Title
Body Mass Index, Adverse Pregnancy Outcomes, and Cardiovascular Disease Risk

Journal
Circulation Research, 133(9)

ISSN
0009-7330

Authors
Khan, Sadiya S
Petito, Lucia C
Huang, Xiaoning
et al.

Publication Date
2023-10-13

DOI
10.1161/circresaha.123.322762

Peer reviewed

Published in final edited form as:

Circ Res. 2023 October 13; 133(9): 725–735. doi:10.1161/CIRCRESAHA.123.322762.

Body Mass Index, Adverse Pregnancy Outcomes, and Cardiovascular Disease Risk

Sadiya S. Khan, MD, MSc[1], **Lucia C. Petito, PhD**[1], **Xiaoning Huang, PhD**[1], **Katharine Harrington, MPH**[1], **Rebecca B. McNeil, PhD**[2], **Natalie A. Bello, MD, MPH**[3], **C. N. Bairey Merz, MD**[3], **Eliza C. Miller, MD, MS**[4], **Rupa Ravi, MPH**[4], **Christina Scifres, MD**[5], **Janet Catov, PhD**[6], **Victoria Pemberton, RNC, MS, CCRC**[7], **Jasmina Varagic, PhD, MD**[7], **Phyllis C. Zee, MD, PhD**[1], **Lynn M Yee, MD, MPH**[1], **Mitali Ray, PhD, RN**[6], **Jin Kyung Kim, MD**[8], **Abbi Lane-Cordova, PhD**[9], **Jennifer Lewey, MD**[10], **Lauren H. Theilen, MD, MS**[11], **George R. Saade, MD**[12], **Philip Greenland, MD**[1], **William A. Grobman, MD, MBA**[13],

NICHD nuMoM2b and NHLBI nuMoM2b Heart Health Study Networks

[1]Northwestern University Feinberg School of Medicine

[2]Research Triangle International

[3]Smidt Heart Institute, Cedars-Sinai Medical Center

[4]Columbia University Irving Medical Center

[5]Indiana University School of Medicine

[6]University of Pittsburgh School of Medicine

[7]National Heart, Lung, and Blood Institute

[8]University of California Irvine School of Medicine

[9]School of Public Health, University of South Carolina

[10]University of Pennsylvania Perelman School of Medicine

[11]University of Utah School of Medicine

[12]University of Texas Medical Branch

[13]The Ohio State University College of Medicine

Abstract

Background: Obesity is a well-established risk factor for both adverse pregnancy outcomes (APOs) and cardiovascular disease (CVD). However, it is not known whether APOs are mediators

Address for Correspondence: Sadiya S. Khan, MD, MS, FACC, Assistant Professor of Medicine; Division of Cardiology, Department of Medicine and Preventive Medicine, Northwestern University Feinberg School of Medicine; 680 N. Lake Shore Drive, 14-002, Chicago, IL 60611, 312-503-2515; s-khan-1@northwestern.edu.

DISCLOSURES:
None

CONFLICTS OF INTEREST:
None

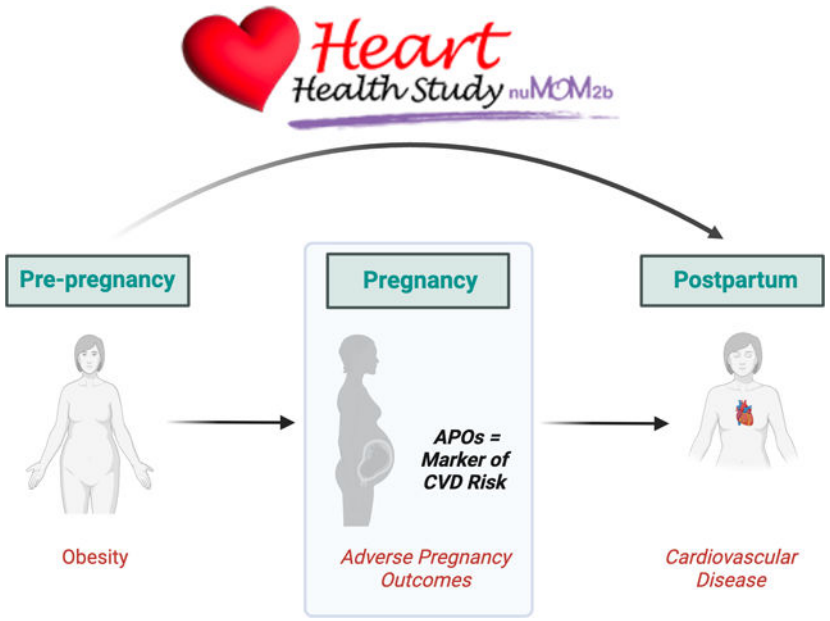
or markers of the obesity-CVD relationship. This study examined the association between body mass index (BMI), APOs, and postpartum CVD risk factors.

Methods: The sample included adults from the nuMoM2b Heart Health Study who were enrolled in their first trimester (6 weeks-13 weeks 6 days gestation) from 8 US sites. Participants had a follow-up visit at 3.7 years postpartum. APOs, which included hypertensive disorders of pregnancy, preterm birth, small-for-gestational age birth, and gestational diabetes, were centrally adjudicated. Mediation analyses estimated the association between early pregnancy BMI and postpartum CVD risk factors (hypertension, hyperlipidemia, and diabetes) and the proportion mediated by each APO adjusted for demographics and baseline health behaviors, psychosocial stressors, and CVD risk-factor levels.

Results: Among 4,216 participants enrolled, mean±SD maternal age was 27±6 years. Early pregnancy prevalence of overweight was 25% and obesity 22%. Hypertensive disorders of pregnancy occurred in 15%, preterm birth in 8%, small-for-gestational age birth in 11%, and gestational diabetes in 4%. Early pregnancy obesity, compared with normal BMI was associated with significantly higher incidence of postpartum hypertension (adjusted odds ratio [OR] 1.14 [1.10, 1.18]), hyperlipidemia (1.11 [1.08, 1.14]), and diabetes (1.03 [1.01, 1.04]) even after adjustment for baseline CVD risk-factor levels. APOs were associated with higher incidence of postpartum hypertension (1.97 [1.61, 2.40]) and hyperlipidemia (1.31 [1.03, 1.67]). Hypertensive disorders of pregnancy mediated a small proportion of the association between obesity and incident hypertension (13% [11–15%]) and did not mediate associations with incident hyperlipidemia or diabetes. There was no significant mediation by preterm birth or small-for-gestational age birth.

Conclusions: There was heterogeneity across APO subtypes in their association with postpartum CVD risk factors and mediation of the association between early pregnancy obesity and postpartum CVD risk factors. However, only a small or non-significant proportion of the association between obesity and CVD risk factors was mediated by any of the APOs, suggesting APOs are a marker of pre-pregnancy CVD risk and not a predominant cause of postpartum CVD risk.

Graphical Abstract



Keywords

obesity; adverse pregnancy outcomes; cardiovascular disease; hypertension; diabetes; Epidemiology; Obesity; Pregnancy; Primary Prevention; Women; Sex; Gender

INTRODUCTION

Approximately 1 in 4 pregnancies in the United States (US) is complicated by an adverse pregnancy outcome (APO).[1] APOs, which include hypertensive disorders of pregnancy, preterm birth, small-for-gestational-age birth, and gestational diabetes, represent a spectrum of heterogeneous syndromes. A vascular phenotype with abnormal placentation has been proposed to contribute to hypertensive disorders of pregnancy, in contrast to a metabolic phenotype for gestational diabetes, which results from an abnormal physiologic response to placental-mediated insulin resistance.[2–4] The etiologies of preterm birth and small-for-gestational age birth are less well understood and can overlap with hypertensive disorders of pregnancy or gestational diabetes, or they can have distinct causes.[5,6] All of these APO subtypes are associated with higher short-term risk of maternal morbidity and mortality,[7–9] and emerging data support an association between APOs and lifetime risk for cardiovascular disease (CVD) with the greatest and most consistent association for hypertensive disorders of pregnancy.[10–13] Even in the short-term, within 5 years postpartum, hypertensive disorders of pregnancy have been consistently associated with higher risk of CVD risk factors, such as hypertension and hyperlipidemia, and these CVD risk factors mediate, in large part, the risk of CVD.[14] As a result, hypertensive disorders of pregnancy were recently recognized as a “risk-enhancing factor” in the 2019 American College of Cardiology/American Heart Association Primary Prevention Guidelines.[15–17] Emerging data also suggest an association between non-hypertensive disorders of pregnancy APO subtypes, CVD risk factors, and CVD.[18,19]

The relationship between APOs and CVD may, in part, be related to shared upstream risk factors, such as pre-pregnancy obesity, that precede onset of CVD risk factors such as hypertension, hyperlipidemia, and diabetes.[17,20] Individuals with higher body mass index (BMI) pre-pregnancy or in early pregnancy (even in the absence of other chronic risk factors) are more likely to experience APOs.[21,22] In addition, evidence links obesity in young adulthood with future risk of CVD, predominantly via traditional risk factors such as hypertension, hyperlipidemia, and diabetes.[23] However, prospectively collected data from nulliparous individuals from early pregnancy (prior to significant gestational weight gain) with rigorous adjudication of APO status and postpartum follow-up on incident development of CVD risk factors are limited. As a result, it remains unclear whether APOs, particularly hypertensive disorders of pregnancy, are a marker of underlying risk associated with obesity or whether hypertensive disorders of pregnancy and other APOs substantially mediate the association with future CVD risk.[17,24]

Therefore, we sought to define the associations between maternal obesity, hypertensive disorders of pregnancy (and other APO subtypes), and cardiovascular health (as measured by incident CVD risk factor development) several years after delivery. We estimated (1) the association between early pregnancy BMI and subsequent CVD risk factors independent of APOs; 2) the extent to which these associations are mediated by APOs; and 3) the influence of BMI on CVD risk factors if the risk of APOs was similar between pregnant individuals with a normal and a high BMI.

METHODS

Study Design and Participants

Data Availability—Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols will be considered by the data coordinating center. Requests to access the data and materials used for this analysis may be submitted to the nuMoM2b-HHS Study at https://numom2b.org. Please see the Major Resources Table in the Supplemental Materials.

Between 2014–2017, 4509 individuals were recruited for an in-person visit as part of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-To-be Heart Health Study (nuMoM2b-HHS). The participants were recruited from the parent study, nuMoM2b, and full study details of nuMoM2b and nuMoM2b-HHS have been previously described.[25,26] Briefly, nulliparous pregnant individuals with singleton pregnancies from 8 clinical centers across the US (Case Western Reserve University; Columbia University; Indiana University; University of Pittsburgh; Northwestern University; University of California at Irvine; University of Pennsylvania; and University of Utah) were recruited at an estimated gestational age at recruitment between 6 weeks 0 days to 13 weeks 6 days. Each site's local Institutional Review Board approved the study and all participants provided written informed consent.

For the current analysis, we included nulliparous individuals who were aged 18 years or older without any history of pre-pregnancy hypertension or diabetes. We excluded

individuals who experienced pregnancy loss (spontaneous abortion, induced abortion, or stillbirth).[27] (Supplemental Figure 1).

Exposure: Maternal BMI in Early Pregnancy—Height and weight were directly measured at the baseline visit, and BMI was calculated as weight in kg divided by height in meters squared. We categorized BMI, as normal (BMI <25 kg/m^2); overweight (25kg/m^2 ≤ BMI < 30 kg/m^2); or obesity (BMI ≥ 30 kg/m^2). Waist circumference was measured at the same visit over the iliac crest to the nearest 0.1cm and dichotomized to high (>88 cm) versus low (≤88 cm) based on the ATP III definition.[28]

Mediators: APOs—APOs were abstracted and verified for all participants according to *a priori* definitions by trained study personnel within 30 days of delivery as previously described.[25,26] The primary mediator in our study was hypertensive disorders of pregnancy, which was defined as preeclampsia (with or without severe features), eclampsia, and gestational hypertension.[29] We also conducted secondary analyses and investigated each of the following hypertensive disorders of pregnancy subtypes (preeclampsia/eclampsia, gestational hypertension) and other APO subtypes categorized as preterm birth (defined as delivery between 20 weeks and $36^{6/7}$ weeks gestation, which included spontaneous and medically-indicated preterm birth), small-for-gestational age birth (defined as birthweight <10^{th} percentile for gestational age using the Alexander curves),[30] and gestational diabetes (defined according to current guidelines)[29]] as mediators to understand the potential for heterogeneity across different APOs.

Outcomes: Cardiovascular Disease Risk Factors—Incident development of CVD risk factors was characterized in three cardiometabolic domains: hypertension (defined as blood pressure ≥130/80 mm Hg or treatment), hyperlipidemia (fasting total cholesterol ≥240 mg/dL or treatment), and diabetes (fasting glucose ≥126 mg/dL or treatment). Secondary outcomes including continuous measures of CVD risk-factor levels: systolic blood pressure (SBP), fasting total cholesterol, and fasting glucose. Outcomes were measured at the in-person nuMoM2b-HHS study visit, which occurred between 2014–2017. BP was directly measured following a standardized research protocol (Omron HEM-907XL) in triplicate and averaged. Serum, plasma, and whole blood specimens were stored at a central core biorepository and enzymatic analyses of total cholesterol and glucose were completed on fasting samples from the follow-up visit.[19]

Confounders—Consistent with published methods for mediation analyses, we identified two sets of confounders *a priori* for the analysis.[31] Confounders of the exposure (early pregnancy BMI) and outcome (CVD risk factors) association included maternal age, self-reported race and ethnicity (non-Hispanic [NH][32] White, NH Black, Hispanic/Latinx, Asian, Other [which included individuals who did not identify according to the aforementioned categories, including those identifying as American Indian or Alaskan Native, Native Hawaiian, or multiracial, and those identifying as not belonging to any of these groups), insurance type (private vs. public), smoking status (pre-pregnancy yes/no), physical activity (standardized minutes per week)[33], dietary quality (Healthy Eating Index 2010)[34], sleep duration, perceived stress (total score of the 10-item perceived stress scale)[35], depression

(total score of the 10-item Edinburgh Postnatal Depression Scale)[36], and CVD risk factor levels. These were all assessed at baseline. Race and ethnicity were self-reported using prespecified categories and were included in the analysis as a socially-defined factor. Fetal sex was included as a confounder of the association between mediators (APOs) and outcomes (CVD risk factors).[37] Gestational weight gain (pre-pregnancy BMI-specific Z-scores) was included as a confounder in sensitivity analyses.[38,39] Serum, plasma, and whole blood specimens were stored at a central core biorepository from the baseline visit and enzymatic analyses of total cholesterol and glucose were completed on the non-fasting samples from the baseline first-trimester visit.[19]

Statistical Analyses—Baseline characteristics of participants are presented as mean ± standard deviation (SD) for continuous variables and sample size (percentages) for categorical variables. According to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, p-values for differences between BMI strata are omitted.[40] We also visually depicted the associations between BMI (continuous) in early pregnancy and CVD risk-factor levels years after delivery.

We used a counterfactual approach for causal mediation analyses[37], as it allows more sophisticated data structures and models than traditional approaches such as exposure-mediator interaction.[41,42] This approach clarifies the assumptions needed for a causal interpretation, namely that there is no unmeasured confounding of the exposure-outcome, mediator-outcome, or exposure-mediator relationships, and that none of the mediator-outcome confounders are affected by the exposure. Using this framework as previously described,[31] we estimated four quantities: the natural direct effect (NDE), the natural indirect effect (NIE), the total effect (TE), and the percent mediated. The NDE is obtained by evaluating the effect of early pregnancy obesity (or overweight) with the incidence of APOs set to the level that would have naturally occurred in an individual with normal BMI in early pregnancy and, as such, represents the influence of obesity or overweight (early pregnancy) on CVD risk-factor levels (years after delivery) that is independent of APO. The NIE is obtained by comparing CVD risk-factor levels associated with obesity or overweight (early pregnancy) when setting the incidence of APOs to what it would have been for obesity or overweight (compared with normal BMI), and represents the influence of excess weight on CVD risk-factor levels years after delivery that can be explained by its influence on APOs. The TE decomposes into the sum of the NDE and NIE. In models where we detected a TE and NIE, we estimated the proportion mediated (NIE/TE x 100, %) and respective 95% confidence intervals (CI), where 100% reflects no NDE and 0% reflects no NIE (i.e., no mediation by the APO).

First, we used unadjusted and adjusted generalized linear models to individually estimate the exposure-outcome (linear), mediator-outcome (linear), and exposure-mediator associations (logistic). Figure 1 visually represents the potential pathways with a causal directed acyclic graph.[43] We calculated adjusted population attributable fractions for the exposure-mediator association for obesity and overweight compared with normal BMI. Next, we applied the counterfactual approach to perform the primary mediation analyses. Separate analyses were performed for each mediator to preserve interpretability of the causal estimands. In all settings, the mediator model was a logistic regression model and the outcome model

was a linear regression model. All models contained fixed effects for site to account for regional differences in unmeasured confounders. Continuous covariates were included as linear terms, and categorical covariates were included as indicator variables in all models. We did not detect any interaction between the exposure and mediator (data not shown), so results are presented for models without said interaction. 95% CI were generated using a nonparametric bootstrap with 1,000 re-samplings.

To assess robustness of our findings, several sensitivity analyses were conducted. First, analyses were replicated for waist circumference as an alternate measure reflecting central adiposity. Second, gestational weight gain z-score was included as a potential confounder for the mediators and outcomes.[44]

This study followed the STROBE reporting guidelines with reporting of the mediation analysis done in accordance with the AGReMA statement.[31] We conducted multiple imputation by chained equations with fully conditional specification using the STATA "mi impute chained" package to impute missing data at baseline using previously published methods.[45,46] The pre-imputed dataset baseline characteristics are displayed in Supplemental Table 1. The levels of missingness and models used to impute the variables are listed in Supplemental Table 2. We created 10 imputed datasets and the distribution of covariates between the observed and imputed datasets were similar. All regression analyses described above were performed separately in each of the imputed datasets and the results were combined using Rubin rules.[47] All mediation analyses were done using "paramed". Analyses were performed in STATA Version 18. P values less than 0.05 based on a 2-tailed test were considered statistically significant.

RESULTS

Participant Characteristics

Table 1 displays the characteristics of 4,216 pregnant individuals enrolled at a mean gestational age of 11.4 weeks (range 6 weeks 0 days −13 weeks 6 days). At the early pregnancy first study visit, mean (SD) maternal age was 27 (6) years old and 53% had a normal BMI, 25% were overweight, and 22% had obesity. Mean (SD) gestational duration was 39 (2) weeks with mean birthweight of 3.3 [range 0.4–5.1] kg. hypertensive disorders of pregnancy occurred in 15% of the participants, of whom 9% had preeclampsia/eclampsia and 6% gestational hypertension. Also, 8% had preterm birth, 11% had small-for-gestational age birth, and 4% had gestational diabetes (Supplemental Table 3). The follow-up visit occurred in participants at a mean 3.7 years (range 2–7) after the baseline study visit.

Association Between Early Pregnancy BMI (Exposure) and APOs (Mediators)

Compared with those with a normal BMI in early pregnancy, individuals with overweight BMI (aOR: 1.64 [1.31–2.06] or obesity (adjusted OR [aOR, 95% CI]: 2.34 [1.85–2.96] had higher risk of hypertensive disorders of pregnancy (Supplemental Table 4). These results were similar in magnitude when examined for overweight or obesity associated with preeclampsia/eclampsia and gestational hypertension individually as well as with gestational diabetes (Supplemental Table 4). In contrast, overweight or obesity, compared with normal

BMI, was not significantly associated with preterm birth or small-for-gestational age birth in adjusted models.

Association Between APOs (Mediators) and Cardiovascular Health Factors (Outcomes)

Next, we evaluated the associations between APOs and incident hypertension, hyperlipdemia, and diabetes at 2–7 years (mean 3.7) after delivery (Table 2, Supplemental Table 5). After adjustment for demographics and baseline health bevhaiors, psychosocial stressors, and CVD risk factor levels, hypertensive disorders of pregnancy were associated with higher risk of incident hypertension (adjusted OR 1.97 [1.61–2.40]) and hyperlipidemia (1.31 [1.03–1.67]). In addition, hypertensive disorders of pregnancy were associated with higher SBP and total cholesterol levels (adjusted mean difference [95% CI] for SBP: 3.33 [2.36–4.31] mm Hg and total cholesterol 3.83 [0.62–7.04]) mg/dL, but not glucose levels. These results were similar for hypertension when preeclampsia/eclampsia and gestational hypertension were examined individually (Supplemental Table 5). In contrast, gestational hypertension was not associated with incident hyperlipidemia or total cholesterol levels. Gestational diabetes was associated with incident hyperlipidemia and diabetes as well as higher cholesterol glucose levels (Supplemental Table 5). Preterm birth was also associated with higher risk of incident hypertension, hyperlipidemia, and diabetes. Small-for-gestational age birth was not associated with any of the CVD risk factors.

Direct and Indirect Associations Between Early Pregnancy BMI and CVD Risk Factors Mediated by APOs

Figure 2 visually displays the distributions and unadjusted associations between early pregnancy BMI and CVD risk factor levels. For hypertensive disorders of pregnancy as a mediator, Table 3 presents the total, direct, and indirect associations, along with estimates of the proportion mediated only where interpretable. Compared with pregnant individuals with normal BMI in early pregnancy, those beginning pregnancy with overweight or obesity had higher risk of incident hypertension, hyperlipidemia, and diabetes at follow-up (total effect). The mean differences between obesity and normal BMI in early pregnancy were significantly higher for SBP (2.05 [1.33–2.78]) mm Hg and fasting glucose levels (1.02 [0.10–1.94]) mg/dL. There was a significant but small proportion of mediation by hypertensive disorders of pregnancy between obesity and incident hypertension (% mediated 12.9 [10.5–15.2]). Associations with hyperlipidemia and diabetes were independent of hypertensive disorders of pregnancy (evidenced by no significant mediation). Similar findings of significance were observed when 99% CI were calculated to account for multiple comparisons (Supplemental Table 6). When each subtype of hypertensive disorders of pregnancy was examined individually (preeclampsia/eclampsia and gestational hypertension), there was no significant mediation observed for the association between obesity and incident CVD risk factors (Supplemental Table 7). While gestational diabetes did not mediate the association between obesity and hypertension or hyperlipidemia, it did mediate a small but significant association between obesity and fasting glucose levels (% mediated 10.0% [7.5–12.5]) (Supplemental Table 8). Preterm birth and small-for-gestational age birth did not mediate the association between obesity and any incident CVD risk factors or risk-factor levels (Supplemental Table 8). Similar patterns of results were observed for overweight vs. normal BMI across the APO subtypes.

Sensitivity Analyses

High waist circumference (>88 cm) was associated with hypertensive disorders of pregnancy (as well as preeclampsia/eclampsia and gestational hypertension, individually) and gestational diabetes, but not preterm birth or small-for-gestational age birth (Supplemental Table 9). Hypertensive disorders of pregnancy mediated a significant proportion of the association between high waist circumference in early pregnancy and incident hypertension that was similar in magnitude to the association observed for high BMI (Supplemental Table 10). Preterm birth, small-for-gestational age birth, and gestational diabetes did not significantly mediate any of the relationship between waist circumference and CVD risk factors (Supplemental Table 11). The addition of gestational weight gain z-score as a confounder did not change the results of our analyses for the primary mediator, hypertensive disorders of pregnancy (Supplemental Tables 12 and 13).

DISCUSSION

The primary finding of this study was that two types of adverse pregnancy outcomes, hypertensive disorders of pregnancy and gestational diabetes, mediated a statistically significant but small proportion of the association between overweight or obesity in early pregnancy and certain CVD risk factors at a mean follow-up of 3.7 years post-partum. Patterns differed across risk factors whereby hypertensive disorders of pregnancy partially mediated the association between early pregnancy BMI and a vascular risk factor (hypertension), and gestational diabetes partly mediated the association between early pregnancy BMI and a metabolic risk factor (glucose). In contrast, preterm birth and small-for-gestational age birth did not mediate any of the associations between overweight or obesity and CVD risk factors post-partum. In aggregate, this study provides important data to support that APOs likely represent a marker of pre-pregnancy CVD risk and are not a clinically significant mediator through which higher BMI early in an individual's first pregnancy may influence CVD risk factors even in the short-term soon after delivery. Importantly, early pregnancy BMI was significantly associated with APOs and incident hypertension, hyperlipidemia, and diabetes, suggesting that interventions should focus in early pregnancy or pre-pregnancy for the greatest yield in CVD prevention.

This study contributes to the growing evidence base that APOs represent a marker of increased CVD risk that is manifest clinically during pregnancy and associated with increased risk of CVD risk after pregnancy.[8,48,49] The significant mediation of the association, even if it is small in magnitude, by hypertensive disorders of pregnancy suggests a small role for an obesity-associated BP pathway and supports the putative mechanistic data linking vascular dysfunction (e.g., angiogenesis)[50–53] as a shared cause of hypertensive disorders of pregnancy and CVD. In fact, pre-pregnancy obesity was associated with a greater than 2-fold risk of hypertensive disorders of pregnancy, even afer adjusting for key covariates at baseline such as SBP in early pregnancy, in this cohort of nulliparous individuals. This work builds upon recent observational data that genetic predisposition for obesity and hypertension via a polygenic risk score was significantly associated with risk for hypertensive disorders of pregnancy[54], and supports the hypothesis that hypertensive disorders of pregnancy may be a manifestation of underlying metabolic and vascular risk.

These data further extend the understanding of heterogeneity in the associations between each APO subtype and cardiovascular health and demonstrates the incremental independent (and potential causal) effect of both hypertensive disorders of pregnancy and gestational diabetes on future CVD risk.[8] The observation that gestational diabetes, which occurs due to placental-mediated insulin resistance[55], partially mediates an obesity-associated metabolic pathway supports the importance of pre-pregnancy risk in the manifestation of gestational diabetes. The lack of significant mediation by preterm birth and small-for-gestational age birth in future cardiovascular health may be related to the diverse phenotypes, etiologies, and severity for these APOs, which may co-occur concurrently or in the absence of either hypertensive disorders of pregnancy or gestational diabetes. It is also important to note that these data confirm and still support the identification of APOs as a "risk-enhancing" factor given the significant association between both hypertensive disorders of pregnancy and gestational diabetes and incident CVD risk factors, and highlights pregnancy as an "early cardiovascular moment".[2] While the present study focused on CVD risk factors and not CVD in this young sample, these risk factors largely mediate the association between APOs and future CVD, and thus represent important intermediate targets for prevention, particularly in young adults before hard or symptomatic CVD events occur.[14] Future research should also evaluate how pregnancy events may affect postpartum weight retention, and in turn, whether postpartum weight retention is a potential target for interventions to improve long-term cardiovasulcar health.[56]

Given the study findings, improved access to preconception health care coupled with support for health behavior interventions to optimize body weight in the pre-pregnancy or early pregnancy period merits investigation as a modifiable target for prevention of both APOs and CVD. While this analysis cannot identify what effective interventions may be (e.g., health behavior counseling before and during pregnancy, pharmacotherapy pre-pregnancy for weight loss), this analysis demonstrates that weight optimization should be an important focus for public health strategies to improve maternal health in the short- and long-term. The US Preventive Services Task Force[57] and the American College of Obstetricians and Gynecologists (ACOG) recommend clinicians provide resources or refer persons of reproductive age to behavioral interventions to enhance healthful behaviors prior to conception, which was also highlighted in a joint statement by the ACOG and AHA.[58,59] However, execution of such counseling and interventions is limited by the inadequacy of the US health care system. Many individuals lack health insurance prior to conception, and other structural and systemic barriers prevent equitable access to comprehensive reproductive and primary care.

The prevalence of pre-pregnancy overweight and obesity is increasing among reproductive-aged birthing people, with nearly half of all individuals with overweight or obesity in the US in 2019.[60] Therefore, the focus on optimizing weight in the critical period before pregnancy is likely to have broad clinical and public health relevance for long-term cardiovascular health, which was highlighted in a recent AHA Scientific Statement focused on optimization of pre-pregnancy cardiovascular health.[61] Our data further support the importance of pre-pregnancy interventions as a priority for long-term cardiovascular health promotion largely independent of APOs. APOs appear to largely represent an important surrogate marker of pre-pregnancy CVD risk given the limited mediation noted between early pregnancy

obesity and CVD risk factors years after delivery. While emerging data also support intergenerational transmission of cardiovascular risk associated with maternal obesity[62], it is not known if APOs mediate some of this risk to the offspring or similarly predominantly represent a marker of shared risk.

Strengths of this study include the geographic and racial and ethnic diversity of participants, high-quality objective measurement of overall and central adiposity at the first prenatal visit in the first trimester in an individual's first pregnancy when gestational weight gain should not substantially influence these measures or CVD risk factor levels, chart abstraction of APOs with rigorous adjudication, and long-term follow-up years after delivery for CVD risk factors with objective measurement.

Limitations

This study has some limitations. First, the cohort only included nulliparous individuals and studies including multiparous individuals are needed for broader generalizability. Second, BMI is an incomplete surrogate for adiposity distribution or degree of visceral adiposity that may more accurately reflect obesity-associated CVD risk. However, consistent results were observed with waist circumference as a measure of central obesity in sensitivity analyses. Third, WC measurements were obtained in the first trimester of pregnancy. However, these measures should not be influenced by the size of the uterus at this early point in pregnancy. Fourth, while our cohort was diverse and included 8 cities across the US, there was a low proportion of Asian individuals, who have a disproportionately higher risk of gestational diabetes, enrolled. Therefore, future studies should focus and prioritize studies on CVH in this population in the peripartum period. Fifth, as with any application of a causal inference framework in observational data, our interpretation is limited by potential for unmeasured confounding. However, our analyses robustly adjusted for key covariates, including demographics, baseline health behaviors, psychosocial stressors, and CVD risk factor levels. Additionally, in sensitivity analyses, in which we adjusted for gestational weight gain, results were consistent with the primary analyses. To truly invalidate our results, an unmeasured confounder must affect pre-pregnancy BMI and post-pregnancy CVD risk factors through pathways that are independent of the measured covariates, which we think is not biologically plausible in this scenario.[63] We also note that, as in all studies, there is the possibility of omitted variable bias, including in regards to clinician bias related to obesity in care and treatment during pregnancy and postpartum.

CONCLUSIONS

In this multicenter, diverse observational cohort, APOs had heterogeneous patterns in the mediation of the association between maternal BMI early pregnancy and CVD risk factors after delivery. Specifically, hypertensive disorders of pregnancy statistically significantly mediated a small proportion of the association with incident hypertension and gestational diabetes statistically significantly mediated a small proportion of the association with fasting glucose after delivery. This contributes to the growing evidence base that APOs largely represent a marker of pre-existing CVD risk that is unmasked during pregnancy and suggests growing emphasis on early pregnancy or pre-pregnancy interventions before an APO occurs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

The authors take responsibility for the decision to submit the manuscript for publication. Drs. Khan and Grobman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SOURCES OF FUNDING:

Supported by grants from the NHLBI (R01 HL161514) to SSK. Grant funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD): U10 HD063036; U10 HD063072; U10 HD063047; U10 HD063037; U10 HD063041; U10 HD063020; U10 HD063046; U10 HD063048; and U10 HD063053. In addition, support was provided by Clinical and Translational Science Institutes: UL1TR001108 and UL1TR000153. Cooperative agreement funding from the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development: U10-HL119991; U10-HL119989; U10-HL120034; U10-HL119990; U10-HL120006; U10-HL119992; U10-HL120019; U10-HL119993; U10-HL120018, and U01HL145358; and the National Center for Advancing Translational Sciences through UL-1-TR000124, UL-1-TR000153, UL-1-TR000439, and UL-1-TR001108; and the Barbra Streisand Women's Cardiovascular Research and Education Program, and the Erika J. Glazer Women's Heart Research Initiative, Cedars-Sinai Medical Center, Los Angeles; with supplemental support to U10-HL119991 from the Office of Research on Women's Health and the Office of Disease Prevention.

DISCLAIMER:

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Non-standard Abbreviations and Acronyms

APO	Adverse Pregnancy Outcomes
BMI	Body mass index
CI	Confidence Intervals
CVD	Cardiovascular Disease
NDE	Natural Direct Effect
NIE	Natural Indirect Effect
NH	Non-Hispanic
nuMoM2b-HHS	Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-To-be Heart Health Study
TE	Total Effect

REFERENCES

1. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK. Births: Final data for 2018. 2019.
2. Khan SS, Cameron NA, Lindley KJ. Pregnancy as an early cardiovascular moment: peripartum cardiovascular health. Circulation Research. 2023;132:1584–1606. [PubMed: 37289905]

3. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circulation research. 2019;124:1094–1112. [PubMed: 30920918]
4. Khan SR, Mohan H, Liu Y, Batchuluun B, Gohil H, Al Rijjal D, Manialawy Y, Cox BJ, Gunderson EP, Wheeler MB. The discovery of novel predictive biomarkers and early-stage pathophysiology for the transition from gestational diabetes to type 2 diabetes. Diabetologia. 2019;62:687–703. [PubMed: 30645667]
5. Benton SJ, Leavey K, Grynspan D, Cox BJ, Bainbridge SA. The clinical heterogeneity of preeclampsia is related to both placental gene expression and placental histopathology. American Journal of Obstetrics and Gynecology. 2018;219:604. e601–604. e625.
6. Gibbs I, Leavey K, Benton SJ, Grynspan D, Bainbridge SA, Cox BJ. Placental transcriptional and histologic subtypes of normotensive fetal growth restriction are comparable to preeclampsia. American Journal of Obstetrics and Gynecology. 2019;220:110. e111–110. e121.
7. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. Paper/Poster presented at: Seminars in perinatology; 2012;
8. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis. Circulation. 2019;139:1069–1079. [PubMed: 30779636]
9. Malhamé I, Danilack VA, Raker CA, Hardy EJ, Spalding H, Bouvier BA, Hurlburt H, Vrees R, Savitz DA, Mehta N. Cardiovascular severe maternal morbidity in pregnant and postpartum women: development and internal validation of risk prediction models. BJOG: An International Journal of Obstetrics & Gynaecology. 2020.
10. Gabbay-Benziv R, Ashwal E, Hadar E, Aviram A, Yogev Y, Melamed N, Hiersch L. Interpregnancy interval and the risk for recurrence of placental mediated pregnancy complications. Journal of Perinatal Medicine. 2020;1.
11. Kvalvik LG, Wilcox AJ, Skjærven R, Østbye T, Harmon QE. Term complications and subsequent risk of preterm birth: registry based study. bmj. 2020;369.
12. Smith DD, Finneran MM, Shellhaas CC, Samuels P, Frey HA. The Importance of Clinical Presentation in Risk and Management of Recurrent Preterm Birth. American Journal of Perinatology. 2020.
13. Svorai M, Aricha B, Erez O. Prior Preterm Birth and Birthweight Below the 5th Percentile are Independent Risk Factors for Recurrence of a Small for Gestational Age Neonate. Maternal-Fetal Medicine. 2020;2:28–33.
14. Stuart JJ, Tanz LJ, Rimm EB, Spiegelman D, Missmer SA, Mukamal KJ, Rexrode KM, Rich-Edwards JW. Cardiovascular Risk Factors Mediate the Long-Term Maternal Risk Associated With Hypertensive Disorders of Pregnancy. Journal of the American College of Cardiology. 2022;79:1901–1913. doi: doi:10.1016/j.jacc.2022.03.335 [PubMed: 35550687]
15. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2019;74:e177–e232. [PubMed: 30894318]
16. Honigberg MC, Zekavat SM, Aragam K, Klarin D, Bhatt DL, Scott NS, Peloso GM, Natarajan P. Long-term cardiovascular risk in women with hypertension during pregnancy. Journal of the American College of Cardiology. 2019;74:2743–2754. [PubMed: 31727424]
17. Lane-Cordova AD, Khan SS, Grobman WA, Greenland P, Shah SJ. Long-term cardiovascular risks associated with adverse pregnancy outcomes: JACC review topic of the week. Journal of the American College of Cardiology. 2019;73:2106–2116. [PubMed: 31023435]
18. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Merz CNB, Cheng S. Sex differences in blood pressure trajectories over the life course. JAMA cardiology. 2020;5:19–26. [PubMed: 31940010]
19. Haas DM, Parker CB, Marsh DJ, Grobman WA, Ehrenthal DB, Greenland P, Bairey Merz CN, Pemberton VL, Silver RM, Barnes S. Association of adverse pregnancy outcomes with hypertension 2 to 7 years postpartum. Journal of the American Heart Association. 2019;8:e013092. [PubMed: 31564189]

20. Freaney PM, Khan SS, Lloyd-Jones DM, Stone NJ. The Role of Sex-Specific Risk Factors in the Risk Assessment of Atherosclerotic Cardiovascular Disease for Primary Prevention in Women. Curr Atheroscler Rep. 2020;22:46. doi: 10.1007/s11883-020-00864-6 [PubMed: 32671475]
21. Macdonald-Wallis C, Lawlor DA, Fraser A, May M, Nelson SM, Tilling K. Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. Hypertension. 2012;59:1241–1248. [PubMed: 22526257]
22. Nobles CJ, Mendola P, Mumford SL, Silver RM, Kim K, Andriessen VC, Connell M, Sjaarda L, Perkins NJ, Schisterman EF. Preconception Blood Pressure and Its Change Into Early Pregnancy: Early Risk Factors for Preeclampsia and Gestational Hypertension. Hypertension. 2020;76:922–929. [PubMed: 32755413]
23. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA cardiology. 2018;3:280–287. [PubMed: 29490333]
24. Stuart JJ, Tanz LJ, Cook NR, Spiegelman D, Missmer SA, Rimm EB, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Hypertensive disorders of pregnancy and 10-year cardiovascular risk prediction. Journal of the American College of Cardiology. 2018;72:1252–1263. [PubMed: 30190003]
25. Haas DM, Ehrenthal DB, Koch MA, Catov JM, Barnes SE, Facco F, Parker CB, Mercer BM, Bairey-Merz CN, Silver RM. Pregnancy as a window to future cardiovascular health: design and implementation of the nuMoM2b Heart Health Study. American journal of epidemiology. 2016;183:519–530. [PubMed: 26825925]
26. Haas DM, Parker CB, Wing DA, Parry S, Grobman WA, Mercer BM, Simhan HN, Hoffman MK, Silver RM, Wadhwa P. A description of the methods of the Nulliparous Pregnancy Outcomes Study: monitoring mothers-to-be (nuMoM2b). American journal of obstetrics and gynecology. 2015;212:539. e531–539. e524.
27. Oberg AS, VanderWeele TJ, Almqvist C, Hernandez-Diaz S. Pregnancy complications following fertility treatment—disentangling the role of multiple gestation. International journal of epidemiology. 2018;47:1333–1342. [PubMed: 29939263]
28. Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. Jama. 2020;323:2526–2528. [PubMed: 32573660]
29. Facco FL, Parker CB, Reddy UM, Silver RM, Koch MA, Louis JM, Basner RC, Chung JH, Nhan-Chang C-L, Pien GW. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. Obstetrics and gynecology. 2017;129:31. [PubMed: 27926645]
30. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstetrics & Gynecology. 1996;87:163–168. [PubMed: 8559516]
31. Lee H, Cashin AG, Lamb SE, Hopewell S, Vansteelandt S, VanderWeele TJ, MacKinnon DP, Mansell G, Collins GS, Golub RM. A guideline for reporting mediation analyses of randomized trials and observational studies: The AGReMA Statement. JAMA. 2021;326:1045–1056. [PubMed: 34546296]
32. McKennan C, Naughton K, Stanhope C, Kattan M, O'Connor GT, Sandel MT, Visness CM, Wood RA, Bacharier LB, Beigelman A, et al. Longitudinal data reveal strong genetic and weak non-genetic components of ethnicity-dependent blood DNA methylation levels. Epigenetics. 2021;16:662–676. doi: 10.1080/15592294.2020.1817290 [PubMed: 32997571]
33. Catov JM, Parker CB, Gibbs BB, Bann CM, Carper B, Silver RM, Simhan HN, Parry S, Chung JH, Haas DM. Patterns of leisure-time physical activity across pregnancy and adverse pregnancy outcomes. International Journal of Behavioral Nutrition and Physical Activity. 2018;15:1–10. [PubMed: 29291739]
34. Yee LM, Silver RM, Haas DM, Parry S, Mercer BM, Iams J, Wing D, Parker CB, Reddy UM, Wapner RJ. Quality of periconceptional dietary intake and maternal and neonatal outcomes. American journal of obstetrics and gynecology. 2020;223:121. e121–121. e128.
35. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of health and social behavior. 1983:385–396. [PubMed: 6668417]

36. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. The British journal of psychiatry. 1987;150:782–786. [PubMed: 3651732]
37. VanderWeele T. Explanation in causal inference: methods for mediation and interaction. Oxford University Press; 2015.
38. Hutcheon JA, Platt RW, Abrams B, Himes KP, Simhan HN, Bodnar LM. A weight-gain-for-gestational-age z score chart for the assessment of maternal weight gain in pregnancy. The American of Clinical Nutrition. 2013;97:1062–1067.
39. Hutcheon JA, Platt RW, Abrams B, Himes KP, Simhan HN, Bodnar LM. Pregnancy weight gain charts for obese and overweight women. Obesity. 2015;23:532–535. [PubMed: 25707378]
40. Ghaferi AA, Schwartz TA, Pawlik TM. STROBE reporting guidelines for observational studies. JAMA surgery. 2021;156:577–578. [PubMed: 33825815]
41. Interpretation Pearl J. and identification of causal mediation. Psychological methods. 2014;19:459. [PubMed: 24885338]
42. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of personality and social psychology. 1986;51:1173. [PubMed: 3806354]
43. Lipsky AM, Greenland S. Causal Directed Acyclic Graphs. JAMA.
44. Bodnar LM, Hutcheon JA, Parisi SM, Pugh SJ, Abrams B. Comparison of gestational weight gain z-scores and traditional weight gain measures in relation to perinatal outcomes. Paediatric and perinatal epidemiology. 2015;29:11–21. [PubMed: 25492396]
45. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey methodology. 2001;27:85–96.
46. Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR Jr, Kiefe CI. Associations of clinical and social risk factors with racial differences in premature cardiovascular disease. Circulation. 2022;146:201–210. [PubMed: 35607988]
47. Marshall A, Altman DG, Royston P, Holder RL. Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. BMC medical research methodology. 2010;10:1–16. [PubMed: 20053272]
48. Parikh NI, Gonzalez JM, Anderson CA, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D, Epidemiology AHACo, et al. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. Circulation. 2021;143:e902–e916. [PubMed: 33779213]
49. O'Kelly AC, Michos ED, Shufelt CL, Vermunt JV, Minissian MB, Quesada O, Smith GN, Rich-Edwards JW, Garovic VD, El Khoudary SR. Pregnancy and reproductive risk factors for cardiovascular disease in women. Circulation research. 2022;130:652–672. [PubMed: 35175837]
50. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. American Journal of Obstetrics and Gynecology. 2020.
51. Gray KJ, Saxena R, Karumanchi SA. Genetic predisposition to preeclampsia is conferred by fetal DNA variants near FLT1, a gene involved in the regulation of angiogenesis. American journal of obstetrics and gynecology. 2018;218:211–218. [PubMed: 29138037]
52. Garrido-Gimenez C, Mendoza M, Cruz-Lemini M, Galian-Gay L, Sanchez-Garcia O, Granato C, Rodriguez-Sureda V, Rodriguez-Palomares J, Carreras-Moratonas E, Cabero-Roura L. Angiogenic factors and long-term cardiovascular risk in women that developed preeclampsia during pregnancy. Hypertension. 2020;76:1808–1816. [PubMed: 33012203]
53. Suvakov S, Bonner E, Nikolic V, Jerotic D, Simic TP, Garovic VD, Lopez-Campos G, McClements L. Overlapping pathogenic signalling pathways and biomarkers in preeclampsia and cardiovascular disease. Pregnancy Hypertension. 2020;20:131–136. [PubMed: 32299060]
54. Honigberg MC, Chaffin M, Aragam K, Bhatt DL, Wood MJ, Sarma AA, Scott NS, Peloso GM, Natarajan P. Genetic variation in cardiometabolic traits and medication targets and the risk of hypertensive disorders of pregnancy. Circulation. 2020;142:711–713. [PubMed: 32804569]

55. Tanaka K, Yamada K, Matsushima M, Izawa T, Furukawa S, Kobayashi Y, Iwashita M. Increased maternal insulin resistance promotes placental growth and decreases placental efficiency in pregnancies with obesity and gestational diabetes mellitus. Journal of Obstetrics and Gynaecology Research. 2018;44:74–80. [PubMed: 29027303]

56. Yuhas M, Moore CF, Garay J, Brown SD. Improving Maternal Cardiovascular Health in Underserved Populations: A Narrative Review of Behavioral Intervention Trials Targeting Postpartum Weight Retention. Current Atherosclerosis Reports. 2022;24:689–699. [PubMed: 35781777]

57. Cantor AG, Jungbauer RM, McDonagh M, Blazina I, Marshall NE, Weeks C, Fu R, LeBlanc ES, Chou R. Counseling and behavioral interventions for healthy weight and weight gain in pregnancy: evidence report and systematic review for the US Preventive Services Task Force. Jama. 2021;325:2094–2109. [PubMed: 34032824]

58. Obstetricians ACo Gynecologists, Practice CoG. Prepregnancy counseling: committee opinion No. 762. Fertility and sterility. 2019;111:32–42. [PubMed: 30611411]

59. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, Rosen SE, Rosser ML, Wenger NK. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. Circulation. 2018;137:e843–e852. [PubMed: 29748185]

60. Wang MC, Freaney PM, Perak AM, Greenland P, Lloyd-Jones DM, Grobman WA, Khan SS. Trends in Prepregnancy Obesity and Association With Adverse Pregnancy Outcomes in the United States, 2013 to 2018. Journal of the American Heart Association. 2021;10:e020717.

61. Khan SS, Brewer LC, Canobbio MM, Cipolla MJ, Grobman WA, Lewey J, Michos ED, Miller EC, Perak AM, Wei GS. Optimizing Prepregnancy Cardiovascular Health to Improve Outcomes in Pregnant and Postpartum Individuals and Offspring: A Scientific Statement From the American Heart Association. Circulation. 2023;147:e76–e91. [PubMed: 36780391]

62. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, Lowe LP, Grobman WA, Lawrence JM, Lloyd-Jones DM. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. JAMA. 2021;325:658–668. [PubMed: 33591345]

63. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Annals of internal medicine. 2017;167:268–274. [PubMed: 28693043]

Novelty and Significance

What is Known?

- Adverse pregnancy outcomes complicate nearly 20% of pregnancies in the United States and are associated with future risk of cardiovascular disease
- Both adverse pregnancy outcomes and cardiovascular disease share upstream risk factors, such as obesity
- However, the causal role of adverse pregnancy outcomes in the development of cardiovascular disease remains unclear (i.e., are adverse pregnancy outcomes a marker or mediator in the association between obesity and cardiovascular disease risk)

What New Information Does this Article Contribute

- This study demonstrates a significant association of maternal obesity with adverse pregnancy outcomes and cardiovascular health (as measured by incident hypertension and diabetes)
- The proportion of risk mediated by adverse pregnancy outcomes varied significantly by type of pregnancy complication with a small proportion of the association between obesity and cardiovascular health mediated by hypertensive disorders of pregnancy and no significant mediation by preterm birth or small-for-gestational age birth

This study suggests that adverse pregnancy outcomes are a marker of pre-pregnancy cardiovascular disease risk that becomes clinically manifest during the stress of pregnancy and does not significantly independently contribute to cardiovascular disease risk after pregnancy. However, adverse pregnancy outcomes are an important marker of high cardiovascular disease risk and may serve as an important clincial marker for more intensive preventive interventions to reduce lifetime risk of cardiovascular disease.

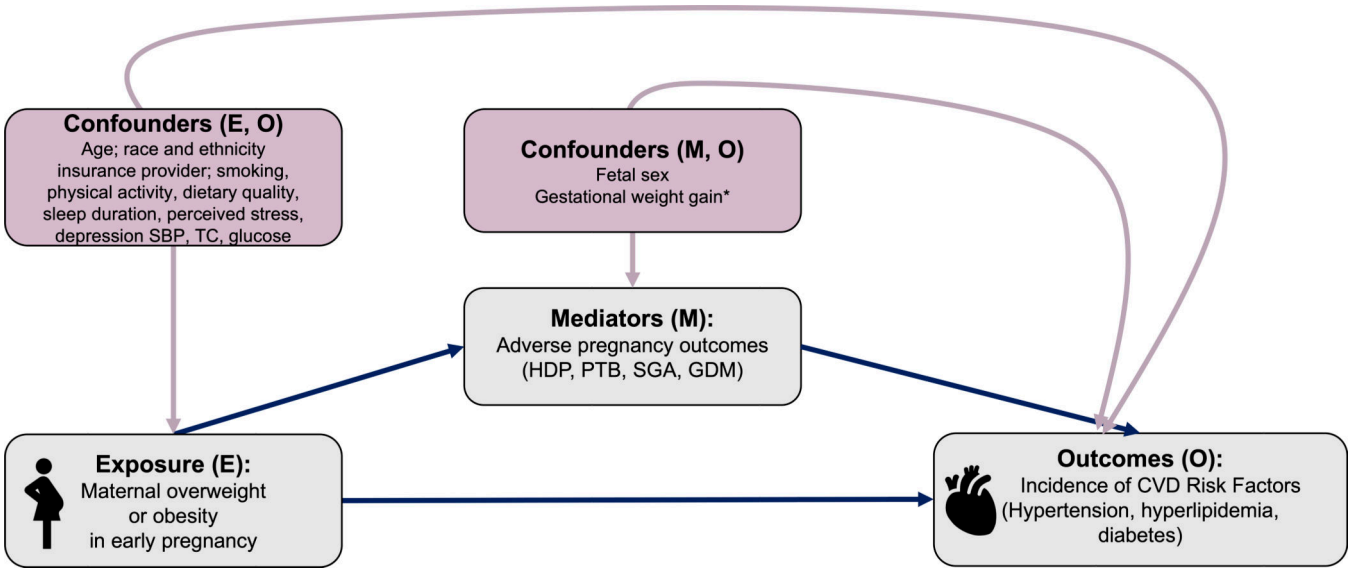


Figure 1. Direct Acyclic Graph Representing a Causal Structural Model Of Mediation of the Association Between Obesity in Early Pregnancy and Cardiovascular Health After Delivery.

Mediating pathway via adverse pregnancy outcomes of the association between obesity in early pregnancy and CVD risk factor levels years after delivery.

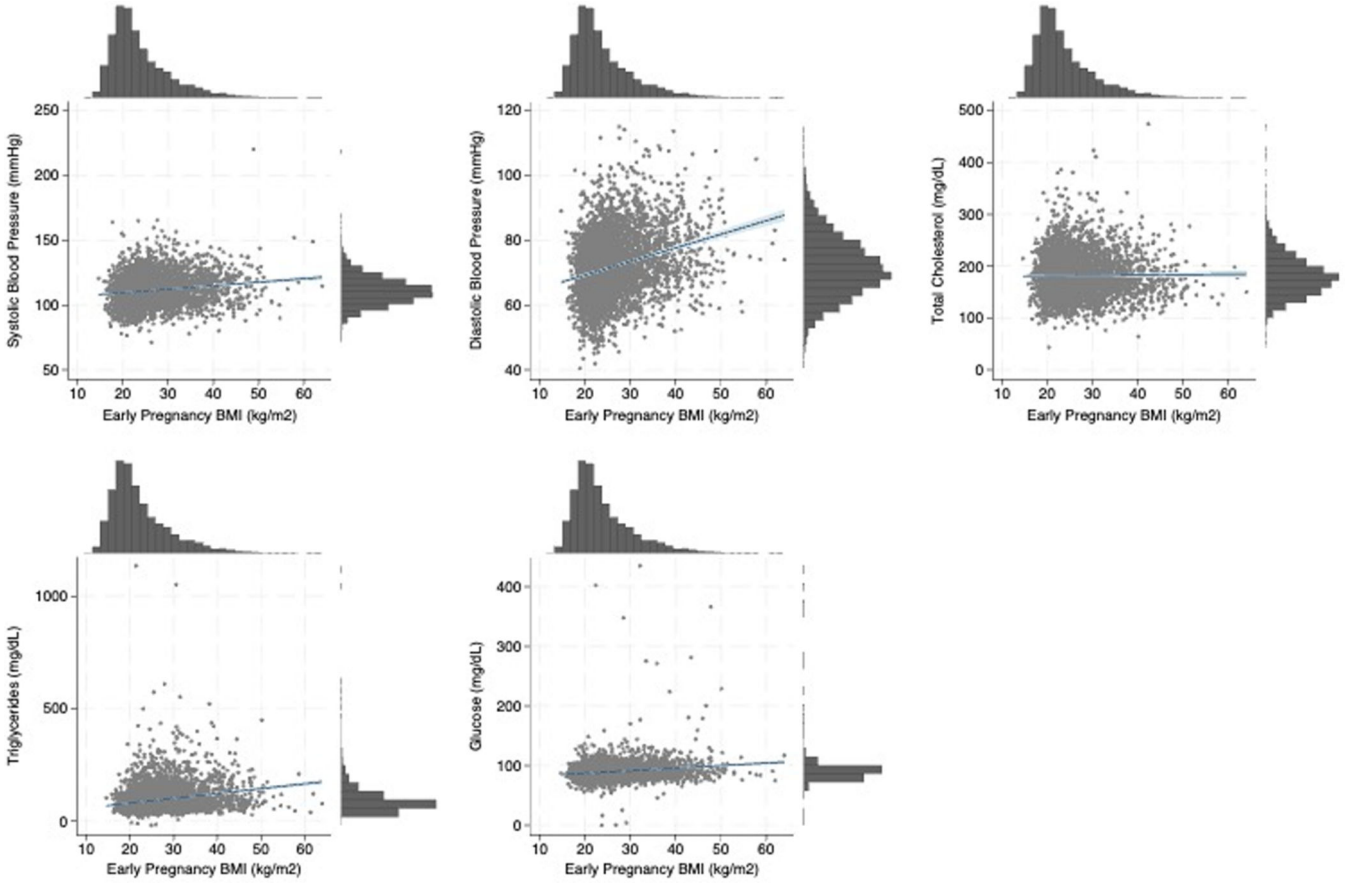


Figure 2. Associations Between Body Mass Index in Early Pregnancy and CVD Risk Factors after Delivery.

The data represent individuals at study enrollment (mean gestational age 11.4 weeks) and CVD risk factor levels measured at a mean follow-up of 3.7 years after delivery. Best-fit lines estimated via ordinary least squares regression were superimposed on the scatterplots to visualize associations. Statistics are based on 10 imputed datasets; N=4,216 participants.

Table 1.

Participant Characteristics in Early Pregnancy Overall and Stratified by Body Mass Index Categories

% or mean (SD)	Overall Cohort	Normal BMI (<25 kg/m^2)	Overweight (25kg/m^2 ≤ BMI < 30 kg/m^2)	Obesity (≥30 kg/m^2)
Maternal age, years	27.1 (5.5)	27.3 (5.3)	27.3 (5.6)	26.5 (5.6)
Self-reported race and ethnicity, %				
Non-Hispanic White	63.0%	68.6%	60.7%	52.5%
Non-Hispanic Black	13.0%	8.5%	12.5%	24.1%
Hispanic/Latinx	16.3%	14.2%	20.5%	16.6%
Asian	3.2%	4.6%	2.2%	0.7%
Other[a]	4.5%	4.1%	4.0%	6.0%
Health insurance type, %				
Public or other	29.9%	25.3%	31.8%	38.6%
Private	70.1%	74.7%	68.2%	61.4%
BMI, kg/m^2	26.4 (6.3)	21.9 (1.9)	27.1 (1.4)	36.0 (5.3)
Waist circumference, cm	95.2 (14.5)	86.0 (7.0)	96.9 (7.3)	115.0 (13.0)
SBP, mmHg	109.2 (10.7)	106.2 (9.8)	109.8 (9.8)	115.6 (10.6)
Glucose, mg/dL[b]	87.6 (14.8)	85.8 (14.4)	88.4 (15.2)	90.9 (14.6)
Total cholesterol, mg/dL[b]	186.8 (35.7)	184.2 (34.5)	192.4 (36.1)	186.8 (37.5)
Ever used tobacco, %	39.1%	36.3%	39.6%	45.1%
Physical activity, min	181.3 (175.3)	195.0 (174.7)	176.8 (171.3)	153.8 (177.6)
Healthy eating index 2010	62.7 (12.7)	64.2 (12.8)	62.6 (12.4)	59.2 (12.3)
Sleep duration, hours per night	8.0 (1.2)	8.0 (1.2)	8.0 (1.2)	7.9 (1.4)
Depression score (0–30)	5.7 (4.2)	5.4 (4.1)	5.7 (4.2)	6.2 (4.4)
Perceived stress score (0–40)	12.6 (6.6)	12.0 (6.4)	12.6 (6.5)	13.9 (7.0)

[a]Individuals whose racial or ethnic identity is “other” than that of the listed categories and represents those who identify as American Indian or Alaskan Native, Native Hawaiian, multiracial, and individuals who did not identify as belonging to any of these groups.

[b]Laboratory values are non-fasting at baseline visit

BMI represents body mass index calculated as weight in kilograms divided by height in meters squared.

Statistics are based on 10 imputed datasets; N=4,216 participants.

Table 2.

Associations Between Hypertensive Disorders of Pregnancy and Cardiovascular Disease Risk Factors After Delivery

CVD Risk-Factor Levels 2–7 Years Postpartum	**β (95% CI)**		**Adjusted β (95% CI)***	
Systolic blood pressure, mmHg	4.95	(3.97, 5.92)	3.33	(2.36, 4.31)
Fasting total cholesterol, mg/dL	5.72	(2.17, 9.27)	3.83	(0.62, 7.04)
Fasting glucose, mg/dL	1.57	(0.42, 2.72)	0.21	(−1.02, 1.44)
CVD Outcomes 2–7 Years Postpartum	**OR (95% CI)**		**Adjusted OR (95% CI)**	
Hypertension	2.73	(2.27, 3.29)	1.97	(1.61, 2.40)
Hyperlipidemia	1.67	(1.34, 2.08)	1.31	(1.03, 1.67)
Diabetes	0.97	(0.51, 1.84)	0.67	(0.34, 1.31)

Top panel presents coefficients and 95% confidence intervals based on linear regression models.

Bottom panel presents odds ratios and 95% confidence intervals based on logistic regression models.

*All models above adjusted for maternal age, race and ethnicity, insurance, fetal sex, and visit 1 body mass index, smoking, physical activity, diet, sleep, stress, depression, systolic blood pressure, cholesterol, and glucose.

Hypertensive disorders of pregnancy include pre-eclampsia, eclampsia, and gestational hypertension.

Statistics are based on 10 imputed datasets; N=4,216 participants.

Table 3.

Adjusted Direct and Indirect Associations Between Early Pregnancy Body Mass Index and Cardiovascular Disease Risk Factors Years After Delivery and Proportion Mediated via Hypertensive Disorders of Pregnancy

Early pregnancy overweight vs. normal body mass index								
CVD Risk Factor Levels	**Total effect β**		**Direct effect β**		**Mediated β**		**% Mediated** *	
SBP, mmHg	2.05	(1.33, 2.78)	1.90	(1.18, 2.62)	0.15	(0.03, 0.27)	7.4	(5.5, 9.3)
Fasting TC, mg/dL	0.06	(−2.68, 2.81)	0.05	(−2.70, 2.81)	0.01	(−0.30, 0.31)		---
Fasting Glucose, mg/dL	1.02	(0.10, 1.94)	0.94	(−0.01, 1.88)	0.08	(−0.04, 0.20)		---
Early pregnancy obesity vs. normal body mass index								
CVD Risk Factor Levels	**Total effect β**		**Direct effect β**		**Mediated β**		**% Mediated**	
SBP, mmHg	0.80	(−0.21, 1.80)	0.43	(−0.58, 1.45)	0.36	(0.16, 0.56)		---
Fasting TC, mg/dL	1.35	(−1.61, 4.32)	0.68	(−2.31, 3.67)	0.67	(0.02, 1.33)		---
Fasting Glucose, mg/dL	5.17	(3.49, 6.86)	5.38	(3.58, 7.18)	−0.21	(−0.46, 0.05)		---
Early pregnancy overweight vs. normal body mass index								
CVD Risk Factors	**Total effect OR**		**Direct effect OR**		**Mediated OR**		**% Mediated**	
Hypertension	1.08	(1.05, 1.11)	1.07	(1.04, 1.10)	1.01	(1.00, 1.01)		---
Dyslipidemia	1.03	(1.01, 1.06)	1.03	(1.01, 1.06)	1.00	(1.00, 1.00)		---
Diabetes	1.01	(1.00, 1.01)	1.01	(1.00, 1.01)	1.00	(1.00, 1.00)		---
Early pregnancy obesity vs. normal body mass index								
CVD Risk Factors	**Total effect OR**		**Direct effect OR**		**Mediated OR**		**% Mediated**	
Hypertension	1.14	(1.10, 1.18)	1.12	(1.08, 1.16)	1.02	(1.01, 1.03)	12.9	(10.5, 15.2)
Dyslipidemia	1.11	(1.08, 1.14)	1.10	(1.07, 1.13)	1.01	(1.00, 1.02)		---
Diabetes	1.03	(1.01, 1.04)	1.03	(1.01, 1.05)	1.00	(0.99, 1.00)		---

* Proportion mediated = Mediated β/Total effect β; when all or none of the effect is mediated (no statistically significant direct or mediated effect, respectively), the percent mediated may be estimated outside of 0–100%.

All models above adjusted for maternal age, race and ethnicity, insurance, fetal sex, and visit 1 smoking, physical activity, diet, sleep, stress, depression, SBP, cholesterol, and glucose.

Abbreviations. CVD: Cardiovascular disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides. Statistics are based on 10 imputed datasets; N=4,216 participants.