 221)	64 (29.0)
Former smoker	53 (24.0)
Current smoker	11 (5.0)
BMI >30 kg/m2	82 ± 36.9
Sex-specific CV risk factors	
Preterm delivery (<37 wk)	70 (32.1)
Severe preterm delivery (<34 wk)	21 (9.7)
Hypertensive disorders of pregnancy	29 (13.0)
Preeclampsia	21 (9.5)
Gestational hypertension	16 (7.2)
Gestational diabetes	29 (13.1)
Early menopause (<40 y) (n = 109)	12 (11.0)
Child characteristics	
Age in days at first surgery	8 (3-80)

Sex of child	
Female	95 (42.8)
Male	127 (57.2)
Child status is deceased	10 (4.5)
Birth weight	3.08 ± 0.66
Class of heart disease	
I. 2 ventricles, no obstruction	129 (58.1)
II. 2 ventricles, with obstruction	22 (9.9)
III. 1 ventricle, no obstruction	11 (5.0)
IV. 1 ventricle, with obstruction	60 (27.3)
STAT score	
Category 1 (lowest mortality risk)	82 (36.9)
Category 2	39 (17.6)
Category 3	19 (8.6)
Category 4	22 (9.9)
Category 5 (highest mortality risk)	60 (27.3)

Values are mean ± SD or n (%).

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; M-CHOP = Maternal-Children's Hospital of Philadelphia; HTN = hypertension; STAT = Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery.

Prevalence of cardiovascular disease in the M-CHOP cohort is shown in the **Central Illustration**. Of 222 M-CHOP participants, 34 (15.3%) self-reported a history of any cardiovascular disease, including ASCVD (4.5%), structural heart disease (3.6%), and arrhythmia (8.6%). The distribution of CHD severity was significantly different among those with and without self-reported cardiovascular disease (P = 0.03) (**Table 2**). Specifically, class I CHD was less prevalent in participants with self-reported cardiovascular

disease compared to those without cardiovascular disease (33.3% vs 60.3%). This correlation of maternal cardiovascular disease and severity of child's CHD was similarly found when using the STAT score to determine severity of the child's CHD.

Table 2Risk Factors Associated With Cardiovascular Disease Among Participants in the M-CHOP Cohorta	**No CVD (n = 204)**	**CVD (n = 18)**	**P Value**
HTN	48 (23.5)	11 (61.1)	0.001
Any HDPb	33 (16.3)	10 (55.6)	<0.001
Preeclampsia	16 (7.9)	5 (27.8)	0.018
Gestational DM	21 (10.3)	8 (44.4)	0.001
Diabetes	18 (8.8)	8 (44.4)	<0.001
Female sex of child	88 (43.1)	7 (38.9)	0.807
Child's class of CHD			0.030
2 ventricles no obstruction (I)	123 (60.3)	6 (33.3)	
2 ventricles with obstruction (II)	19 (9.3)	3 (16.7)	
1 ventricle no obstruction (III)	8 (3.9)	3 (16.7)	
1 ventricle with obstruction (IV)	54 (26.5)	6 (33.3)	
STAT score of CHD			0.058
Category 1	75 (36.8)	7 (38.9)	
Category 2	39 (19.1)	0 (0.0)	
Category 3	15 (7.4)	4 (22.2)	
Category 4	21 (10.3)	1 (5.6)	
Category 5	54 (26.5)	6 (33.3)	

Values are n (%).

CHD = congenital heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; HDP = hypertensive disorder of pregnancy; other abbreviations as in **Table 1**.

a Cardiovascular disease as defined by presence of atherosclerotic cardiovascular disease and/or structural heart disease.

b Hypertensive disease of pregnancy, including gestational hypertension and pre-eclampsia.

Participants with self-reported cardiovascular disease comprised of either ASCVD and/or structural heart disease (n = 18) had higher rates of traditional and sex-specific cardiovascular risk factors (**Table 2**). A history of diabetes was more common in patients who reported cardiovascular disease (44.4% vs 8.8%, P < 0.001). Hypertension was also more prevalent in participants with cardiovascular disease (61% vs 23.5%; P = 0.001). Notably, participants with cardiovascular disease had significantly higher rates of preeclampsia compared to those without cardiovascular disease (27.8% vs 7.9%; P = 0.018).

In order to examine the association between child's severity of CHD and maternal cardiovascular disease, we compared differences in cardiovascular risk factors among participants stratified by child's class of CHD (**Supplemental Table 2**). In this small cohort, there were no statistically significant differences in the rates of hypertension, diabetes mellitus, preeclampsia, gestational diabetes mellitus, and gestational hypertension between different classes of child's heart disease.

Comparison of M-CHOP to matched NHANES participants

A total of 188 M-CHOP participants were matched to individuals in the NHANES cohort (**Figure 2**). One participant was not matched due to missing demographic data and 33 were unmatched due to NHANES not having sufficient participants to match on baseline characteristics. The unmatched participants were non-Hispanic white, college graduates or higher, and ages 50 to 57 years. There were no significant differences between the matched

M-CHOP and NHANES groups with regard to marital status or education (**Supplemental Table 3**). Data on several traditional cardiovascular risk factors were able to be obtained from the NHANES cohort and compared to the M-CHOP group. Overall, rates of traditional cardiovascular risk factors were similar between the groups, aside from a higher rate of family history seen among M-CHOP compared to NHANES participants (46.7% vs 11.4%, P < 0.001) (**Table 3**). There were no statistically significant differences in rates of ASCVD between the M-CHOP and the NHANES cohorts (4.8% vs 4.3%, P = 1.00). While there were no statistically significant differences in rates of hypertension in our group compared to the matched NHANES cohort (27.2% vs 28.2%, P = 1.00), participants with a diagnosis of hypertension were much more likely to be taking antihypertensive medication in the M-CHOP group compared to those with hypertension in the NHANES group (90.4% compared to 73.5%, P = 0.037); overall 25% of the matched M-CHOP cohort reported use of antihypertensive meds compared to 19% of the NHANES group.

Table 3Self-Reported Prevalence of Cardiovascular Disease Risk Factors and ASCVD Among Matched Participants in the M-CHOP Cohort Compared to Those in the NHANES Cohort	**M-CHOP Cohort (n = 188)**	**NHANES Cohort (n = 188)**	**P Value**
Smoking history	54 (28.7)	72 (38.3)	0.063
Family history of ASCVD	42 (46.7)	21 (11.4)	<0.001
High cholesterol	55 (29.3)	51 (27.1)	0.731
Prediabetes	18 (11.0)	29 (16.9)	0.156
Diabetes	24 (12.8)	16 (8.5)	0.241
HTN	52 (27.7)	53 (28.2)	1.00
HTN meds	47 (90.4)	36 (73.5)	0.037
ASCVD	9 (4.8)	8 (4.3)	1.00

NHANES = National Health and Nutrition Examination Survey; other abbreviations as in **Table 1**.

Discussion

In our cross-sectional survey study of mothers who delivered a child with CHD 18 years prior, we identified a statistically significant relationship between child's severity of CHD and diagnosis of maternal cardiovascular disease, despite finding similar rates of traditional cardiovascular risk factors between the 2 groups of participants with and without CVD in the M-CHOP cohort. This finding is hypothesis-generating given the size of our cohort, but may suggest an association between risk of maternal cardiovascular disease and complexity of CHD in their infant.

Previous studies have described increased risk of cardiovascular disease and mortality in women and birthing individuals who delivered a child with any type of congenital anomaly.**3**,**18** As congenital heart defects are the most common congenital anomaly, with an estimated prevalence of 7.7 per 1,000 births worldwide, it is possible a significant portion of this risk is mediated through congenital heart defects.**19** A longitudinal cohort analysis of over 1 million women and birthing individuals who had delivered infants in Quebec, Canada, between 1989 and 2013 found that the rates of cardiovascular disease-related hospitalizations were higher in individuals whose infants had any severity of congenital heart defects compared to those whose infants had no heart defects.**2** This large population-based study also found higher hazard ratios for cardiovascular disease-related hospitalization in individuals whose infants had critical heart defects compared to those with noncritical defects, although these were not statistically significant differences.

In contrast to this larger study, our smaller cross-sectional study did not find that mothers who delivered an infant with CHD had a higher overall prevalence of maternal cardiovascular disease. Our study results may differ for several reasons. First, we assessed self-reported cardiovascular disease outcomes in contrast to those identified through administrative data. Second, our sample size was small in comparison to the large cohort analysis of over 1 million individuals, which may limit our ability to detect

uncommon outcomes. Our cohort study, however, focuses on collecting granular medical and sociodemographic factors that may link their child's CHD with the maternal development of cardiovascular disease.

While we were not able to directly compare rates of sex-specific risk factors between participants in the M-CHOP and NHANES cohorts, we did note high rates sex-specific risk factors among M-CHOP participants. Specifically, 32% of participants reported at least one preterm birth before 37 weeks, with 9.7% of the cohort reporting preterm delivery <34 weeks. Rates of preterm birth have been increasing over the past several decades, however recent estimates of the incidence of late preterm birth (34-36 weeks gestation) were around 7% nationally.**20** This number includes only incident births and does not compare to our survey which included any history of preterm delivery in any pregnancy.

Preeclampsia is strongly associated with development of both acute cardiovascular dysfunction, as well as future maternal cardiovascular disease.**21-23** The association between preeclampsia and fetal congenital heart defects has been well described in the literature, noting both an increased risk of future preeclampsia in women and birthing individuals who have a fetus with CHD, as well as increased risk of fetal CHD in those who have had prior preeclampsia.**24** The mechanism linking HDP to future cardiovascular disease is not well understood but may offer some insight in understanding the relationship between infant CHD and maternal cardiovascular disease. In our study, we found that preeclampsia was associated with maternal self-reported cardiovascular disease at 18 years after delivery. Preeclampsia did not appear to be associated with child's class of CHD (**Supplemental Table 2**), however this analysis is limited due to sample size.

The concept of shared angiogenic imbalance is promising as a possible mechanism for fetal CHD conferring maternal cardiovascular disease risk, given the known association of angiogenic imbalance linking preeclampsia to future maternal vascular dysfunction and maternal cardiovascular

disease.**25** Prior studies have noted abnormal levels of angiogenic growth factors such as vascular endothelial growth factor, soluble fms-like tyrosine kinase-1, and placental growth factor in maternal circulation of individuals with preeclampsia.**26**,**27** Abnormalities in these growth factors are also seen in maternal and cord blood samples from pregnancies with fetal CHD compared to controls.**4** Similar to the mechanism in preeclampsia, these abnormal levels of growth factors in pregnancies with CHD may affect the maternal systemic circulation during and after the pregnancy and could predispose to development future maternal cardiovascular disease. Although hypothesis generating due to small sample size, our study found an association with severity of fetal CHD and development of maternal cardiovascular disease. This effect could be driven by a greater degree of angiogenic imbalance, which may be found in more severe forms of CHD or in the setting of preeclampsia.

There were several limitations to our study. First, our study relied on self-reported diagnoses, which may lead to overreporting or underreporting of specific conditions. Second, responders and nonresponders differed according to several important characteristics, including race, socioeconomic status, and severity of child's CHD, which contributes to selection bias; in particular, respondents to our survey had higher socioeconomic status compared to nonresponders, which may be associated with lower cardiovascular risk. Additionally, non-English speaking households were excluded from the prospective cohort. Third, our study was a cross-sectional study, and although intervals between pregnancy and development of disease were able to be estimated based on participants' responses, it is possible this data collection was obtained before a signal for higher rates of cardiovascular disease has occurred. Fourth, the original cohort of children was stratified by severity of their CHD—notably, this population only included those who underwent surgery in infancy, thus by definition excluding children with truly mild CHD. Fifth, although we compared our results to a matched cohort drawn from the U.S. population, it is possible that these cohorts differed on other unmatched characteristics

that we could not measure. Finally, due to the low event rate of our primary outcomes, we were unable to control for confounding factors.

Conclusions

In this cross-sectional study, mothers who delivered an infant with CHD did not have higher rates of age-adjusted cardiovascular risk factors or disease compared to normative data. Severity of fetal CHD was associated with maternal cardiovascular disease, and future studies should explore whether this association mediates increased maternal cardiovascular disease risk in larger cohorts.

15. Gender disparity in morbidity and mortality among patients with ST-elevation myocardial infarction due to spontaneous coronary artery dissection complicated by cardiogenic shock

Background

There is limited data on gender differences among patients with spontaneous coronary artery dissection (SCAD) who present as ST-elevation myocardial infarction (STEMI) and develop cardiogenic shock (CS).

Objectives

To describe outcomes of SCAD patients presenting with STEMI and CS and outline the differences between men and women.

Methods

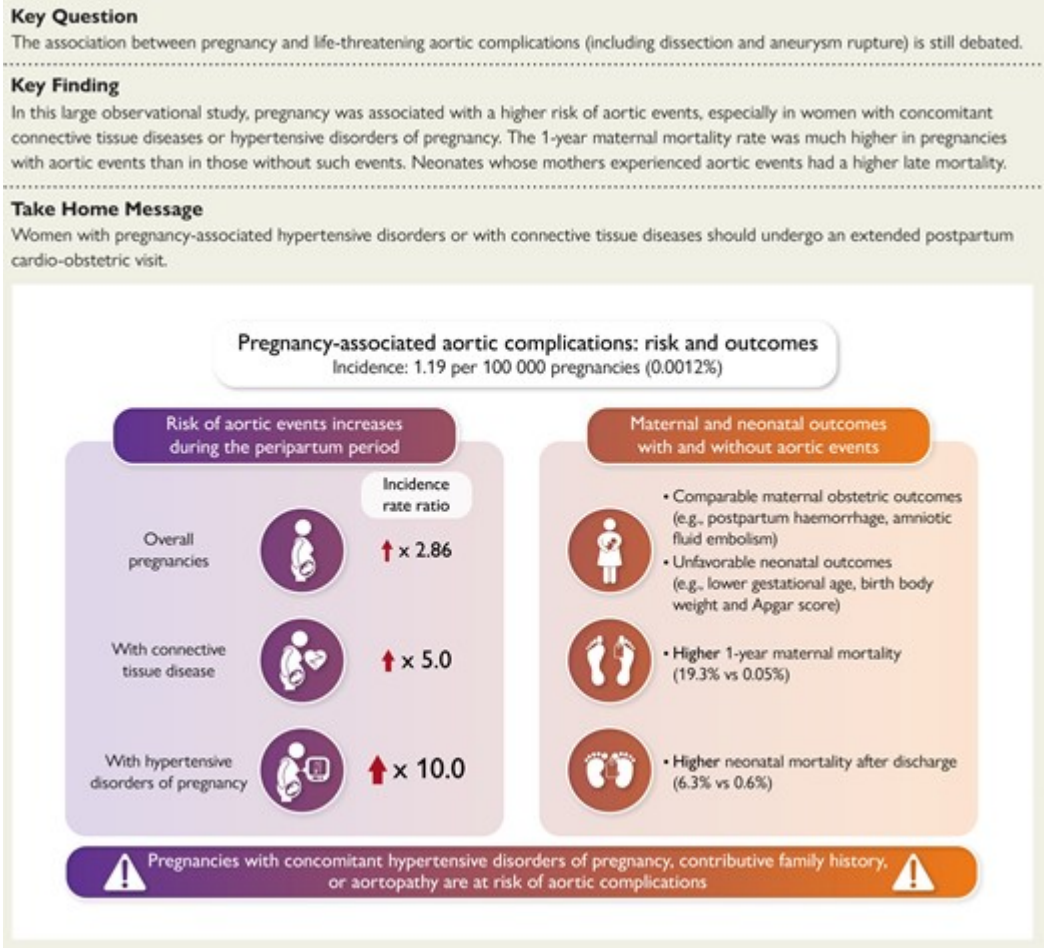
We queried the US Nationwide Readmissions Database (NRD) from January 2016 to December 2020 to identify patients with SCAD presenting with STEMI who developed CS. We compared the characteristics, trends, and outcomes between men and women in this cohort.

Results

Out of 582,633 hospitalizations with STEMI, 0.2 % (1176 patients) had SCAD, of which 346 (29.4 %) had CS. There was no difference in median age between men and women (64 years (IQR 57–71) vs. 63 years (IQR 49–72), p = 0.181). Men had a higher prevalence of prior myocardial infarction (MI) (14.2 % vs. 6.2 %, p = 0.021). The overall mortality rate of SCAD patients with AMI-CS was 28.2 %, with no difference between men and women. Patients with SCAD who had CS and underwent CABG had a mortality of 20.3 %. ECMO was used in 6.1 % of SCAD patients presenting with STEMI and CS, with a survival rate of 49.9 %.

Conclusion

There were no differences in the baseline characteristics, rates of revascularization, or in-hospital mortality between men and women who had SCAD complicated by CS (SCAD-CS). Patients with SCAD-CS patients who underwent CABG had around 80 % in-hospital survival. CABG should be considered as a method of revascularization in this patient cohort.



16.Neurohormonal response is associated with mortality in women with ST-elevation myocardial infarction

Abstract

Aims

Women continue to have a worse prognosis following ST-elevation myocardial infarction (STEMI) compared to men, despite advancements in treatment. This study investigates whether neurohormonal biomarker differences contribute to sex-related disparities in mortality.

Methods and results

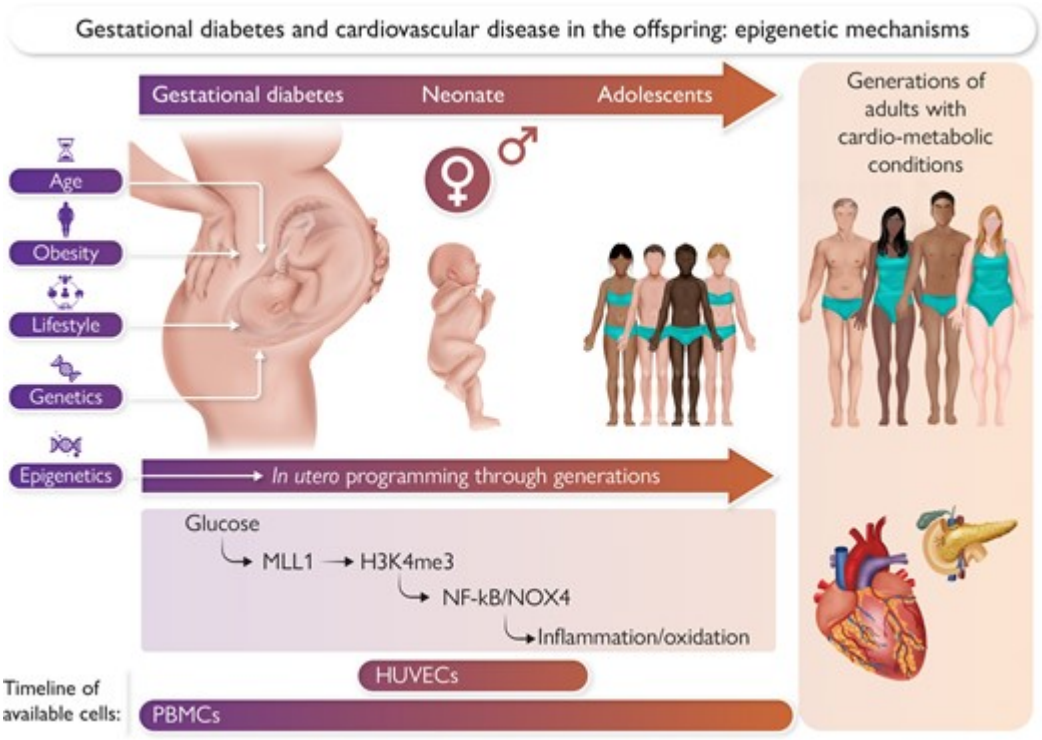
A total of 1892 consecutive STEMI patients from two tertiary heart centres were included. Admission neurohormonal activation defined as pro-atrial natriuretic peptide (proANP) and mid-regional pro-adrenomedullin (MR-proADM) was measured in blood drawn prior to acute coronary angiography

(CAG). The primary endpoint was 1-year mortality stratified according to sex and biomarker level. Of 1782 (94%) with biomarkers available, 476 (27%) of patients were women. They were older (68 vs. 62 years), had longer symptom-to-angiography delay (211 vs. 181 min), and displayed a higher one-year mortality rate (12% vs. 7.4%, P < 0.001) compared to men. The neurohormonal response was higher in women compared to men [median (interquartile range) proANP 1050 (671–1591) vs. 772 (492–1294) pmol/L, P < 0.001); MR-proADM 0.80 (0.63–1.03) vs. 0.70 (0.58–0.89) nmol/L, P < 0.001]. In women, a level at or above the median was independently associated with a significantly higher mortality risk when adjusting for age, left ventricular ejection fraction, diabetes, heart failure, symptom onset to CAG, left-sided culprit lesion, obesity, renal dysfunction, primary percutaneous intervention, admission systolic blood pressure, and multivessel disease (HR proANP 6.05, 95% CI 1.81–20.3, P = 0.004; HR MR-proADM 3.49, 95% CI 1.42–8.62, P = 0.007). In men, there was an independent prognostic association for proANP but not for MR-proADM (HR proANP 2.38, 95% CI 1.18–4.81, P = 0.015; HR MR-proADM 1.74, 95% CI 0.89–3.40, P = 0.11).

Conclusion

Increased neurohormonal activation (MR-proADM and proANP) is associated with higher mortality in women compared to men. Neurohormonal activation may contribute to the observed sex-related differences in mortality.

17.Do epigenetic echoes of gestational diabetes craft a transgenerational path to cardio-metabolic disease?



The epigenetic biomarker H3K4me3 driving pro-oxidant and pro-inflammatory features propagates from mother with gestational diabetes to neonates and adolescents, promoting the predisposition to cardio-metabolic disease in adults. Using peripheral blood mononuclear cells (PBMC) and umbilical cord endothelial cells (HUVEC), the study demonstrates the transfgenerational spread of epigenetic alterations that, can determine long term outcomes along with genetic, lifestyle and environmental risk factors.

18.The inflammatory and oxidative phenotype of gestational diabetes is epigenetically transmitted to the offspring: role of methyltransferase MLL1-induced H3K4me3

Background and Aims

Hyperglycaemia during gestational diabetes (GD) predisposes women and their offspring to later cardiometabolic disease. The hyperglycaemia-mediated epigenetic changes remain to be elucidated. Methyltransferase MLL1-induced trimethylation of histone 3 at lysine 4 (H3K4me3) activates

inflammatory and oxidative phenotype. This epigenetic mark in GD women and its transmission to the offspring were investigated.

Methods

Peripheral blood mononuclear cells (PBMC) were collected from GD and control (C) women and also from adolescents born to women of both groups. Endothelial human umbilical vein endothelial cells (HUVEC) and cord blood mononuclear cells (CBMC) were from umbilical cords. The NF-κBp65 and NOX4 expressions were investigated by reverse transcription quantitative polymerase chain reaction and immunofluorescence (IF). MLL1 and H3K4me3 were investigated by immunoblotting and IF. H3K4me3 on NF-κBp65 and NOX4 promoters was studied by chromatin immunoprecipitation. Superoxide anion generation was measured by electron spin resonance spectroscopy. Plasma cytokines were measured by enzyme-linked immunosorbent assay. To investigate the role of MLL1, HUVEC were exposed to inhibitor MM102 or siRNA transfection.

Results

PBMC, CBMC, and HUVEC showed an increase of NF-κBp65, IL-6, ICAM-1, MCP-1, and VCAM-1 mRNAs. These findings were associated with H3K4me3 enrichment in the promoter of NF-κBp65. Elevated H3K4me3 and cytokine levels were observed in GD adolescents. MLL1 drives H3K4me3 not only on NF-kB p65, but also on NOX4 promoter. Inhibition of MLL1 blunted NF-κBp65 and NOX4 by modulating inflammatory and oxidative phenotype.

Conclusions

Such proof-of-concept study shows persistence of MLL1-dependent H3K4me3 in offspring born to GD women, suggesting an epigenetic-driven transmission of maternal phenotype. These findings may pave the way for pharmacological reprogramming of adverse histone modifications to mitigate abnormal phenotypes underlying early ASCVD.

Key Question

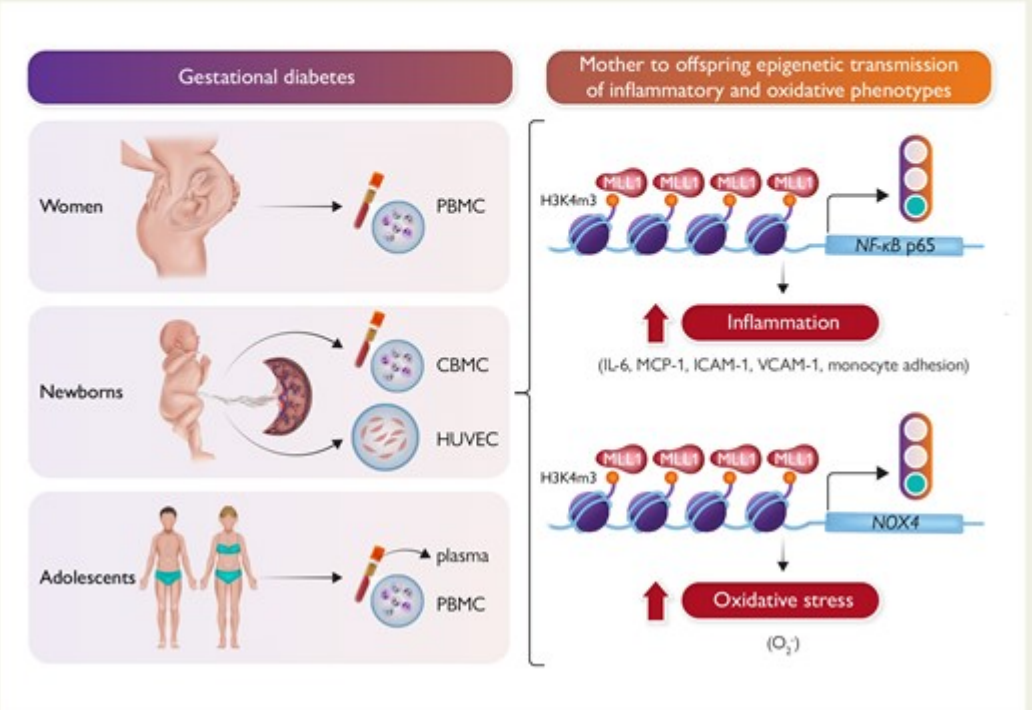
Does methyltransferase MLL1-induced trimethylation of histone 3 at lysine 4 (H3K4me3) activate an inflammatory and oxidative phenotype in women with gestational diabetes (GD) and their offspring?

Key Finding

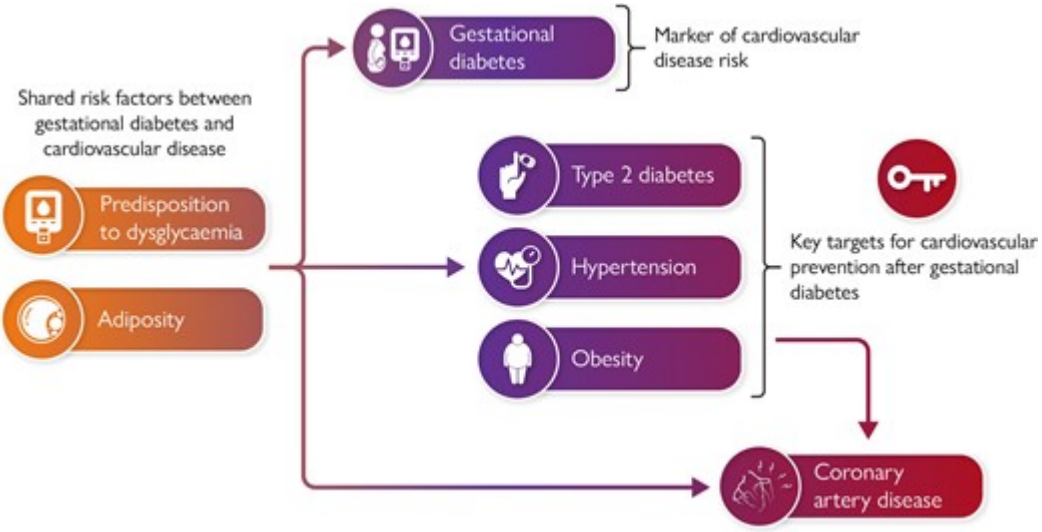
H3K4me3 enrichment in the promoter of both NF-κBp65 and NOX4 was positively associated with oxidative stress and cytokine levels in women with GD and their offspring.

Take Home Message

These findings suggest a potential early identification of abnormal phenotypes underlying early atherosclerotic cardiovascular disease, paving the way for pharmacological reprogramming of adverse histones in individuals at risk.



21. Gestational diabetes and cardiovascular disease: lessons for primordial prevention in women and for interpreting Mendelian randomization studies



19.Gestational diabetes and future cardiovascular diseases: associations by sex-specific genetic data

Background and Aims

Observational studies have highlighted that gestational diabetes mellitus is associated with a higher risk of cardiovascular diseases, but the causality remains unclear. Herein, the causality between genetic predisposition to gestational diabetes mellitus and the risk of cardiovascular diseases was investigated using sex-specific Mendelian randomization analysis.

Methods

Linkage disequilibrium score regression analysis and two-sample Mendelian randomization analysis were applied to infer the genetic correlation and causality, respectively. Mediation analysis was conducted using a two-step Mendelian randomization approach. Sensitivity analyses were performed to differentiate causality from pleiotropy. The genome-wide association study summary statistics for gestational diabetes mellitus were obtained from FinnGen consortium, while for cardiovascular diseases were generated based on individual-level genetic data from the UK Biobank.

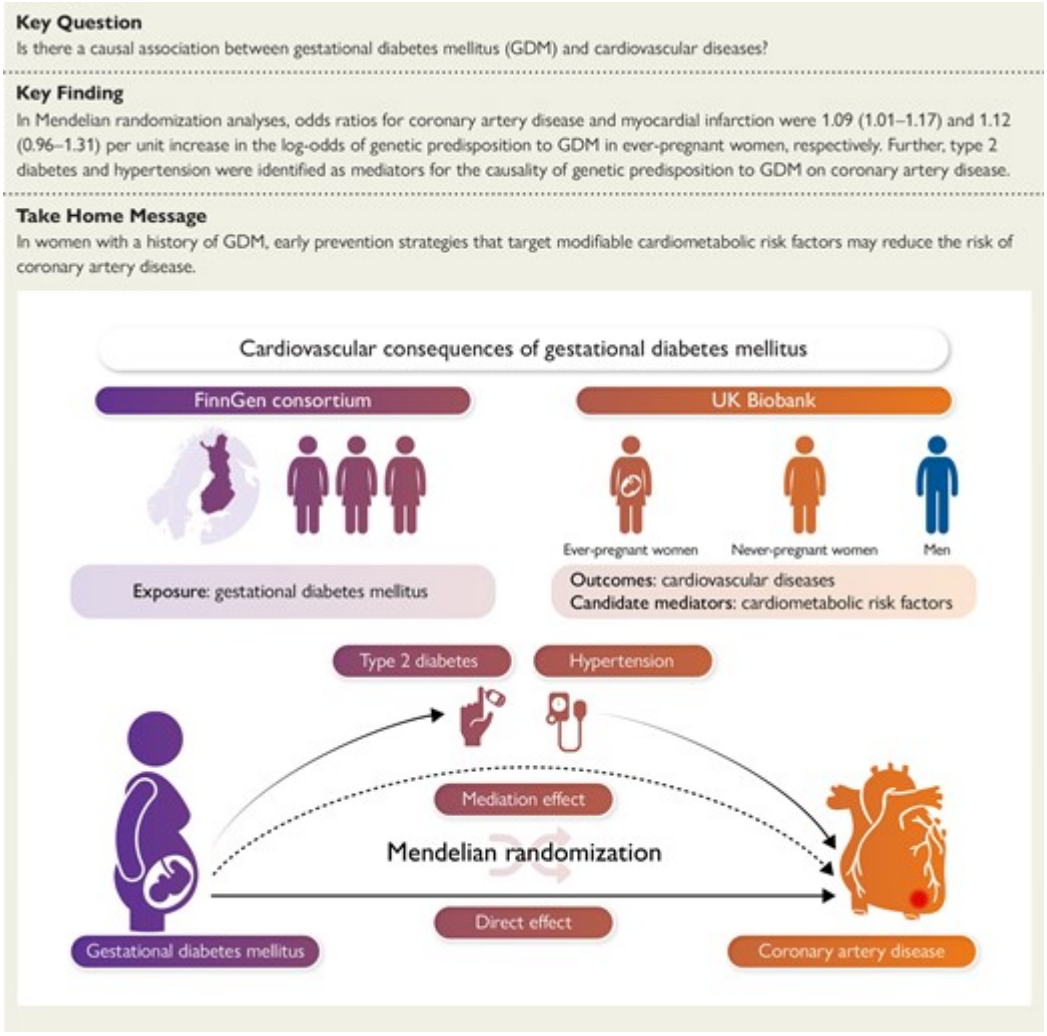
Results

Linkage disequilibrium score regression analyses revealed that gestational diabetes mellitus had a significant genetic correlation with coronary artery disease and myocardial infarction after Benjamini–Hochberg correction in ever-pregnant women. In Mendelian randomization analyses, odds ratios (95% confidence interval) for coronary artery disease and myocardial infarction were 1.09 (1.01–1.17) and 1.12 (.96–1.31) per unit increase in the log-odds of genetic predisposition to gestational diabetes mellitus in ever-pregnant women, respectively. Further, Type 2 diabetes and hypertension were identified as mediators for the causality of genetic predisposition to gestational diabetes mellitus on coronary artery disease. In sensitivity analyses, the direction of odds ratio for the association between instrumental variables with gestational diabetes mellitus-predominant effects and the risk of coronary artery disease was consistent with the

primary results in ever-pregnant women, although not statistically significant.

Conclusions

This study demonstrated a suggestive causal relationship between genetic predisposition to gestational diabetes mellitus and the risk of coronary artery disease, which was mainly mediated by Type 2 diabetes and hypertension. These findings highlight targeting modifiable cardiometabolic risk factors may reduce the risk of coronary artery disease in women with a history of gestational diabetes mellitus.



20.Pregnancy in obese women and mechanisms of increased cardiovascular risk in offspring

Introduction

The World Health Organization describes obesity as a condition of epidemic proportions, with one in eight individuals and over 1.9 billion adults worldwide living with obesity.1 This rising prevalence of obesity matches a rising incidence of cardiovascular disease, which is now responsible for nearly 30% of all deaths in the UK.2–6 Increased adiposity leads to insulin resistance and hypertension, promoting a greater risk of cardio-metabolic disorders in obese individuals.7,8

The health implications of obesity rise exponentially to a much greater level of importance when considering maternal obesity.9 Over half of women in the UK are now overweight or obese during pregnancy.10 This is of the gravest concern as obesity during pregnancy not only has immediate detrimental effects on the mother but also on her children, thereby propagating adverse health conditions onto the next generation.11 Accumulating evidence derived from human studies and experimental animal models shows that maternal obesity can markedly increase the risk of cardiovascular disease in offspring,6–30 even when the progeny is fed a healthy diet and in the absence of them becoming obese.23 This highlights that it is something about the exposure of the embryo or foetus to an obesogenic environment during gestation itself that either triggers a foetal origin of cardiovascular dysfunction and/or increases susceptibility to heart disease in the adult offspring, consistent with the Developmental Origins of Health and Disease hypothesis.31

In humans, the best evidence to support developmental origins of cardiovascular health and disease in offspring of obese pregnancy comes from studies in women who were obese during a first pregnancy, lost weight through bariatric surgery, and were leaner during a second pregnancy.13,32,33 These studies show that siblings born before bariatric surgery have signs of an increased cardiovascular risk compared with those born after surgery.13,32,33 Therefore, such studies highlight that a different environment in the same womb can programme a differential risk

of heart disease in offspring of the same family. This provides compelling evidence in humans that the environment experienced during critical periods of development directly influences long-term cardiovascular health. Therefore, when considering strategies to reduce the burden of heart disease on every nation's health and wealth, there needs to be a greater focus on prevention rather than treatment (Figure 1).

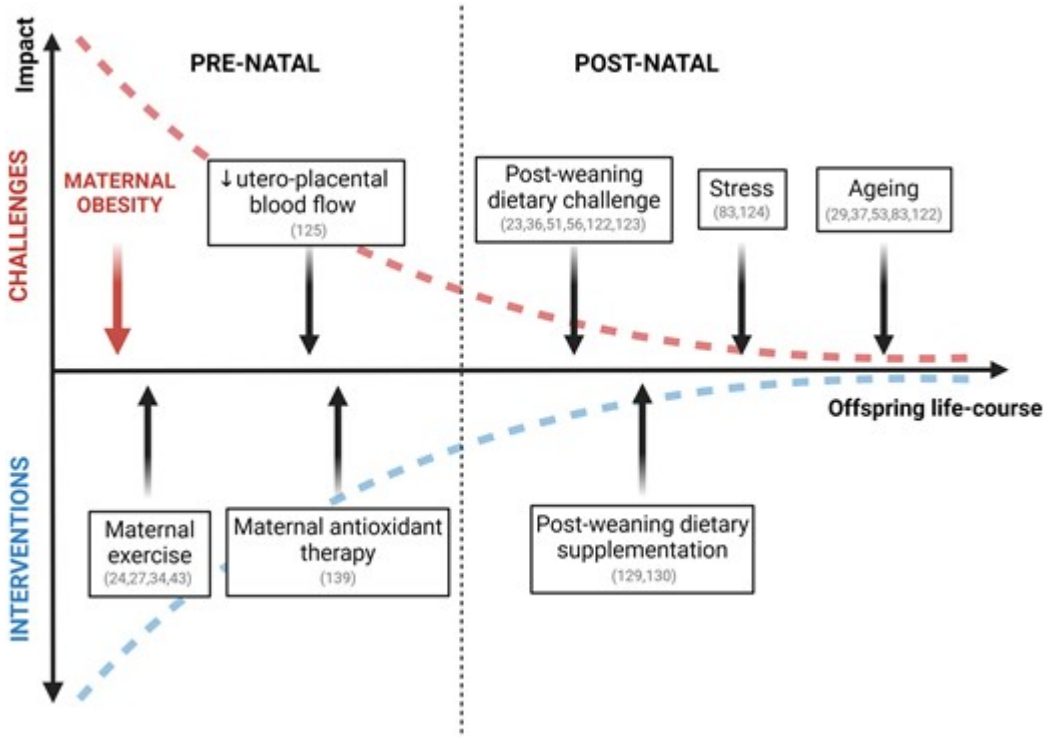


Figure 1

Timeline for intervention and secondary challenges over the life-course in offspring of obese pregnancy. The diagram shows that the younger we are the greater the impact that maternal obesity has upon us. Similarly, the opportunity for correction is greatest in younger life and diminishes progressively as we grow older. Therefore, candidate interventions should start as early as possible during the developmental trajectory, rather than waiting until disease is established. The diagram also shows that exposure to additional challenges in pre-natal and post-natal life, secondary to obese pregnancy, exacerbates the offspring cardiovascular dysfunction. The degree of impact of maternal obesity during pregnancy, superimposed challenges, and interventions is greatest in early pre-natal life, where the environmental

sensitivity of progeny is highest, and falls exponentially across the offspring life-course. Key publications supporting statements are cross-referenced. Created with BioRender.com

This review summarizes the evidence derived from human clinical studies and experimental animal models that reflects the impact of maternal obesity on the cardiac and vascular health of the adult offspring. Mechanistically, the work describes how alterations in the intrauterine environment during maternal obesity, such as foetal hypoxia and hyperinsulinaemia34,35 can lead to oxidative stress,20,36 mitochondrial dysfunction and metabolic inflexibility,26,37–41 contributing to sympathetic hyper-reactivity21,22,36,42 and cardiovascular dysfunction21,37,38 in offspring. How postnatal diet, stress, or ageing may reveal or exacerbate an underlying cardiovascular susceptibility originating in utero is also highlighted. Finally, the review focuses on current interventions, such as maternal exercise or dietary supplementation during pregnancy, against the developmental programming of cardiovascular dysfunction in offspring of obese pregnancy.

Maternal obesity impacts offspring cardiovascular function during the postnatal period

Evidence from human studies

An association between maternal obesity and offspring cardiovascular dysfunction postnatally is evident across many studies in humans (Table 1 and Figure 2). Increased maternal body mass index (BMI) during pregnancy is associated with higher rates of hospital admissions due to cardiovascular events in adult offspring aged between 31 and 6412,78 and in a larger cohort aged between 27 and 76,15 with cardiovascular disease risk also higher in young human offspring aged between 1 and 25.14 Studies in children born to obese mothers reveal structural and functional cardiovascular alterations which likely drive this increased disease risk. In young children, increased maternal BMI during pregnancy is associated with left ventricular hypertrophy16 and greater epicardial

adiposity.17 This is associated with diastolic dysfunction at 12 months of ages.71

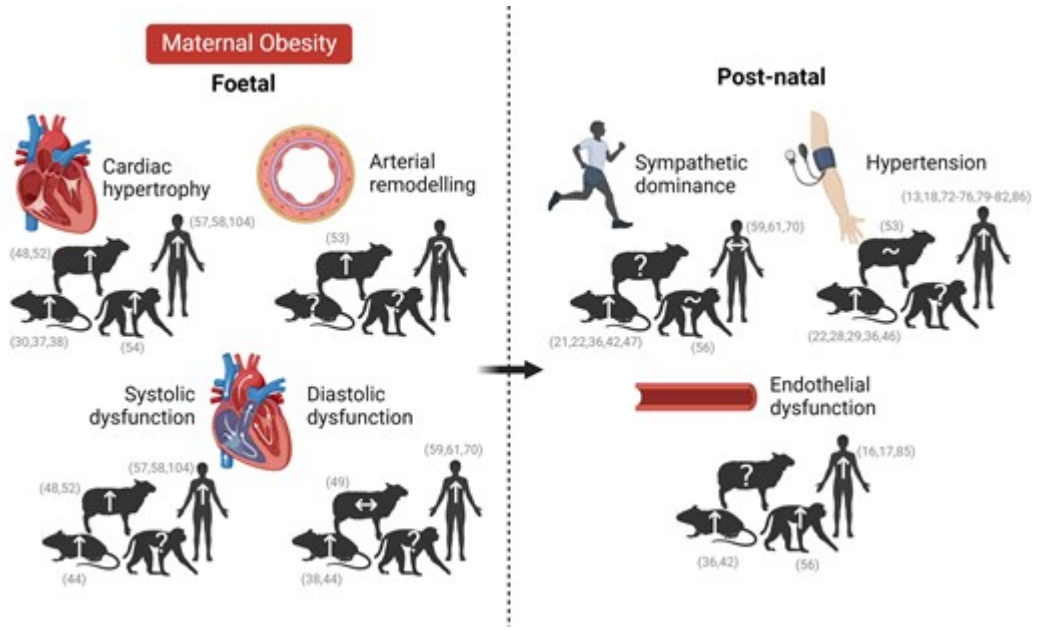


Figure 2

Cardiovascular phenotype of foetal and adult offspring of obese pregnancy in human and pre-clinical animal models. Maternal obesity induces cardiac hypertrophy,30,37,38,48,52,54,57,58,104 arterial remodelling,53 and systolic and diastolic dysfunction38,104,44,48,49,52,57–59,61,70 in the foetal offspring, leading to sympathetic dominance,21,22,36,42,47,56,59,61,70 endothelial dysfunction16,17,36,42,56,85, and hypertension79–82,13,18,22,28,29,36,46,53,72–76,86 in post-natal life. Key publications supporting statements are cross-referenced. Created with BioRender.com

Cardiovascular outcomes in offspring of obese pregnancy

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
Rodents						
Mouse C57 BL/6J	3% fat, 7% sugar	16% fat, 33% sugar	6 weeks pre-pregnancy, throughout pregnancy and lactation	Altered cardiac lipidome (↑sphingomyelins and acyl-carnitines, ↓cholesteryl esters at d18.5) ↑ primary cardiomyocyte oleate oxidation and expression of genes associated with sterol, fatty acid and carnitine metabolism (at d18.5) ↑ cardiac HIF-1α and Ppara targets (d18.5)	↑ heart weight and cardiac hypertrophy (at 3 and 8 weeks) Re-expression of foetal genes (↑ NPPB, ACTA1, MYH 7:MYH6 ratio at 3 weeks) Cardiac systolic and diastolic dysfunction (at 12 weeks) ↓ LV ejection fraction and cardiac output (at 8 weeks) ↑ cardiac insulin and	20,21,23,24,39,42

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					proliferative signalling (at 8 weeks) Cardiac oxidative stress (at 8 weeks) Cardiac and resistance artery sympathetic dominance (at 12 weeks) ↓ cardiac SERCA2a, total and phosphorylated troponin-I (at 12 weeks) ↑ active SBP and MAP but ↓ active heart rate and locomotion (at 12 weeks) Endothelial	

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					dysfunction in resistance arteries (at 12 weeks)	
Mouse C57BL/6J	10% fat	40% fat, 20% sucrose soln.	4–6 weeks pre-pregnancy, throughout pregnancy and lactation	↑ heart weight (at d18.5) Altered cardiac expression of genes involved in metabolism (↑Pparg, Cd36 and Prkaa1) with predicted ↓ neoplasia and DNA repair/synthesis and ↑ lipid synthesis and metabolism in males, ↓	Cardiac diastolic dysfunction in males (at 3, 6 and 24 months) and females (at 6, 9 and 24 months) ↑ heart weight in females (at 6 months) and ↑ cardiomyocyte cross-sectional area in males (at 3 months) ↑ cardiac foetal gene expression	25,37

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
				immune cells and ↑ uptake of mono- and polysaccharides in females	(at 3 months) ↑ cardiac Akt and mTOR signalling in males and ↓ERK1/2 signalling (at 3 months) Dysregulation of metabolism-related genes with ↑ expression of Pparg and targets related to lipid synthesis, storage and oxidation (at 6 months) ↑ myocardial mitochondrial fatty acid oxidation in	

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					males (at 6 months) ↓ myocardial glucose uptake in females (at 6 months)	
Mouse C57BL/6J	10% fat	60% fat/45% fat	8 weeks pre-pregnancy, 45% fat throughout pregnancy	↓ placental vascular density		43
Mouse C57BL/6J	10% fat	60% fat	12 weeks pre-pregnancy, to necro	Systolic dysfunction (↓ ejection fraction and fractional shortening) and diastolic		44

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			scopy	dysfunction (↑ Tei index) at d16.5 ↑ cardiac ROS content (at d16.5)		
Mouse C57BL/6J	25% fat, 3% sugar	60% fat, 13% sugar	6 weeks pre-pregnancy, throughout pregnancy and lactation		↑ absolute and relative left ventricular mass and internal diameter (at 8 weeks) ↓ fractional shortening in females (at 8 weeks) Circular cardiac mitochondrial morphology and disorganized sarcomere alignment ↓	26

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					cardiac mitochondrial oxygen consumption, CI and CII activity (at 8 weeks)	
Mouse C57BL/6N	10% fat	45% fat	13 weeks pre-pregnancy, throughout pregnancy and lactation		Sympathetic dominance (↑ aortic adrenergic vasoconstriction at 14 weeks)	27
Mouse C57BL/6	10% fat	45% fat	6 weeks pre-pregnancy, throu		↑ systolic blood pressure (at 10 months)	28

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			ghout pregnancy and lactation			
Mouse C57BL/6	5% fat	60% fat	4 weeks pre-pregnancy, throughout pregnancy and lactation		↑ systolic and diastolic blood pressure (at 12 months)	29
Mouse C57BL/6J	21%	45%	4 weeks pre-pregnancy, throughout		↑ systolic blood pressure (at 30 weeks) ↓ Acetylcholine-mediated	36

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			pregnancy and lactation		vasorelaxation in femoral arteries (at 15 and 30 weeks) ↓ Basal NO production (at 30 weeks) ↑ oxidative stress in femoral arteries (at 15 weeks)	
Rat Sprague-Dawley	4.3% fat	24% fat	From weaning, throughout pregnancy	↑ neonatal heart weight, cardiac fat deposition and apoptosis	↑ heart weight, cardiac fat deposition and apoptosis (at 1 and 3 months)	30
Rat Sprague-Dawley	18% fat	40% fat	4 weeks pre-pregn	↑ heart:body weight ratio and myocardial		38,40,45

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			ancy, throughout pregnancy and lactation	lipid deposits (in neonates) ↓ heart rate and E:A ventricular filling ratio with ↑ isovolumetric contraction time (in neonates) ↓ cardiomyocyte basal oxygen consumption ↑ smaller, wider and fragmented cardiac mitochondria with ↓ mitochondrial fusion and fission and sex-specific		

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
				alterations in expression of dynamism-related proteins (in neonates) Cardiac lipid peroxidation (in neonates) ↓ Cardiac FGF-activated PI3K/AKT signalling and ↑ PGC1α mitochondrial biogenesis signalling (in neonates)		
Rat Sprague-Dawley	3% fat, 7% sugar	16% fat, 33% sugar	6 weeks pre-pregnancy, throughout		↑ night-time MAP and MAP response to stress (at 4 and 12 weeks)	22

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			pregnancy and lactation		↓ HR in females (at 4 weeks) and males (at 12 weeks) Sympathetic dominance with ↑ renal tissue noradrenaline (at 4 and 12 weeks) ↑ changes in MAP to NO donor, α−adrenergic agonist and leptin, with ↓ baroreflex sensitivity of HR (at 12 weeks and 6 months)	
Rat Sprague-Dawley	10% fat	60% fat	8 weeks pre-		↑ systolic and diastolic blood	46

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			pregnancy, throughout pregnancy and lactation		pressure (at 6 months) Altered renin-angiotensin pathway in adipose (at Day 1 and 6 months)	
Rat Sprague-Dawley	4.5% fat	12.1% fat	12 weeks pre-pregnancy, throughout pregnancy and lactation		Mesenteric artery hypertrophy (at 4 months) Sex-specific alterations in vasodilator pathway dependence, with DNA methylation changes in vascular function genes (potassium channels and	47

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					NO synthase in males, guanylate cyclase and angiotensin receptor I in females) (at 4 months)	
Sheep						
Sheep Rambouillet/Columbia cross	100% NRC	150% NRC	60 days pre-pregnancy, to necroscopy at d75 or d135 (.5 or .9 gestation)	↑ left ventricular weight and left ventricular wall thickness (at d135) ↑ hypertrophic signalling (Foxo3a, mTOR and calcineurin pathways) and cardiac	↑ Left and right ventricular wall thickness, ↑ myocardial collagen content and crosslinking and ↑ expression of pro-inflammatory cytokines (at 22 months, after a 3	48–53

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
			or term	hyperplasia (at d75) ↑ cardiomyocyte cross-sectional area Irregular myofibre orientation, and perivascular fibrosis (at d75) ↓ cardiac contractile function in response to a high workload stress challenge (at d135) ↓ cardiomyocyte	month ad libitum feeding challenge) ↑ systolic blood pressure and heart rate at 2.5 months but ↓ systolic and diastolic blood pressure at 9 years Systolic dysfunction with ↓ fractional shortening, cardiac output and ejection fraction (at 9 years)	

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
				contractility, disrupted Ca2+ handling and ↑ myosin heavy chain β:α (slow twitch) expression (at d135) ↔ heart rate (at d135) ↓ cardiac insulin signalling Activation of fibrogenic genes (at d75 and d135), associated with increased collagen concentration (at d135) ↓ cotyledonary		

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
				vascularity (at d75) ↑ aortic wall thickness and collagen:elastin ratio (at d135)		
Non-human primates						
Baboon	12% fat, .61% sugar	45% fat, 12.58% sugar	4 months pre-pregnancy and throughout pregnancy to d165 (.9 gestation)	↑ myocardial fibrosis (d165) Dysregulated expression of cardiac microRNAs associated with cardiovascular disease ↑ cardiomyocyte proliferation rates		54

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
Japanese macaque	14% fat	32% fat	4+ years pre-pregnancy to necroscopy at d130 (.75 gestation)	↓ foeto-placental volume blood flow (at d120)		55
Japanese macaque	14% fat	36% fat	4+ years pre-pregnancy, throughout pregnancy and lactation		Altered aortic endothelial function depending on post-weaning diet: ↑ sensitivity to acetylcholine in control diet fed offspring, ↓ sensitivity and max	56

Species	Control diet	Experimental diet	Diet exposure period	Foetal/neonatal cardiovascular outcomes	Juvenile/adult offspring cardiovascular outcomes	References
					relaxation to acetylcholine and in high fat diet fed offspring associated with hyperinsulinaemia (at 13 months, juvenile) ↑ aortic intima thickness and expression of pro-inflammatory markers and ↓ fibrinolytic signalling, regardless of post-weaning diet (at 13 months)	
Humans						

Maternal phenotype	Offspring age	Foetal/neonatal offspring	Child/adult offspring	References
Obese: mean pre-pregnancy BMI 35 kg/m2 Control: mean pre-pregnancy BMI 21 kg/m2	Foetal: 14, 20 and 32 weeks of gestation	↑ interventricular septum thickness ↓ left and right ventricular global strain rate and strain (at 14, 20 and 32 weeks) ↓ tissue Doppler systolic and late diastolic velocities (at 20 and 32 weeks) ↔ heart rate		57
Obese: BMI >30 kg/m2 Control: BMI <30 kg/m2	Foetal: 25 weeks of gestation	↓ left ventricular ejection fraction and strain ↔ intra-ventricular septal		58

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
		thickness, myocardial performance index and mitral E/A ratio		
Obese: pre-pregnancy BMI >30 kg/m2 Control: pre-pregnancy BMI 18.5–24.9 kg/m2	Foetal: 26–38 weeks of gestation	↑ heart rate and heart rate variability ↓ sympathetic dominance (LF:HF ratio)		59
Obese: pre-pregnancy BMI of ≥30 kg/m2 Control: pre-pregnancy BMI <25 kg/m2	Foetal: 26–38 weeks of gestation	Diastolic dysfunction with ↑isovolumetric relaxation time		60
Pre-pregnancy BMI range: 18.2–34.9 kg/m2	Foetal: during parturition	↑ sympathetic dominance (LF:HF ratio) with ↑ maternal BMI		61

Humans					
Maternal phenotype		**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
Obese: pre-pregnancy ≥30 kg/m2 Control: pre-pregnancy 18.5–24.9 kg/m2	pre-BMI pre-BMI	Foetal	ER stress and reduced NO synthesis in HUVECs ↓ NO-dependent dilation of umbilical vein segments in response to insulin ↓ Insulin signalling (↑ inhibitor phosphorylation of IRS-1 and ↓ activator phosphorylation of Akt)		62,63
Obese: ≥25 kg/m2 Control: <25 kg/m2	BMI BMI	Foetal	Alterations in expression of genes related to lipid and mitochondrial		64

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
		metabolism in HUVECs		
Obese: 32 weeks BMI ≥30 kg/m2 Control: 32 weeks BMI 18.5–24.9 kg/m2/37 weeks BMI <30 kg/m2	Foetal: 32 and 37 weeks of gestation	↑ umbilical artery pulsatility at 32 weeks ↔ umbilical artery pulsatility and foetal middle cerebral artery pulsatility at 37 weeks		65,66
Obese: parturition BMI ≥30 kg/m2 Control: parturition BMI 19.8–25.9 kg/m2	Foetal	↑ umbilical artery contractility		67
Obese: BMI ≥30 kg/m2 Control: BMI	Foetal	↓ chorionic plate artery endothelium-		68

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
18.5–24.9 kg/m2		independent vasodilatation to nitric oxide donor		
Obese (LGA infant): BMI 31.5 ± 2.5 kg/m2 Control (AGA infant): BMI 22.0 ± .6 kg/m2	Foetal	↓ chorionic plate artery endothelium-dependent vasodilatation to adiponectin in LGA pregnancies		69
Obese: Pre-pregnancy BMI ≥30 kg/m2 Control: pre-pregnancy BMI 10–15 kg/m2	Neonatal	↑ heart rate and ↓ heart rate variability ↓ left ventricular end diastolic volume and stroke volume		70
Overweight/obese: BMI	Neonatal and 12	↑ left ventricular		71

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
≥25 kg/m2 Control: < 25 kg/m2	months.	posterior wall ↑end-diastolic and stroke volume		
Obese: BMI >30 kg/m2 Control: BMI 18.5–24.9 kg/m2	1–25 years		↑ rates of cardiovascular disease	14
Obese: pre-pregnancy BMI ≥30 kg/m2 Control: pre-pregnancy BMI 18.5–24.9 kg/m2	4–6 years		↑ systolic and diastolic blood pressure ↔ autonomic balance	18,72
Obese: BMI >30 kg/m2 Control: BMI 18.5–24.9 kg/m2	6 years		↑ systolic blood pressure ↑ left ventricular eccentric hypertrophy and aortic root diameter with ↑ maternal BMI ↔ fractional	16,19,73,74

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
			shortening, E/A ratio, systolic and diastolic strain	
Obese: gestational BMI of ≥30 kg/m2, body weight >91 kg or above normal by 110%–120% Control: mean gestational BMI 18 kg/m2	7–9 years		↑ epicardial adipose tissue thickness Arterial hypertrophy (↑ carotid intima-media thickness Reduced arterial compliance with ↓ arterial distensibility and strain and ↑ arterial stiffness	17
Obese: BMI >30 kg/m2 Control: BMI 18.5–24.9kg/m2	6–10 years		↑ systolic and diastolic blood pressure	75,76
Pre-bariatric surgery (obese): mean BMI 45 kg/m2 Post-bariatric	9–15 years		↑ blood pressure in offspring born pre-bariatric surgery	13

Humans				
Maternal phenotype	**Offspring age**	**Foetal/neonatal offspring**	**Child/adult offspring**	**References**
surgery: mean BMI 27.6 kg/m2				
Overweight/obese: BMI >25 kg/m2 Control: BMI 18.5–24.9 kg/m2	9–15 years		Maternal BMI positively associated with offspring waist circumference, and negatively associated with offspring cardiorespiratory fitness No association between maternal BMI and offspring blood pressure	77
Obese: BMI >30 kg/m2 Control: BMI 18.5–24.9 kg/m2	Adult: 27–76 years		↑ risk of hospital admission for cardiovascular event ↑ systolic and diastolic blood pressure	12,15,78–80
There is extensive evidence of cardiovascular dysfunction in offspring of obese pregnancy, in both pre-natal and post-natal life, across pre-clinical				

rodent, sheep and non-human primate models, and studies in humans. Diet % in kcal.

Abbreviations: AGA, average for gestational age (foetal weight); Akt, protein kinase B; ACTA1, actin alpha 1; BMI, body mass index; Cd36, a plasma membrane fatty acid translocase; E/A ratio, early/atrial ratio; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor 1 alpha; HUVEC, human umbilical vein endothelial cell; IRS-1, insulin receptor substrate 1; LF:HF ratio, low frequency: high frequency ratio; LGA, large for gestational age (foetal weight); MAP, mean arterial pressure; mTOR, mammalian target of rapamycin; MYH6/7, myosin heavy chain beta 6/7; NO, nitric oxide; NPPB, natriuretic peptide B; Pparg/a, nuclear peroxisome proliferator activated receptor.

Vascular alterations are also present, with increased aortic root diameter, arterial hypertrophy, and reduced arterial compliance in children of obese pregnancy.16,17,85 Together, these changes likely contribute to the increased prevalence of hypertension in children and adolescents born to mothers with obesity,13,18,72–76,81,86 showing a positive association between maternal pre-pregnancy BMI and offspring blood pressure even in the first year of life,82 that persists into adulthood.79,80 Evidence from human studies also indicates that cardiovascular disease risk in adult offspring is related to the degree of maternal obesity, with increased rates of cardiovascular disease only seen in offspring of mothers with obesity Grade II or higher (BMI over 35 kg/m2), which may be partly due to increased risk of additional complications such as neonatal asphyxia.14

Evidence from animal studies

To further understand the cardiovascular phenotype of offspring of obese pregnancy, rodent, ovine, and non-human primate models of maternal obesity have been generated, each showing different technical and translational advantages and limitations, summarized in Table 2. Across mammalian preclinical models, exposure to maternal obesity during pregnancy leads to alterations in the heart structure and function in the

progeny (Table 1 and Figure 2). Rodent offspring of obese pregnancy show increased heart weight,20,21,25,30,83,84 with increased cardiomyocyte size.20,21,25,26,83,84 These alterations occur with the activation of hypertrophic signalling pathways including the re-expression of foetal genes20,25 and increased insulin signalling through AKT, ERK, and the mammalian target rapamycin (mTOR).20,25 Cardiac hypertrophy with greater myocardial collagen content has also been reported in adult offspring in an ovine model of maternal overnutrition.51

Table 2

Advantages and limitations of rodent, sheep and non-human primate models

	Rodents	**Sheep**	**Non-human primates**
Advantages			
Translational	Invasive, haemochorial placentation with trophoblast-mediated spiral artery remodelling, comparable to humans87 Feeding of highly translational ‘cafeteria’ and ‘Western-style’	Sheep are a precocial species with comparable cardiovascular developmental milestones to human pregnancy89,90 Certain breeds (e.g. welsh Mountain and Merino) are primarily uniparous with neonatal lamb	Relevant for highly species-dependent processes such as the mechanisms promoting parturition94 Similar hormonal changes and duration of menstrual cycle95

	Rodents	Sheep	Non-human primates
	diets to rodents leads to obesity and metabolic profiles comparable to humans88	weights comparable to full-term human infants89 Human and sheep placentas have a villous tree structure, concurrent exchange, and similar glucose and amino acid transport systems91,92 Treatments developed in sheep have been highly successful in humans e.g. antenatal maternal corticosteroid therapy for pre-term infants93	
Technical	Short gestational length and reproductive cycle facilitates	Chronic surgical instrumentation of the foetus is possible89,96–99 Longitudinal	Longitudinal maternal blood sampling possible across gestation

	Rodents	Sheep	Non-human primates
	adult offspring and multi-generational studies Multiple pregnancy allows for study of sex differences within litter and using siblings for different outcomes (e.g. freezing vs. fixing) Cross-fostering and embryo transfer possible to isolate the critical periods of peri-conception, gestation and lactation	maternal and foetal blood sampling possible across gestation89,96–99 Ex vivo studies of foetal resistance arteries is possible100	Ex vivo studies on foetal cardiovascular system possible Life span and time to maturity are shorter than in humans
Limitations			
Translational	Rodents are an altricial species	Lack of translational	Non-human primates show

	Rodents	Sheep	Non-human primates
	with cardiovascular developmental milestones that differ from humans89,91 Differences in basal metabolic rate and glucose disposal between rodents and humans may influence metabolic adaptations occurring with obesity and pregnancy Multiple pregnancy leads to differences from humans in foetal nutrient allocation	relevance for highly species-dependent processes such as the mechanisms promoting parturition101 Placentation is cotyledonary and synepitheliochorial 102 Ruminant metabolism in sheep may result in different metabolic profile occurring with diet-induced obesity	differences in placentation, with superficial blastocyst implantation, fewer interstitial trophoblasts and earlier onset of placental circulation103
Technical	Foetal long-term surgical instrumentation	Length of gestation and life span make adult	Foetal instrumentation very limited

	Rodents	Sheep	Non-human primates
	not feasible	offspring and multi-generational studies costly and time-consuming	Foetal blood sampling across gestation limited Length of gestation and life span make adult offspring studies costly and time-consuming

The primary pre-clinical models of maternal obesity in pregnancy are rodent, ovine and non-human primate models. Each of these models presents its own translational and technical advantages and limitations, which relate to the use of this animal model as a study of obesity and as a model of reproductive biology.

Maternal obesity also leads to systolic dysfunction in the adult offspring, with impaired cardiac output seen in mice23,26,83 and sheep.53 Reductions in left ventricular developed pressure,21 fractional shortening,24,26,83 ejection fraction,23,24,26,83 and heart rate22,42 all contribute to a lower cardiac output in rodent offspring. However, there are several discrepancies in heart rate and blood pressure changes in offspring of obese pregnancy; juvenile sheep show a trend towards tachycardia at 2.5 months associated with hypertension, both of which are absent at 9 years.28 In contrast, mouse offspring showing bradycardia at 1 and 3 months that reverses to tachycardia at 6 months, while showing a hypertensive phenotype at all time points.16,35 These differences may be age-dependent and influenced by a range of factors including species differences. Systolic dysfunction is associated with impairments in

cardiomyocyte Ca2+ handling and activation of contractile proteins in mouse offspring.21 Diastolic dysfunction in mouse offspring of obese pregnancy results from an increase in left ventricular end-diastolic pressure,21,37 a reduced ratio of early-to-late left ventricular wall displacement and mitral inflow,25,37,83 together with longer isovolumetric relaxation time.83

Vascular alterations have also been reported, with mesenteric artery hypertrophy in adult rat offspring47 and thickening of the aortic intima in non-human primate offspring56 of obese pregnancy. Vascular dysfunction is evident, with a reduction in endothelium-dependent relaxation in resistance arteries of adult mice offspring of obese pregnancy.36,42 The effect on conduit arteries is less clear, with Macaque offspring of obese pregnancy showing increased aortic endothelial sensitivity to acetylcholine.56 In contrast, thoracic aorta endothelium-dependent and independent vasodilatation remained unaltered in adult mice offspring of obese pregnancy.27 This conflicting evidence may arise from species differences, study of resistance versus conduit vessels, and/or due to investigation of outcomes at different stages of maturity of the adult offspring. For instance, Macaque offspring were studied during the juvenile period56 while mouse offspring were studied as mature adults.27 Despite species and vascular bed differences, it is clear that offspring exposed to maternal obesity during gestation show alterations in vascular structure and function, which may contribute to the development of cardiovascular disease later in adulthood.

Maternal obesity impacts offspring cardiovascular dysfunction during the prenatal period

While impacts on adult offspring cardiovascular risk are well established, there is now accumulating evidence suggesting that cardiovascular dysfunction in human offspring of obese pregnancy may originate before birth (Figure 2).

Evidence from human studies

A reduction in bi-ventricular global strain is present in human foetuses of obese mothers at 14 weeks of gestation.57,58,104 Tissue Doppler imaging of foetal cardiac systolic and diastolic velocities and left ventricular ejection fraction reveals a reduction in all variables in human foetuses of obese mothers by 20–25 weeks, while an increased interventricular septum thickness becomes evident by 32 weeks of gestation.57,58,104 Basal foetal heart rate and heart rate variability are increased from mid-gestation in obese compared with healthy human pregnancies, associated with a reduction in the low frequency: high frequency (LF:HF) ratio.59 However, echocardiography studies during stimulated conditions, such as during parturition, revealed an increase in the foetal heart LF:HF ratio in obese pregnancy61 and neonatal recordings show decreased heart rate variability.70

Vascular dysfunction is also apparent in the human foetus of obese pregnancy, with increased umbilical artery constriction to serotonin,67 and impaired endothelium-dependent dilatation of the umbilical vein to insulin, an effect associated with vascular insulin resistance and oxidative and endoplasmic reticulum stress.62,63 These changes occur with an increase in the umbilical artery pulsatility index in offspring of obese women, measured at 32,65 but not at 3766 weeks of gestation. Impairments in endothelium-dependent and independent vasodilatation have also been reported in chorionic plate arteries of obese human pregnancy.68,69 However, no difference was found in the foetal middle cerebral artery pulsatility index with obese pregnancy.66

Evidence from animal studies

Evidence derived from preclinical animal models, including rodent, sheep, and non-human primates, show cardiac structural alterations in offspring of obese pregnancy in prenatal life, which match the hypertrophy seen in adulthood (Table 1 and Figure 2). Maternal obesity leads to increased heart weight in foetal mice37 and neonatal rats.30,38 The late-gestation foetal baboon shows increased cardiomyocyte proliferation and myocardial fibrosis

in obese pregnancy, indicative of pathological hypertrophy.54 Similarly, foetal sheep exposed to maternal obesity show increased left ventricular weight and wall thickness with higher cardiomyocyte cross-sectional area, activation of hypertrophic signalling, and evidence of cardiac fibrosis.48,52

Evidence derived from preclinical animal models also supports impairments in cardiac function in foetal life during obese pregnancy. Foetal mice of obese pregnancy show systolic and diastolic dysfunction, with lower values for ejection fraction and fractional shortening, increased time spent in isovolumetric contraction and relaxation, and a reduction in the early atrial to ventricular (E:A) filling ratio.44 Foetal sheep cardiomyocyte contractility is also reduced in obese pregnancy, associated with impaired Ca2+ handling and an increased proportion of slow-twitch myosin heavy chains, resulting in impaired systolic function.49,52

Relatively few animal studies have explored the prenatal origin of vascular dysfunction in offspring of obese pregnancies, in part due to the practical size limitations of evaluating vascular reactivity of resistance circulations in foetal rodents. Placental vascular density is reduced during pregnancy in obese mice and sheep mothers,43,105 and foeto-placental blood flow is impaired in the obese Japanese macaques.55 Arterial hypertrophy is also evident, with an increased aortic wall thickness and in the aortic collagen:elastin ratio in the foetus of over-nourished ewes.53 Therefore, the available literature supports that obese pregnancy leads to alterations in the vascularization of tissues and in vascular structure in foetal life. However, the impact of maternal obesity on foetal vascular function appears entirely unknown, warranting further investigation.

Mechanisms of cardiovascular dysfunction in offspring of obese pregnancy

Animal models have been indispensable to identify causal mechanisms of cardiovascular disease programming by maternal obesity. Although several mechanisms have been proposed, the most prevalent leading to a persistent

offspring phenotype can be summarized in four broad areas: sympathetic hyper-reactivity, mitochondrial dysfunction and metabolic inflexibility, oxidative stress, and epigenetic dysregulation including via miRNAs (Figure 3).

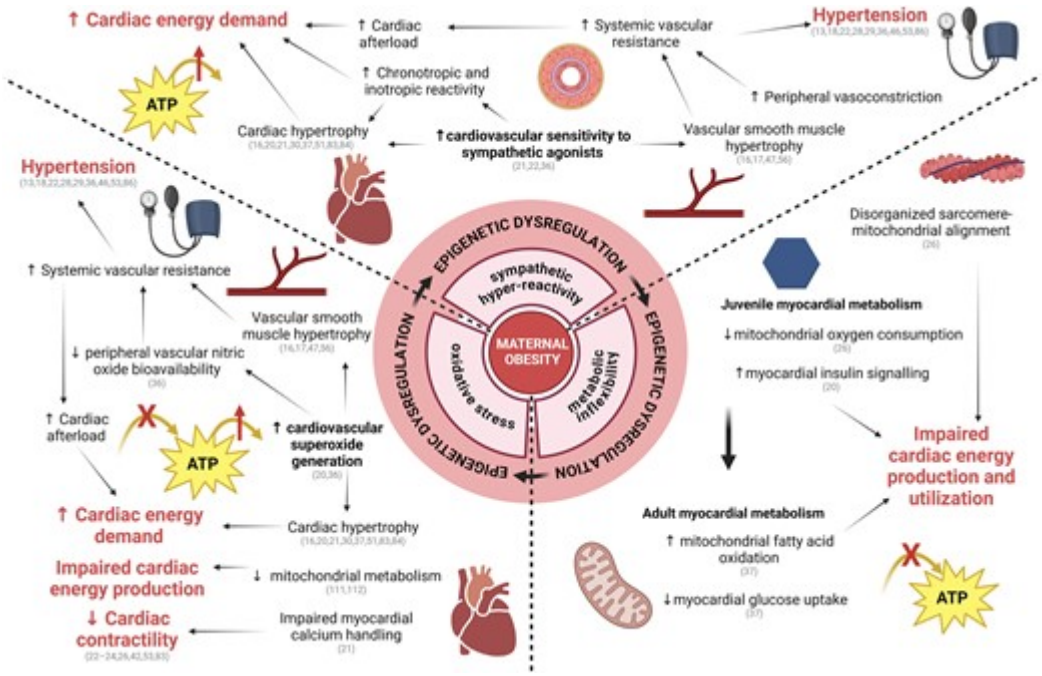


Figure 3

Mechanisms mediating cardiovascular dysfunction in offspring of obese pregnancy. Exposure to maternal obesity in utero leads to sympathetic hyper-reactivity,21,22,36 metabolic inflexibility20,26,37, and oxidative stress20,36 in the offspring, maintained through persistent epigenetic regulation,52,120,122 and eventually leading to overt cardiovascular dysfunction. Key publications supporting statements are cross-referenced.

Sympathetic hyper-reactivity

Sympathetic dominance in the cardiovascular system of adult offspring of obese pregnancy can be seen in many forms, including increased cardiac and vascular sensitivity to sympathetic agonists.21,36,42 There is also greater dose-dependent arterial pressure response to alpha-adrenergic agonists in adult offspring of obese rat pregnancy.22 Sympathetic hyper-reactivity of the peripheral vasculature can precipitate cardiovascular

dysfunction as enhanced basal sympathetic tone and arterial hypertrophy independently promote an increase in peripheral vascular resistance, thereby increasing arterial blood pressure.107 Therefore, sympathetic hyper-reactivity contributes to the offspring hypertensive phenotype observed across several animal models of obese pregnancy.22,28,29,36,46,53,86 Increased arterial blood pressure also leads to a greater cardiac afterload, resulting in increased cardiac work. While an enhanced sympathetic drive helps to maintain cardiac output, it is known to be unsustainable, eventually becoming a hallmark of early-stage heart failure.108,109

An increased LF:HF ratio of foetal heart rate variability during parturition has been reported in pregnancies with increased maternal BMI in humans, consistent with a foetal origin of cardiac sympathetic dominance.61 However, a reduction in LF:HF has been measured during mid-to-late gestation,59 and no difference was found in the cardiac autonomic regulation of 5–6-year-old children born to obese compared with healthy weight mothers.18 This suggests that underlying sympathetic hyper-reactivity in the offspring heart resulting from maternal obesity may only be revealed in the presence of a superimposed challenge, such as during labour and delivery. However, detailed studies of the impacts of maternal obesity on foetal cardiovascular function during acute stressful conditions, such as during acute hypoxia, acute asphyxia, or acute hypotension, which trigger foetal sympathetic compensatory responses, await investigation.

Mitochondrial dysfunction and metabolic inflexibility

Mouse offspring exposed to maternal obesity during gestation show increased cardiac insulin signalling20 and a reduction in mitochondrial oxygen consumption26 at 2 months of age. These data suggest that there may be increased dependence on glycolytic pathways for ATP generation. Cardiac mitochondria show circular morphology and a disorganized alignment relative to sarcomeres, which may result in poorer coupling of ATP production with consumption.26 However, -month-old mouse offspring

of obese pregnancy show a reversed cardiac metabolic phenotype with increased mitochondrial fatty acid oxidation and a reduction in glucose uptake.37 This cardiac phenotype in adulthood may be an indication of metabolic inflexibility arising due to hyperinsulinaemia resulting from peripheral insulin resistance.20 Interestingly, a metabolic shift with increased dependence on fatty acid metabolism is characteristic of the cardiac phenotype in animal models of diabetic cardiomyopathy.110

The literature also supports that alterations in cardiac metabolism in offspring of obese pregnancy may originate in foetal life. Oleate oxidation is increased in foetal primary cardiomyocytes along with higher cardiac expression of lipid metabolism-related genes in foetal mice of obese pregnancy.37,39 Maternal obesity results in increased cardiac lipid deposition in neonatal rats, likely secondary to changes in myocardial lipid metabolism and hyperlipidaemia.30,38 Metabolic inflexibility is evident at this early stage, presenting a contrasting phenotype to adult offspring, with reductions in cardiac insulin signalling in the foetal sheep49 and fibroblast growth factor (FGF)-activated PI3K/Akt signalling in the neonatal rat45 during exposure to obese gestation. Mitochondrial fragmentation and reduced cardiomyocyte oxygen consumption in the neonatal rat also support that metabolic capacity is impaired and that this may be contributing to the reduced cardiac contractile function in offspring of obese pregnancy.38,40

Oxidative stress

Mouse offspring of obese pregnancy show increased lipid peroxidation consistent with excess superoxide production, which limits basal and acetylcholine-induced nitric oxide production in the femoral artery.36 This shift in vascular oxidant tone results in endothelial dysfunction that becomes exacerbated over time, consistent with an increase in vascular oxidative stress in offspring of obese pregnancy.36 Cardiac oxidative stress is also evident in mouse offspring exposed to maternal obesity. Increased cardiac lipid peroxidation correlates with a reduction in the mitochondrial superoxide dismutase (MnSOD), and an upregulation of catalase

levels.20 These alterations in expression of antioxidant enzymes are similar to those described in heart failure, and they are linked with impaired myocardial mitochondrial metabolism.111,112

Excess generation of reactive oxygen species (ROS) and increased HIF-1α target gene expression levels have both been reported in the hearts of foetal mice exposed to maternal obesity.39,44 As ROS generation is reported to stabilize HIF-1α, this is consistent with elevated oxidative stress.39,44 Neonatal rats of obese pregnancy also show higher levels of cardiac lipid peroxidation.38 Damage to mitochondrial metabolism due to oxidative stress further exacerbates existing perturbation of cardiac energy balance, with reduced flexibility of ATP production pathways and poorer coupling of myocardial ATP production and use. Therefore, oxidative stress creates and exacerbates impairments in systolic and diastolic dysfunction in offspring of obese pregnancy.

Epigenetic regulation by miRNAs

Alterations in epigenetic signals, including DNA methylation, histone modifications, and miRNA expression, may provide a mechanism for persistent offspring cardiovascular dysfunction from foetal life into adulthood.113,114 Of particular interest are miRNAs, as their epigenetic dysregulation can modulate networks of genes in a coordinated fashion.115 MiRNAs are small non-coding RNAs that base-pair to specific sequences within the 3′ untranslated region of mRNA-target transcripts and act to decrease mRNA stability and/or block translation.116 Foetal cardiac miRNA expression is dysregulated by maternal high-fat feeding in non-human primates54,106 and in genetically obese-prone mice.117 Predicted targets of miRNAs dysregulated in the foetal baboon heart are p53, PPAR-γ, and HIF-1α, which are known to play key roles in cell cycle regulation, metabolism, and oxidative stress signalling, thus providing a mechanistic framework by which dysregulated miRNA expression could lead to increased risk of cardiovascular disease.54,106 MiRNA dysregulation has been shown to persist into adulthood, with miRNA-15b increased in the myocardium of

adult mouse offspring and in the serum of human offspring exposed to obesity during pregnancy.118 MiRNA-15b is released in response to ischaemia-reperfusion of mouse hearts ex vivo, with increased release in hearts of offspring from obese pregnancy.118 MiRNA-15b overexpression reduces cardiomyocyte mitochondrial outer membrane stability and fatty acid oxidation in vitro, demonstrating a role of miRNA-15b in cardiac metabolism.118 Programmed changes in cardiac miRNAs are consistent with a growing body of evidence suggesting that miRNAs play an important role in the pathogenesis of cardiovascular disease (see119). The mechanisms by which an in utero obesogenic environment leads to permanent changes in miRNA expression are unknown but could involve programmed changes in DNA methylation and histone modifications of DNA regions regulating miRNA transcription. In addition to contributing to programming mechanisms, miRNAs could also be exploited as disease biomarkers120 and therapeutic targets.121

Secondary insults reveal latent cardiovascular susceptibility in offspring of obese pregnancy

Offspring of obese pregnancy can show evidence of sympathetic hyper-reactivity, mitochondrial dysfunction, oxidative stress, and epigenetic dysregulation as the most prevalent or persistent phenotype, even decades after birth. However, overt cardiovascular dysfunction is not always seen. It is possible that such aspects of the cardiovascular phenotype in these offspring may enhance sensitivity to secondary insults that unveil latent susceptibility to future cardiovascular risk. Increasing evidence supports this concept, and focuses on alterations in diet, stress and ageing as likely secondary stressors (Figure 1).

Post-weaning diet

Cardiac hypertrophy and inflammation are present in lambs exposed to maternal obesity during gestation only after a 12-week feeding challenge, compared with lambs of control pregnancy exposed to the same feeding

challenge.51 While exposure to maternal obesity during gestation leads to cardiac hypertrophy and reduced ejection fraction in 8-week-old mouse offspring, the development of myocardial fibrosis and hypertension is only present at this stage in offspring exposed to an obesogenic post-weaning diet.23 Vascular dysfunction is also evident in macaque offspring of obese pregnancy dependent on post-weaning diet, with offspring on a control diet showing enhanced endothelium-dependent vasodilatation in the aorta, an effect which is reversed in offspring fed a high-fat diet.56 Importantly, in these pre-clinical studies, cardiovascular dysfunction is identified as compared with offspring of control pregnancy also exposed to the same altered post-weaning diet, demonstrating that maternal obesity leads to a heightened susceptibility to cardiovascular dysfunction induced by a dietary challenge.23,51,56 15 week-old mouse offspring of obese pregnancy are hypertensive with impaired basal vascular nitric oxide production only when exposed to a high fat post-weaning diet.36 However, these changes were comparable to offspring of control pregnancy with high-fat post-weaning diet.36 An obesogenic post-weaning diet has also been shown to suppress the compensatory upregulation of myocardial fatty acid oxidation in offspring of obese pregnancy, and to increase expression of uncoupling proteins.122 Similarly, platelet hyperactivation is only observed in male mouse offspring of obese pregnancy which were also exposed to a high fat post-weaning diet.123 Therefore, a superimposed dietary challenge exacerbates cardiac dysfunction in adult offspring of obese pregnancy through structural, inflammatory, and metabolic pathways.

Possible mechanisms for increased sensitivity to a post-weaning dietary challenge in offspring of obese pregnancy include dysregulation of appetite control, poor nutrient handling, and metabolic inflexibility. Mouse offspring of obese pregnancy are hyperphagic,42 increasing susceptibility to diet-induced obesity. Mouse offspring of obese pregnancy also show increased serum insulin levels in the absence of hyperglycaemia, indicative of insulin resistance, resulting in greater metabolic vulnerability.42 For instance, mouse offspring of obese pregnancy show exacerbated hyperinsulinaemia

following exposure to a high-fat/high-sugar post-weaning diet.23 Mouse offspring of obese pregnancy also show myocardial metabolic inflexibility, with increased dependence on fatty acid oxidation over glucose metabolism.37

Combined, hyperphagia and dysregulated glucose handling exacerbate disruption to the metabolic and endocrine milieu with a dietary challenge, imposing additional challenges to a heart that already has reduced flexibility in the metabolic pathways available for myocardial ATP production.

Stress

Maternal obesity may also prime offspring to show dysregulated cardiovascular responses to stress, revealing a heightened vulnerability to cardiac injury. Mouse offspring of obese pregnancy show enhanced myocardial fibrosis, systolic and diastolic dysfunction compared with offspring of healthy pregnancy in response to a 2-week stress challenge.83 Similarly, mouse offspring from Ay-mutant obese dams showed significantly higher infarct size than control offspring following an ischaemia-reperfusion challenge,124 indicating reduced coronary reserve to maintain cardiac function with the superimposed challenge. A plausible mechanism for enhanced sensitivity to stress is sympathetic hyper-reactivity. Rodent offspring of obese pregnancy show elevated cardiac and vascular sensitivity to adrenergic agonists, which may result in a greater increase in peripheral and coronary vascular resistance in the presence of stress, leading to increased cardiac afterload and poorer myocardial perfusion, alongside enhanced stimulation of cardiac hypertrophy.21,36,42

Ageing

The onset of maternal obesity-induced hypertension is known to be age-dependent across a range of animal models (Table 1). Mouse offspring of obese pregnancy show no difference in systolic blood pressure at 4–6 months, but by 7–12 months show a significant elevation compared with age-matched controls.29,122 In contrast, juvenile sheep offspring exposed

to maternal obesity during gestation show hypertension, which appears to resolve during adulthood.53 However, echocardiography reveals the progression of significant impairments in systolic function in ageing sheep offspring of obese pregnancy compared with ageing offspring of control pregnancy.53 Ageing in mouse offspring of obese pregnancy has also been associated with the development of both systolic and diastolic dysfunction.37,83 These preclinical studies highlight that it is the interaction between developmental exposure to maternal obesity and ageing which mediates cardiovascular dysfunction due to heightened susceptibility, not seen in aged offspring of control pregnancy.

While several studies highlight the impact of exposure to secondary insults postnatally, superimposed challenges in the prenatal environment may also play a significant role in exacerbating maternal obesity-induced cardiovascular dysfunction in offspring. For instance, a study in rats showed that uterine artery ligation in obese pregnancy results in increased relative heart weight and exacerbated alterations in arterial wall structure in 60-day-old offspring.125 Therefore, the interaction between maternal obesity and other intrauterine challenges may also be important in determining offspring cardiovascular health. However, our analysis highlights a gap in the literature of studies investigating the interaction between an in utero obesogenic environment and common stressors in foetal life, such as foetal hypoxia or excess foetal glucocorticoid exposure.

Interventions against the developmental programming of cardiovascular dysfunction in offspring of obese pregnancy

Independent of whether secondary insults occur pre- or post-natally, their occurrence can reveal latent susceptibilities, leading to the expression of overt cardiovascular dysfunction in adult offspring of obese pregnancy later in life. This highlights the need for intervention, while also providing potential windows of opportunity for preventative therapy (Figure 1). To date, interventional strategies have focussed primarily on either maternal exercise or dietary supplementation during obese pregnancy.

Maternal exercise

In mice, maternal exercise ameliorated maternal hyperinsulinaemia, prevented foetal hyperinsulinaemia, and normalized placental HIF-1α expression.34 These changes occurred with attenuation of cardiac hypertrophy and systolic dysfunction in 8-week-old adult offspring of obese pregnancy subjected to a maternal exercise intervention.24 Maternal exercise also alters the vasculature, improving placental vascularization in obese mouse pregnancy,43 and reversing vascular endothelial dysfunction in 23 week-old mouse offspring exposed to maternal obesity and a western diet post-weaning.27 Evidence from mouse models indicates that maternal exercise is an effective intervention to prevent cardiovascular disease programming, with protective effects observed in offspring even when using mild maternal exercise regimes that do not result in the normalization of maternal weight. Exercise interventions that improve the maternal metabolic phenotype, despite no effect on maternal BMI, may prevent the development of oxidative stress and metabolic inflexibility in the offspring cardiovascular system, leading to a reduced cardiovascular risk in offspring. This is an important message to convey to overweight women, that despite having no effect on their body weight, exercise during pregnancy still benefits the cardiometabolic health of their offspring.

Lifestyle interventions, such as maternal exercise, have been trialled in human subjects with no significant improvement in neonatal cardiac structure or function.126 However, a recent systematic review of randomized controlled trials highlighted that maternal lifestyle interventions, such as diet and physical activity, reduced cardiac remodelling and improved systolic and diastolic function in children exposed to maternal obesity in pregnancy.127 Interestingly, maternal lifestyle interventions did not have any effects on offspring blood pressure across trials,127 consistent with the persistence of offspring hypertension in a mouse model of maternal obesity with exercise intervention during pregnancy.24 However, with poor adherence to physical activity guidelines in pregnant women,128 alternative intervention strategies will likely need to be considered.

Offspring and maternal dietary supplementation

Intervention through offspring dietary supplementation with glucose-lowering berberine has been shown to improve cardiac function, together with improved cardiac mitochondrial function in mouse offspring exposed to gestational diabetes.129,130 However, evidence points towards a foetal origin of cardiac dysfunction in obese pregnancy, and so prevention by maternal treatment during pregnancy compared with postnatal intervention may increase the effectiveness of the approach, providing optimal protection against offspring cardiovascular dysfunction (Figure 1). Several studies have reported that maternal antioxidant treatment is effective in protecting against cardiovascular dysfunction in offspring exposed to hypoxic pregnancy by attenuating oxidative stress in the placenta and the foetal cardiovascular system.89,100,131–136 Therefore, as offspring exposed to maternal obesity also show oxidative stress, maternal antioxidant therapy may provide an effective intervention against the programming of cardiovascular dysfunction in offspring of obese pregnancy. For example, antioxidant treatment of obese mice rescues oocyte mitochondrial dysfunction137 and oxidative stress.138 Treatment of obese mice with the antioxidant pyrroloquinoline quinone from conception and throughout lactation increased adult offspring oxidative defences and metabolic flexibility.139 Whether the beneficial effects of maternal antioxidant treatment during obese pregnancy extend to protection against the programming of cardiovascular dysfunction in offspring remains to be tested.

A key limitation of translating antioxidant therapies to human populations lies in identifying a safe, but effective dose. For example, the maternal supplementation with the antioxidant vitamin C during rat pregnancy has been shown to be protective against cardiovascular dysfunction of adult rat offspring exposed to chronic hypoxia in utero, however, the dose used was over 50 times the dose given to pregnant women in clinical trials.133 Therefore, there is an urgent need to identify alternative antioxidant therapies with increased human translational potential. Mitochondria are a major site of ROS production, therefore targeting these

organelles should be one of the most effective antioxidant strategies. However, conventional antioxidants are ineffective because they cannot penetrate the mitochondria. A mitochondria-targeted ubiquinone that overcomes the problem of direct delivery to the mitochondria has now been developed (Figure 4). MitoQ is composed of a lipophilic triphenylphosphonium cation covalently attached to a ubiquinol antioxidant.140–142 Lipophilic cations can easily move through phospholipid bilayers without requiring a specific uptake mechanism. Therefore, the triphenylphosphonium cation concentrates MitoQ several hundred-fold within the mitochondria, driven by the large mitochondrial membrane potential.140–142 Only within the mitochondria, MitoQ is reduced by the respiratory chain to its active ubiquinol form, which is a particularly effective antioxidant that prevents lipid peroxidation and mitochondrial damage.140–142 The benefits of MitoQ have been revealed in a range of in vivo studies in rats and mice and have also been assessed in two Phase II human trials.143–147 In contrast to vitamin C and other conventional antioxidants, MitoQ demonstrates no pro-oxidant activity at high doses143 and long-term administration to mice145 and to human patients in Phase II trials, including one that lasted 12 months and revealed no toxicity.146,147 However, the antioxidant benefits of MitoQ in protecting the foetal and adult cardiovascular system in offspring of obese pregnancy remain to be investigated.

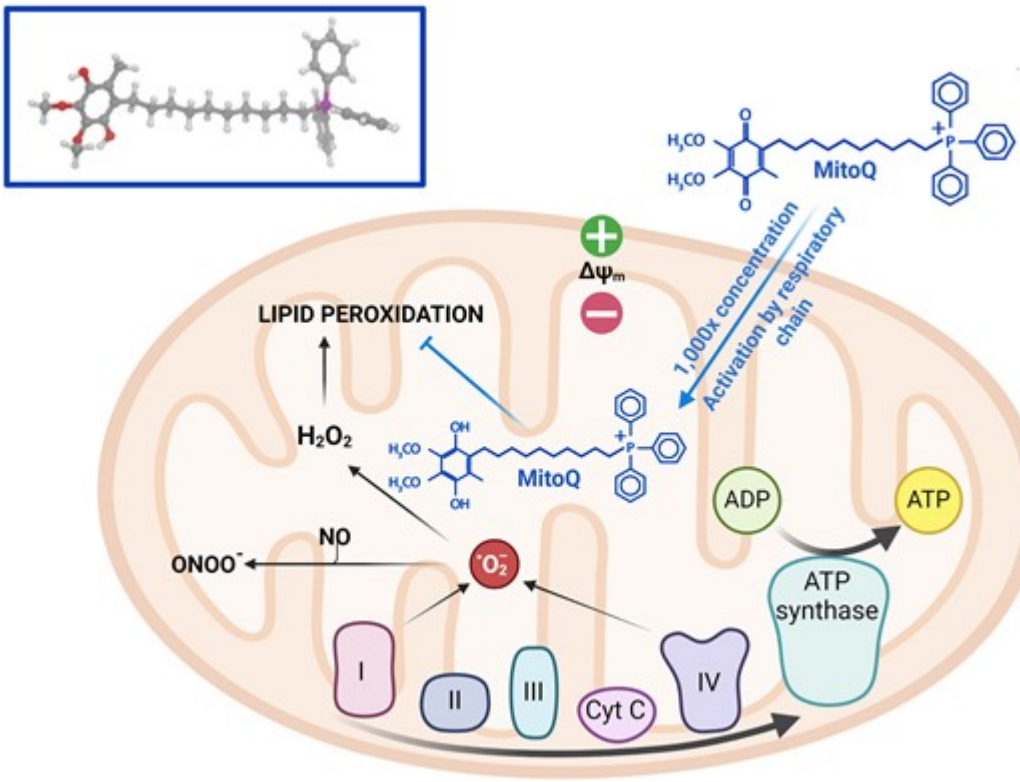


Figure 4

MitoQ: a mitochondria-targeted antioxidant. MitoQ is composed of a lipophilic triphenylphosphonium cation covalently attached to a ubiquinol antioxidant.140–142 The lipophilic cations facilitate free movement of MitoQ through phospholipid bilayers, while the triphenylphosphonium cation concentrates MitoQ ~ 1000 fold within the mitochondria, driven by the large mitochondrial membrane potential.140–142 MitoQ is reduced by the respiratory chain to its active ubiquinol form once inside the mitochondrial matrix.140–142 This activated ubiquinol form of MitoQ inhibits lipid peroxidation, ameliorating mitochondrial damage.140–142

Concluding remarks

There is extensive evidence derived from human studies and preclinical animal models for the programming of an increased risk of cardiovascular disease in offspring exposed to maternal obesity in utero (Table 1 and Figure 2). Cardiovascular susceptibility in offspring has an early origin, with many

aspects of the cardiac dysfunctional phenotype emerging in foetal life across mammalian species. This suggests that candidate interventions should start as early as possible during the developmental trajectory, rather than waiting until disease is established and has become irreversible. The effects of novel treatments like mitochondria-targeted antioxidant therapy during obese pregnancy in preclinical animal models should be explored. The literature also highlights a limited understanding of how vascular structure and function is altered in offspring of obese pregnancy before birth. Large mammalian animal models permitting functional assessment of foetal vascular reactivity in resistance circulations must be employed to address this gap in our knowledge. This review also addressed key programming mechanisms linking maternal obesity with offspring cardiovascular dysfunction, including sympathetic hyper-reactivity, the development of oxidative stress, mitochondrial dysfunction, metabolic inflexibility, and epigenetic dysregulation via miRNAs. Data also support that exposure to a secondary insult in adult life, or even the process of ageing, often reveals latent impairments in the cardiovascular system in offspring of obese pregnancy. It is likely that secondary insults occurring prenatally in offspring of obese pregnancy may also exacerbate latent susceptibility to cardiovascular dysfunction. Therefore, further research is required to understand how maternal obesity may impact the foetal cardiovascular defence to common acute stresses in utero, such as acute foetal hypoxia, acute foetal asphyxia, or acute foetal hypotension. In turn, further research is also required to understand how longer-term intrauterine complications in adverse pregnancy, such as chronic foetal hypoxia or excess foetal glucocorticoid exposure, may interact with maternal obesity to affect cardiovascular function in offspring.

22. **Sex-specific risk factors: new light shed on gestational diabetes and obesity**

This Focus Issue on diabetes and metabolic disorders contains the **'Great debate: pre-diabetes is not an evidence-based treatment target for cardiovascular risk reduction'** by Nikolaus Marx from the University

Hospital Aachen in Germany, and colleagues.1 The authors note that with the increasing burden of diabetes as a cause of macro- and microvascular disease linked to the epidemics of obesity, attention is being paid to dysglycaemic states that predict and precede the development of type 2 diabetes.2–7 Such conditions, termed pre-diabetes, are characterized by fasting plasma glucose, or plasma glucose levels on an oral glucose tolerance test, or values of glycated haemoglobin intermediate between 'normal' values and those characterizing diabetes. These last are associated, in epidemiological terms, with a higher incidence of microvascular disease—mostly retinopathy. There is little doubt that pre-diabetes has important prognostic implications, especially for the occurrence of myocardial infarction, ischaemic stroke, and peripheral arterial disease. It is disputed, however, whether pre-diabetes is itself an actionable disease entity, in addition to the risk factors characterizing it (Figure 1). Because of this uncertainty, the latest European Society of Cardiology guidelines chose not to include pre-diabetes as a treatment target for atherosclerotic cardiovascular disease, at variance from the three previous editions of such guidelines.8 This is spurring a debate, the Pro and Contra arguments featured in the present debate article.

Figure 1

A schematic representation of the time course of development of type 2 diabetes in the context of excess calorie intake. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) occur years before blood glucose exceeds the so-called diabetic threshold, above which microangiopathy starts to occur and type 2 diabetes is diagnosed. Much before the diagnosis of diabetes, however, the progressive decline in insulin sensitivity and initially compensatory insulin hypersecretion lead to the earlier occurrence of macroangiopathy (large vessel atherosclerosis) and the development of atherosclerotic vascular disease (circled in red). The time frame of IFG, higher than normal glycated haemoglobin (HbA_{1c}), and—probably more

relevant—IGT revealed at the oral glucose tolerance test (OGTT) is termed ‘pre-diabetes’. Whether pre-diabetes is an actionable target for interventions, independent of risk factors common to all vascular disease, is debated. CV, cardiovascular1

The consequences of cardiovascular and metabolic diseases during pregnancy are receiving growing interest.9–16 Pregnancy complicated by maternal obesity contributes to an increased cardiovascular risk in offspring, which is increasingly concerning as the rates of obesity and cardiovascular disease are higher than ever before and still growing. In a State of the Art Review article entitled **‘Pregnancy in obese women and mechanisms of increased cardiovascular risk in offspring’**, Anna Cochrane from the University of Cambridge in the UK, and colleagues note that there has been much research in humans and pre-clinical animal models to understand the impact of maternal obesity on offspring health.17 This review summarizes what is known about the offspring cardiovascular phenotype, describing a mechanistic role for oxidative stress, metabolic inflexibility, and mitochondrial dysfunction in mediating these impairments. It also discusses the impact of secondary post-natal insults, which may reveal latent cardiovascular deficits that originated in utero. Finally, current interventional efforts and gaps of knowledge to limit the developmental origins of cardiovascular dysfunction in offspring of obese pregnancy are highlighted.

The increasing prevalence of diabetes, obesity, and their cardiometabolic sequelae present major global health challenges and highlight shortfalls of current approaches to the prevention and treatment of these conditions. In a State of the Art Review article entitled **‘Diabetes and obesity: leveraging heterogeneity for precision medicine’**, Paul Franks from Lund University in Sweden, and colleagues indicate that representing the largest global burden of morbidity and mortality, the pathobiological processes underlying cardiometabolic diseases are in principle preventable and, even when disease is manifest, sometimes reversable.18 Nevertheless, with current clinical and public health strategies, goals of widespread prevention and

remission remain largely aspirational. Application of precision medicine approaches that reduce errors and improve accuracy in medical and health recommendations has potential to accelerate progress towards these goals. Precision medicine must also maintain safety and ideally be cost-effective, as well as being compatible with an individual's preferences, capabilities, and needs. Initial progress in precision medicine was made in the context of rare diseases, with much focus on pharmacogenetic studies, owing to the cause of these diseases often being attributable to highly penetrant single gene mutations. By contrast, most obesity and type 2 diabetes are heterogeneous in aetiology and clinical presentation, underpinned by complex interactions between genetic and non-genetic factors. The heterogeneity of these conditions can be leveraged for development of approaches for precision therapies. Adequate characterization of the heterogeneity in cardiometabolic disease necessitates diversity of and synthesis across data types and research methods, ideally culminating in precision trials and real-world application of precision medicine approaches. This State of the Art Review provides an overview of the current state of the science of precision medicine, as well as outlining a roadmap for study designs that maximize opportunities and address challenges to clinical implementation of precision medicine approaches in obesity and diabetes.

Observational studies have highlighted that gestational diabetes mellitus is associated with a higher risk of cardiovascular diseases, but the causality remains unclear. In a Clinical Research article entitled **'Gestational diabetes and future cardiovascular diseases: associations by sex-specific genetic data'**, Yeshen Zhang from the Southern Medical University in Guangzhou, China, and colleagues investigated the causality between genetic predisposition to gestational diabetes (GD) and the risk of cardiovascular diseases using sex-specific Mendelian randomization analysis.19 Linkage disequilibrium score regression analysis and two-sample Mendelian randomization analysis were applied to infer the genetic correlation and causality, respectively. Mediation analysis was conducted using a two-step Mendelian randomization approach. Sensitivity analyses

were performed to differentiate causality from pleiotropy. The genome-wide association study summary statistics for gestational diabetes mellitus were obtained from the FinnGen consortium, while those for cardiovascular diseases were generated based on individual-level genetic data from the UK Biobank. Linkage disequilibrium score regression analyses revealed that GD had a significant genetic correlation with coronary artery disease and myocardial infarction after Benjamini–Hochberg correction in ever-pregnant women. In Mendelian randomization analyses, odds ratios for coronary artery disease and myocardial infarction were 1.09 (1.01–1.17) and 1.12 per unit increase in the log-odds of genetic predisposition to GD in ever-pregnant women, respectively. Further, type 2 diabetes and hypertension were identified as mediators for the causality of genetic predisposition to GD on coronary artery disease.

Zhang et al. conclude that this study demonstrates a suggestive causal relationship between genetic predisposition to GD and the risk of coronary artery disease, which is mainly mediated by type 2 diabetes and hypertension. These findings highlight that targeting modifiable cardiometabolic risk factors may reduce the risk of coronary artery disease in women with a history of GD. This manuscript is accompanied by an **Editorial** by Maddalena Ardissino from the University of Cambridge in the UK and Michael Honigberg from the Broad Institute of Harvard and MIT in Cambridge, MA, USA.20 The authors note that the study of Zhang et al. adds valuable insight to the ongoing investigation into the relationship between GD and cardiovascular disease. Using Mendelian randomization, the results of the study contradict the notion of a direct causal link between GD and cardiovascular disease, and rather support the notion of shared upstream risk factors between GD and cardiovascular disease. Furthermore, when interpreted from a clinical angle, the results suggest an important opportunity: even if GD itself is not causal, the excess cardiovascular disease burden that has been demonstrated in affected women can be substantially mitigated with high-quality primordial and primary prevention to prevent and mitigate traditional cardiovascular risk factors. To effectively

translate these insights into clinical practice, a coordinated multidisciplinary effort will be essential to leverage this unique primordial prevention opportunity in our efforts to reduce the global burden of cardiovascular disease in women.

Hyperglycaemia during GD predisposes women and their offspring to later cardiometabolic disease. In a Translational Science article entitled **'The inflammatory and oxidative phenotype of gestational diabetes is epigenetically transmitted to the offspring: role of methyltransferase MLL1-induced H3K4me3'**, Nadia Di Pietrantonio from the Karolinska Institutet in Stockholm, Sweden, and colleagues remind us that the hyperglycaemia-mediated epigenetic changes remain to be elucidated.21 Methyltransferase MLL1-induced trimethylation of histone 3 at lysine 4 (H3K4me3) activates an inflammatory and oxidative phenotype. This epigenetic mark in GD women and its transmission to the offspring were investigated. Peripheral blood mononuclear cells (PBMCs) were collected from GD and control women and also from adolescents born to women of both groups. Human umbilical vein endothelial cells (HUVECs) and cord blood mononuclear cells (CBMCs) were obtained from umbilical cords. To investigate the role of MLL1, HUVECs were exposed to the inhibitor MM102 or small interfering RNA (siRNA) transfection. PBMCs, CBMCs, and HUVECs showed an increase of NF-κBp65, IL-6, ICAM-1, MCP-1, and VCAM-1 mRNAs in GD women as compared with controls. These findings were associated with H3K4me3 enrichment in the promoter of NF-κBp65. Higher H3K4me3 and cytokine levels were observed in GD adolescents as compared with control adolescents. MLL1 drove H3K4me3 not only on NF-κB p65, but also on the NOX4 promoter. Inhibition of MLL1 blunted NF-κBp65 and NOX4 by modulating the inflammatory and oxidative phenotype (Figure 2).

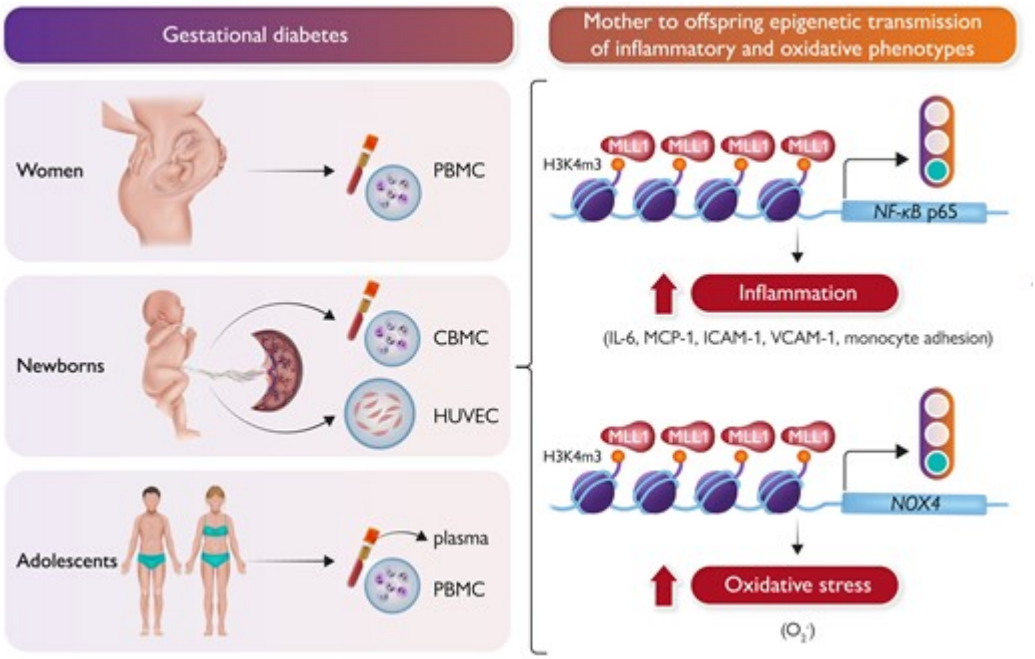


Figure 2

Peripheral blood mononuclear cells (PBMCs) collected from women with gestational diabetes (GD), as well as cord blood mononuclear cells (CBMCs) and human umbilical vein endothelial cells (HUVECs) from their newborns. Methyltransferase MLL1-induced activatory trimethylation of histone H3 at lysine 4 (H3K4me3) in the promoter region of NF-κBp65 and NOX4 genes leads to their up-regulation and downstream inflammation and oxidative stress. Enrichment of H3K4me3 in the NF-κBp65 promoter persists in PBMCs collected from adolescents born to GD women, and it is associated with elevated plasma levels of inflammatory cytokines.21

The authors conclude that such a proof-of-concept study shows persistence of MLL1-dependent H3K4me3 in offspring born to GD women, suggesting an epigenetic-driven transmission of maternal phenotype. These findings may pave the way for pharmacological reprogramming of adverse histone modifications to mitigate abnormal phenotypes underlying early atherosclerotic cardiovascular disease. The contribution is accompanied by an **Editorial** by Gian Paolo Fadini from the University of Padova in Italy.22 Fadini notes that the public health implications of this research are significant and offer a glimmer of hope. If the link between GD and cardio-metabolic diseases in offspring is not primarily genetic, then the risk passed

down through generations is something we can potentially change. This realization opens up exciting possibilities for investing in strategies that focus on epigenetic reprogramming of metabolism. While the idea of epigenetic drugs might seem like science fiction, it is worth remembering that our epigenetic footprint can also be reshaped with something as accessible as diet and lifestyle. These tried-and-true methods could be key players in turning the tide against the cardio-metabolic pandemic. It is a reminder that in the complex world of epigenetics, we have the power to rewrite the story.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled **'Subgroup effects of ticagrelor treatment strategies: credibility considerations in an individual patient data meta-analysis'**, Tengfei Li from the Gansu University of Chinese Medicine in China and colleagues comment on the recent publication **'Ticagrelor monotherapy for acute coronary syndrome: an individual patient data meta-analysis of TICO and T-PASS trials'** by Yong-Joon Lee from the Yonsei University College of Medicine in Seoul, Korea.23,24 Lee et al. respond in a separate comment.25

23.Long-Term Impact of Pregnancy on Clinical Outcomes in Individuals With Hypertrophic Cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited form of cardiomyopathy with an estimated prevalence of 1:200-1:500 in the general population.**1** The reported prevalence of HCM in pregnancies ranged from 1:1,000 to 1:5,000 pregnancies worldwide.**2-5**

Sudden cardiac death (SCD) is a known complication associated with HCM. Over the past 2 decades, the burden of SCD in HCM has dramatically decreased by two-fold owing to better risk stratification, increased awareness, and early management.**6** Indeed, the presentation of HCM is heterogeneous across different age groups, including individuals those of reproductive age.

However, the majority have favorable long-term outcomes with contemporary therapies and early diagnosis. The question regarding the impact of HCM on maternal pathophysiology is not yet fully understood among pregnant individuals. Historically, physicians have been concerned regarding the potential for the elevated risk of unfavorable fetal and maternal outcomes in patients with HCM. It is imperative to understand the cardiac physiologic changes that occur in pregnancy and the potential effect on those individuals with HCM. During pregnancy, there is an increase in blood volume and subsequent increase in preload, coupled with an increase in cardiac output (mediated by a risk in heart rate and increase in stroke volume) and a drop in peripheral vascular resistance individuals.**7** Such changes occurring in those with obstructive HCM (oHCM) may elicit or worsen obstructive physiology leading to progressive symptoms and heart failure (HF) exacerbation.**8** In addition, during the active stages of labor, the heightened cardiovascular stress might mediate stress-related tachyarrhythmias and lead to hemodynamic and clinical deterioration.**9** However, it appears that the majority of individuals with HCM tolerate pregnancy well based on previous reports.**2**,**10**,**11** Of note, the previously published studies were mainly small case series or retrospective studies with heterogeneous definitions of SCD, and major adverse cardiovascular events (MACE), limiting generalizability. Hence, we sought to provide an extensive population-based investigation of individuals with HCM and to determine whether pregnancy is associated with worse long-term clinical outcomes.

Methods

Study oversight

Institutional Review Board approval was exempted by the University of Texas Institutional Review Board, given that aggregate deidentified data were used from a research network database. These study findings are reported per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.**12**

Data source

Data were obtained from the TriNetX Analytics Network database. TriNetX is a largely U.S.-based multicenter federated health research network aggregating anonymized data from electronic health records of more than 120 million patients at the time of our search and from more than 80 U.S. health care organizations. Although the data are organized in an aggregate deidentified form, built-in analytics allow for the generation of patient-level data for cohort selection and matching, analyzing the incidence and prevalence of events in a cohort, and comparing characteristics and outcomes over time between matched cohorts at the patient level. TriNetX provides data, including demographics, diagnostic and procedural information, and standard measurements (including vital signs, laboratory results, and medications) using standardized coding systems (International Classification of Diseases-10th Revision-Clinical Modification [ICD-10] and Current Procedural Terminology codes for diagnoses and procedures, Logical Observation Identifiers names and codes for vital signs and laboratory values, and RxNorm for medications). More information on the database can be found elsewhere (**Supplemental Appendix**).**13**

Study population and design

We conducted a retrospective propensity-matched cohort analysis of individuals with reproductive age ≥18 to 45 years with a diagnosis of HCM using the ICD-10th Revision codes (HCM) (I42.1 or 142.2 for obstructive and non-obstructive HCM, respectively) between April 1, 2012, and November 30, 2022. The population was further stratified into 2 cohorts: 1) individuals with pregnancy/high-risk pregnancy supervision (this cohort further had 2 subsequent health care encounters confirming the diagnosis of pregnancy first/second/third-trimester monitoring with HCM diagnosis within 1 to 3 months of the index encounter); and 2) individuals without a history of pregnancy or subsequent antenatal/pregnancy supervision encounters throughout the study period (**Supplemental Appendix**). To minimize the potential inclusion of other common causes of left ventricular hypertrophy,

we excluded patients with a history or new diagnosis of peripartum cardiomyopathy in the pregnant group, and patients with follow-up data of <1 year from both groups. Moreover, sensitivity analyses were performed after excluding patients with hypertension or aortic stenosis in attempt to mitigate ICD-10 miscoding bias for patients with left ventricular hypertrophy. Cohorts were matched with the use of propensity score matching (PSM).

Study endpoints

The primary outcome of this study was all-cause mortality. Secondary outcomes included a composite outcome of arrhythmic events (defined as SCD, appropriate implantable cardioverter shocks, sustained ventricular tachycardia/ventricular fibrillation, SCD), MACE (defined as all-cause mortality, stroke, myocardial infarction, HF exacerbation) (**Supplemental Appendix**). All outcomes were analyzed from day 1 to 10 years after the index event.

Statistical analysis

Continuous variables are presented as mean ± SD and were compared between the cohorts using independent sample t-tests for continuous variables. Categoric variables are reported as n (%) and compared using the chi-square test. To control for baseline differences in the patient cohorts, 1:1 PSM was performed, leveraging a built-in PSM algorithm that uses the greedy nearest-neighbor algorithm with a caliper of 0.1 pooled SDs, to generate balanced subsets of the cohorts for over 50 covariates, including the following characteristics: demographics, baseline characteristics, septal reduction, medications, and laboratory data. Any characteristic with a standardized mean difference between cohorts of <0.1 was considered to be well-matched. Adjusted ORs with 95% CIs were calculated for primary and secondary outcomes. Survival analysis was performed by plotting Kaplan-Meier curves with log-rank tests to compare the 2 cohorts. Patients were censored at the last date of clinical encounter follow-up within the database if there was no recorded death date. To account for possible bias with inclusion of other

common causes of left ventricular hypertrophy, we performed a sensitivity analysis after excluding patients with ICD-10 codes for combined HCM and hypertension or aortic stenosis diagnoses. All patients who had an event prior to the index enrollment date were excluded from the cohort. Statistical significance was set at a 2-sided P value of <0.05. Statistical analyses were performed using the TriNetX online platform using R for statistical computing.

Results

Patient characteristics

In total, 10,936 adult individuals of reproductive age (18-45 years) with a diagnosis of HCM were identified between 2012 and 2022 with at least 1 year of follow-up. Of these, 4,087 (37.4%) patients had a pregnancy/high-risk pregnancy encounter, while 6,849 (62.6%) patients had no prior or future pregnancy encounter throughout the follow-up study (**Figure 1**).

Download FigureDownload PowerPoint

Figure 1

Consort Flow Diagram of Study Population

Consort diagram depicting inclusion and exclusion criteria. HCM = hypertrophic cardiomyopathy; HCO = health care organizations.

Prior to PSM, individuals with a pregnancy history were older (30.6 vs 27.5) than individuals with no history of pregnancy. Moreover, about 50% of the population was White, with Black individuals comprising about one-third of the population. Pregnant HCM patients had a higher prevalence of comorbidities including hypertension, diabetes mellitus, atrial fibrillation, smoking, cerebrovascular accident, transient ischemic attack, and history of septal reductive therapies, compared to individuals with no history of pregnancy. The baseline characteristics in both groups were similar with no residual imbalance following PSM (standard difference: <0.1 for all covariates). The mean follow-up for pregnancy and no-pregnancy cohorts was 3.5 years

and 3.2 years, respectively. Subgroup analysis was performed for oHCM patients (**Supplemental Table 2**).

Following 1:1 PSM for the characteristics described in the methods, the matched cohorts comprised 3,399 patients each. **Table 1** summarizes the characteristics of the unmatched and propensity-matched cohorts. Patients in the pregnancy-matched cohort were 30.2 years of age; 54% were White, 33.7% Black, and 1.6% Asian. The most common comorbidities were hypertension (26.7%), diabetes mellitus (13.1%), and smoking (8.8%). All characteristics of the matched HCM with pregnancy cohort demonstrated standardized mean differences <0.1 vs the HCM without pregnancy cohort, except for hemoglobin A1c which was significantly lower (5.9 vs 6.22; standardized mean difference 0.14) in the pregnancy cohort.

Table 1Baseline Characteristics of HCM Patient Population Before and After PSM	**Before PSM**				**After PSM**			
	HCM With Pregnancy (n = 4,087)	**HCM Without Pregnancy (n = 6,849)**	**P Value**	**Standardized Difference**	**HCM With Pregnancy (n = 3,399)**	**HCM Without Pregnancy (n = 3,399)**	**P Value**	**Standardized Difference**
Demographics								
Age, y								
Current age	34.7 ± 7.17	32.3 ± 8.73	<0.0001	0.303	34.4 ± 7.18	34.6 ± 8.08	0.36	0.022
Age at index	30.6 ± 7.23	27.5 ± 9.48	<0.0001	0.37	30.2 ± 7.22	30.4 ± 8.39	0.19	0.031
Female	4,087 (100)	6,849 (100)	-		3,399 (100)	3,399 (100)	-	
Race								
White	2,035 (49.8)	4,120 (60.2)	<0.0001	0.21	1,834 (54)	1,858 (54.6)	0.56	0.01

Table 1Baseline Characteristics of HCM Patient Population Before and After PSM	**Before PSM**				**After PSM**			
	HCM With Pregnancy (n = 4,087)	**HCM Without Pregnancy (n = 6,849)**	**P Value**	**Standardized Difference**	**HCM With Pregnancy (n = 3,399)**	**HCM Without Pregnancy (n = 3,399)**	**P Value**	**Standardized Difference**
Black/African American	1,588 (38.8)	1,639 (24)	<0.0001	0.32	1,144 (33.7)	1,150 (33.8)	0.88	0.003
Asian	60 (1.5)	145 (2.1)	0.015	0.05	56 (1.65)	49 (1.4)	0.49	0.017
Hispanic	531 (12.7)	778 (10.9)	0.004	0.05	450 (12.8)	436 (12.4)	0.61	0.012
Unknown ethnicity	237 (5.9)	785 (11)	<0.0001	0.19	233 (6.6)	214 (6.1)	0.35	0.022
Comorbidities								
Hypertension	1,199 (29.3)	1,201 (17.6)	<0.0001	0.28	907 (26.7)	915 (26.9)	0.83	0.005
Diabetes mellitus	644 (15.8)	547 (8)	<0.0001	0.24	446 (13.1)	441 (12.9)	0.86	0.004
Smoking	567 (13.9)	285 (4.2)	<0.0001	0.34	299 (8.8)	273 (8)	0.26	0.03
Atrial fibrillation and flutter	105 (2.6)	141 (2)	0.08	0.03	81 (2.4)	86 (2.5)	0.69	0.009
Paroxysmal atrial fibrillation	29 (0.7)	39 (0.6)	0.37	0.01	23 (0.7)	24 (0.7)	0.88	0.003
Persistent atrial	10 (1)	13 (1.6)	0.55	0.01	10 (0.3)	10 (0.3)	1.00	<0.0001

Table 1Baseline Characteristics of HCM Patient Population Before and After PSM	**Before PSM**				**After PSM**			
	HCM With Pregnancy (n = 4,087)	**HCM Without Pregnancy (n = 6,849)**	**P Value**	**Standardized Difference**	**HCM With Pregnancy (n = 3,399)**	**HCM Without Pregnancy (n = 3,399)**	**P Value**	**Standardized Difference**
fibrillation								
HF	315 (7.7)	462 (6.7)	0.06	0.03	259 (7.6)	1,261 (7.7)	0.92	0.002
Systolic (congestive) HF	97 (2.4)	178 (2.6)	0.45	0.01	88 (2.6)	86 (2.5)	0.87	0.003
Diastolic (congestive) HF	101 (2.4)	139 (2)	0.13	0.03	83 (2.4)	75 (2.2	0.51	0.01
CVA	166 (4.1)	150 (2.2)	<0.0001	0.11	116 (3.4)	112 (3.3)	0.79	0.006
CKD	234 (5.7)	313 (4.6)	0.007	0.05	196 (5.8)	198 (5.8)	0.91	0.002
Family history of SCD	38 (0.9)	52 (0.8)	0.34	0.02	31 (0.9)	29 (0.9)	0.8	0.006
Personal history of SCD	19 (0.5)	26 (0.4)	0.5	0.01	15 (0.4)	14 (0.4)	0.85	0.004
ICD	80 (2)	110 (1.6)	0.18	0.02	65 (1.9)	65 (1.9)	1.00	<0.0001
PPI	49 (1.2)	59 (0.9)	0.09	0.03	33 (1)	38 (1.1)	0.55	0.01
ASA	10 (0.2)	0	<0.0001	0.07	0	0	-	-

Table 1Baseline Characteristics of HCM Patient Population Before and After PSM	**Before PSM**				**After PSM**			
	HCM With Pregnancy (n = 4,087)	**HCM Without Pregnancy (n = 6,849)**	**P Value**	**Standardized Difference**	**HCM With Pregnancy (n = 3,399)**	**HCM Without Pregnancy (n = 3,399)**	**P Value**	**Standardized Difference**
Surgical myectomy	10 (0.2)	19 (0.3)	0.74	0.006	10 (0.3)	10 (0.3)	1.00	<0.0001
Medications								
Verapamil	127 (3.1)	124 (1.8)	<0.0001	0.08	94 (2.8)	85 (2.5)	0.5	0.01
Metoprolol	529 (12.9)	617 (9)	<0.0001	0.13	431 (12.7)	438 (12.9)	0.8	0.006
Disopyramide	10 (0.2)	10 (0.2)	0.24	0.02	10 (0.3)	10 (0.3)	1.0	<0.0001
Sotalol	12 (0.3)	20 (0.3)	0.99	0.0002	11 (0.3)	10 (0.3)	0.83	0.005
Mexiletine	10 (0.2	10 (0.2)	0.24	0.02	10 (0.3)	10 (0.3)	1.0	<0.0001
Diuretics	808 (19.8)	947 (13.8)	<0.0001	0.15	642 (18.9)	649 (19.1)	0.83	0.005
Laboratory data								
NT-proBNP	3,313 ± 9,762 (4)	4,237 ± 12,013 (2.6)	0.44	0.08	3,583 ± 10,513 (3.8)	3,542 ± 9,841 (3.8)	0.97	0.004
LDL	108 ± 34.7 (42.6)	104 ± 36.6 (24.4)	0.001	0.11	108 ± 35.2 (39)	106 ± 36.8 (36.7)	0.25	0.04
Ferritin	192 ± 1,236 (19.8)	186 ± 823 (11.3)	0.9	0.005	150 ± 615 (17.9	162 ± 476 (17.7)	0.71	0.02

Table 1Baseline Characteristics of HCM Patient Population Before and After PSM	Before PSM				After PSM			
	HCM With Pregnancy (n = 4,087)	HCM Without Pregnancy (n = 6,849)	P Value	Standardized Difference	HCM With Pregnancy (n = 3,399)	HCM Without Pregnancy (n = 3,399)	P Value	Standardized Difference
Creatinine	0.84 ± 1.02 (78)	0.93 ± 1.2 (45)	0.002	0.07	0.85 ± 1.06 (73.6)	0.91 ± 1.16 (73.7)	0.04	0.06
HBA1c	5.9 ± 1.8 (39.5)	6.15 ± 1.9 (20.4)	0.03	0.08	5.9 ± 1.78 (34.7)	6.22 ± 12.06 (34.7)	0.0007	0.14
Follow-up, days	1,269 ± 896	1,139 ± 1,007	-	-	1,282 ± 912	1,088 ± 903	-	-

Values are mean ± SD or n (%). Any characteristic with a standardized mean difference between cohorts <0.10 was considered to be well matched.

Afib = atrial fibrillation; ASA = alcohol septal ablation; CKD = chronic kidney disease; CVA = cerebrovascular accident; HBA1c = hemoglobin A1c; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PPI = permanent pacemaker implantation; PSM = propensity score matching; SCD = sudden cardiac death.

Clinical outcomes

Primary outcome (All-cause survival)

The 10-year all-cause mortality occurred in 3.63% of patients with HCM and pregnancy, as compared to 4.04% in those without pregnancy (OR: 0.89; [95% CI: 0.7-1.14]; P = 0.055) (**Table 2**). Moreover, the probability of event-free survival at 10 years (81.14% vs 81.09%; P = 0.75; HR: 0.79; 95% CI: 0.62-1.005) was similar between both groups (**Table 2**, **Central Illustration**).

In addition, the HRs did not differ at 1, 3, and 5 years of follow-up (**Figure 2**). In the subgroup analysis of oHCM, the risk of all-cause mortality remained similar between both groups at 10-year follow-up (**Supplemental Table 3**, **Supplemental Figure 3**). Following sensitivity analysis after excluding patients with hypertension and aortic stenosis, results were comparable between both cohorts (**Supplemental Table 4**, **Supplemental Figure 5**).

Table 2Outcomes in HCM	**Risk of Events**			
Variables	**HCM With Pregnancy (n = 3,399)**	**HCM Without Pregnancy (n = 3,399)**	**OR (95% CI)**	**P Value**
All-cause mortality	127 (3.63)	142 (4.04)	0.89 (0.7-1.14)	0.37
Arrhythmic events (SCD)	133 (3.93)	142 (4.21)	0.93 (0.73-1.18)	0.55
MACE	268 (9.46)	257 (9.27)	1.02 (0.85-1.22)	0.80

Values are n (%) unless otherwise indicated. Outcomes are compared between 1 d and 10 y after index event.

MACE = major adverse cardiovascular and cerebrovascular events; other abbreviations as in **Table 1**.

Clinical Outcomes in Patients With Hypertrophic Cardiomyopathy With and Without Pregnancy

Diagram of the patient population and main findings. Propensity score matching was conducted to create 2 cohorts of women within the reproductive age period (>18-45 years of age) with Hypertrophic Cardiomyopathy based on pregnancy history. Primary and secondary

outcomes were demonstrated to be favorable in the cohort with pregnancy using odds ratio and log-rank tests. HCM = Hypertrophic Cardiomyopathy; MACE = major adverse cardiovascular events; VT = ventricular tachycardia;

SCD = sudden cardiac death; ICD = implantable cardioverter-defibrillator.

Kaplan-Meier survival curves were used to depict all cause mortality in women with HCM with and without pregnancy. Log-rank tests were used to compare outcome between 2 groups over a 10-year follow-up. HCM = hypertrophic cardiomyopathy.

Secondary outcomes

Arrhythmic events

At 10-year follow-up, the arrhythmic composite outcome occurred in 3.9% of the study group, compared to 4.21% in matched controls without pregnancy (OR: 0.93; [95% CI: 0.73-1.18]) (**Table 2**). At 1, 3, and 5-year follow-up intervals, both groups had a similar probability of event-free survival (**Figure 3A**). In the subgroup analysis of oHCM, the risk of arrhythmic events remained similar between the groups at 10-year follow-up (**Supplemental Table 3**, **Supplemental Figure 3**). Following sensitivity analysis after excluding patients with hypertension and aortic stenosis, results were comparable between both cohorts (**Supplemental Table 4**, **Supplemental Figure 5**).

Long-Term Secondary Outcomes

Kaplan-Meier Analysis of (A) arrhythmic events, (B) major adverse cardiovascular events. Abbreviation as in **Figure 2**.

Major adverse cardiovascular events

At 10-year follow-up, MACE occurred in 9.46% of patients with HCM and pregnancy, compared to 9.27% in those without pregnancy (OR: 1.02; [95% CI: 0.85-1.22]) (**Table 2**). The risk of MACE was similar between both groups

through 10-year follow-up between both groups (HR = 0.96; [95% CI: 0.76-1.076]) (**Figure 3B**). Moreover, in the subgroup analysis of oHCM, the risk of MACE remained similar between both groups at 10-year follow-up (**Supplemental Table 3**, **Supplemental Figure 4**). Following sensitivity analysis after excluding patients with hypertension and aortic stenosis, results were comparable between both cohorts (**Supplemental Table 4**, **Supplemental Figure 5**).

Discussion

In this propensity-matched retrospective population-based cohort study, pregnancy in individuals with HCM was not associated with an increased risk of all-cause mortality or arrhythmic events at 10 years, compared to individuals with no history of pregnancy. Moreover, pregnancy was associated with a lower risk of major adverse cardiovascular events and HF exacerbation, compared to individuals without pregnancy. In subgroup analysis of oHCM phenotype, clinical outcomes were comparable between both cohorts, except for HF exacerbation which was significantly lower in the pregnancy cohort, compared to individuals without pregnancy.

The main focus of our study was the long-term impact of pregnancy on outcomes in individuals with HCM. Notably, the literature investigating long-term sequelae of pregnancy in HCM remains scarce to date. Few retrospective small studies investigated short-term outcomes of pregnancy in individuals with HCM over the past 4 decades, with a sole focus on the peripartum outcomes of this high-risk population.**10**,**11**,**14**,**15** The ROPAC (Registry on Pregnancy and Cardiac Disease) registry, the largest European prospective registry to date for pregnancy-related outcomes in individuals with HCM (2007-2014) (n = 60) with 6-month follow-up, demonstrated no maternal mortalities throughout the study period.**2** In a pooled analysis of 1,624 pregnancies in individuals with HCM, Moolla et al**16** demonstrated concordant reassuring favorable outcomes of maternal mortality of 0.2%. Similarly, in our population-based analysis, the maternal mortality was low in both the pregnancy and no pregnancy cohorts at 1 year from index encounter

(1.5% vs 1.7%, P = 0.43). These findings persisted throughout the 10-year follow-up for all-cause mortality. Moreover, in the oHCM subgroup, our results were in line with the ROPAC registry, demonstrating that oHCM phenotype survival was comparable between individuals with and without pregnancy. This implies that the obstructive phenotype alone does not carry a higher risk of maternal mortality. However, it is plausible that some oHCM patients with fewer forms of left ventricular hypertrophy, lower obstructive gradients, or less symptomatic might have received similar close follow-ups to oHCM patients with more severe forms of obstruction given the possible selection bias based on pregnancy state which might have indirectly led to a lower risk of events on long-term. Overall, our study's inception period over the past decade spanned from 2012 to 2022, allowing the generalizability of our findings using large-scale real-world data on survival outcomes in individuals with HCM. Moreover, several points in our study merit further discussion.

The risk of arrhythmic events remains a major concern during the vulnerable state of pregnancy in HCM. In individuals with HCM, the reported incidence of ventricular arrhythmia during pregnancy and the postpartum stage ranged from 1% to 10%.**2**,**10**,**16** Several factors might have played a role in the heterogeneity of the reported incidences of SCD events during the peripartum period, including the SCD risk profile of the patient population, study designs, partially due to varying definitions of arrhythmic events, and the implications of the ongoing risk stratification before and throughout the peripartum state. In our study, the incidence of composite arrhythmic events was relatively low at around 2% in both cohorts at 1-year follow-up, and the cumulative incidence of arrhythmic events remained comparable throughout the study period (3.9% vs 4.2%; OR: 0.93; [95% CI: 0.73-1.18]; P = 0.55). Arguably, during the high-risk state of pregnancy, one would suspect that the risk of SCD events would be expected to be higher in HCM individuals with pregnancy compared to those without pregnancy, owing to hemodynamic and hormonal stress. However, that has not been reflected in our study. Perhaps, one would speculate that more frequent prescriptions of beta-blockers and

anti-arrhythmics might have played a role, although we were not able to identify this information given the limitations of the database utilized. Close and serial monitoring of HCM individuals during pregnancy is highly emphasized as they fall into classes II and III of the Modified World Health Organization (WHO) with expected maternal cardiac event rates based on the WHO class II: 5.7 to 10.5%, II/III: 10 to 19%, and III: 19 to 27%. Women classified as WHO class II should be evaluated every trimester, while those in class III monthly or bimonthly. To date, the European and American consensus documents for the management of arrhythmias during pregnancy do not fully endorse further interventions for constant perinatal monitoring of arrhythmias in individuals with HCM.**5**,**17** Recent limited randomized data proposed the use of implantable loop recorder in refining risk stratification and guiding management in individuals with HCM during pregnancy. However, given the limited number of included HCM patients, further data are needed to elucidate the benefit of continuous rhythm monitoring among this high-risk group.**18**

The incidence of MACE in the HCM population has been established to be high at around 25%. In particular, women with HCM were found to have worse long-term outcomes compared to men with HCM.**19**,**20** In our study, about one-tenth of the entire population experienced MACE at 10-year follow-up, similar to the general HCM population.**21**,**22** Among the pregnancy population with HCM, several studies showed that the risk of MACE remains elevated ranging from 23% in the ROPAC registry up to 48%**2** in other reports.**10**,**11**,**23** In our study, the risk of MACE throughout 10 years was comparable between the cohorts with and without pregnancy. Although potential bias cannot be excluded in this observational study despite careful matching, we believe that the comparable event rate of MACE might be plausible. Bias toward the high-risk population with pregnancy might be likely with the possibility of undergoing more frequent surveillance and dedicated care in specialized cardio-obstetrics centers. Such observations warrant further investigation in future studies to elucidate the possible contributing factors.

Moreover, it is important to carefully note that the possibility that women with more severe phenotypes of HCM (ie, LV wall thickness >15 mm, LV systolic dysfunction, extensive late gadolinium enhancement) might have not been included in the pregnancy cohort, given the heightened risk of SCD and mortality and subsequently opting not to conceive. Of note, patients with a history of peripartum cardiomyopathy were excluded from this study, with possible overlap with end-stage HCM (ie, LV systolic function <50%). Such selection bias warrants caution in interpreting the reported data among the more severe forms of HCM.

Historically, some individuals with HCM have been advised against pregnancy because of the high risk of SCD and adverse maternal and fetal outcomes associated with early reports. However, over the past 2 decades, extensive efforts have been devoted to enhancing risk stratification. Whether the state of pregnancy alone is considered a risk enhancer in HCM remains a topic of debate. More importantly, a dedicated multidisciplinary team of maternal-fetal medicine physicians, cardiologists specializing in cardio-obstetrics, HCM experts, anesthesiologists, advanced practice practitioners, nurses, social workers, and pharmacists remains the hallmark of ensuring a safe and well-planned pregnancy for this unique population and optimizing maternal and fetal outcomes at short- and long-term follow-up. Overall, the results of our analysis are reassuring that pregnancy did not appear to carry a heightened risk of adverse events throughout the follow-up period. Ultimately, appropriate risk stratification and expert preconception counseling are pivotal to providing patients with the evidence needed for shared decision-making regarding the safety of pregnancy with the coexisting condition of HCM and potential outcomes.

Study limitations

First, the study entry criteria included a diagnostic code-based definition of HCM and did not include detailed phenotyping information with cardiac imaging. Hence, it was not possible to exclude the possibility of residual clinical or echocardiographic cofounders. Second, our retrospectively obtained

data via electronic medical records relied on valid documentation of diagnostic disease codes for both HCM and high-risk pregnancy encounters, leading to inherent limitations related to miscoding. In an attempt to mitigate this limitation, we included only patients with 2 or more encounters with preselected diagnosis codes during the initial follow-up. Third, the individual SCD risk profiles of patients in both groups could not be ascertained, as several high-risk markers (ie, late gadolinium enhancement, magnitude of ejection fraction change over the follow-up period) were not present in the TriNetX database. Hence, the identification of higher-risk patients more susceptible to clinical outcomes was not possible. Fourth, further granular data regarding functional capacity (New York Heart Association), medications, and anti-arrhythmics prescribed during the pregnancy period were lacking in the majority of the population. Finally, the TriNetX database captures outcomes only if a patient remains in the same or another participating health care organization throughout the study period; hence, some events might have been missed.

Conclusions

In summary, this population-based analysis suggests that pregnancy in individuals with HCM is not associated with worse long-term outcomes, compared to individuals without pregnancy. However, given the aforementioned limitations with administrative data, interpretation of these results across more severe forms of HCM should be cautiously considered. Moreover, multidisciplinary cardio-obstetrics teams are integral to optimizing individuals' cardiovascular health, including those with HCM.