Allostatic Load in Pregnancy, Race and Associations with Subsequent Cardiovascular Related Outcomes: Research Article

Amir Lueth[1], Amanda Allshouse[2], Nathan Blue[3], william grobman[4], Lisa Levine[5], Janet Catov[6], George Saade[7], Lynn Yee[8], Wilson Fernando[3], Maureen Murtaugh[3], Noel Merz[9], JUdith Chung[10], Mitali Ray[11], Christina Scifres[12], and Robert Silver (USA)[1]

[1]University of Utah
[2]University of Colorado
[3]University of Utah Health
[4]The Ohio State University
[5]Affiliation not available
[6]University of Pittsburgh School of Medicine
[7]UTMB
[8]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago
[9]Cedars-Sinai Medical Center
[10]University of California Irvine
[11]University of Pittsburgh
[12]Indiana University School of Medicine

November 17, 2022

Abstract

OBJECTIVE To assess the relationship between allostatic load in early pregnancy and CVD, 2 to 7 years postpartum, and potential pathways contributing to racial disparities in CVDs. DESIGN Secondary analysis of an observational cohort study. SETTING nuMom2b Heart Health Study. POPULATION Pregnant individuals. METHODS Our primary exposure was dichotomous high allostatic load in the first trimester, defined as four or more out of 12 biomarkers in the "worst" quartile. The primary outcome was new diagnosis of composite CVD, consisting of HTN and or MD (fasting glucose greater than 100 mg/dL or medication for diabetes). Each outcome and allostatic load component was analyzed secondarily. Multivariable logistic regression was used to test the association between high allostatic load and CVD adjusted for potential confounders. Mediation and moderation analyses assessed the role of high allostatic load in racial disparities of CVD. MAIN OUTCOME MEASURE Composite CVD. RESULTS Among 4,022 individuals, CVD was identified in 1,462 (36.4%); 26.6% had HTN, and had 15.4% MD. High allostatic load was present in 33.0%. After adjustment for covariates, high allostatic load was associated with CVD (aOR 2.0, 1.8-2.3), HTN (2.1, 1.8-2.4), and MD (1.7, 1.5-2.1). There was a reduction in the magnitude of the relationship between race and CVD with the addition of allostatic load. Self-reported race did not significantly moderate the relationship between allostatic load and CVD. CONCLUSION High allostatic load is associated with CVD. Allostatic load was a partial mediator between race and CVD. Race did not moderate the relationship between allostatic load and CVD.

TITLE: Allostatic Load in Pregnancy, Race and Associations with Subsequent Cardiovascular Related Outcomes

[1]Amir Lueth, MPH, [1]Amanda A. Allshouse, MS, [1]Nathan M. Blue, MD,[2]William A. Grobman, MD, MBA,

[3]Lisa D. Levine, MD, [4]Janet Catov, MD, MS,[5]George Saade, MD, [6]Lynn M. Yee, MD,[7]Fernando A. Wilson, Ph.D., [7]Maureen Murtaugh, Ph.D., [10]Noel Merz, MD,[8]Judith Chung, MD, [4]Mitali Ray, Ph.D., [9]Christina Scifres, MD,[1]Robert M. Silver, MD, for the NIH NICHD nuMoM2b and NHLBI nuMoM2b Heart Health Study Networks

DEPARTMENTS AND INSTITUTIONS:

[1]Department of Obstetrics and Gynecology, University of Utah Health, Salt Lake City, Utah

[2]Department of Obstetrics and Gynecology, Ohio State University, Columbus, Ohio

[3]Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Department of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, Pennsylvania

[5]Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, Texas

[6Department] of Obstetrics and Gynecology, Northwestern University, Evanston, Illinois

[7]Department of Population Health Sciences, University of Utah Health, Salt Lake City, Utah

[8]Department of Obstetrics and Gynecology, University of California Irvine, Irvine, California

[9]Department of Obstetrics and Gynecology, School of Medicine, Indiana University

[10]Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California

Corresponding author: Amir Lueth, MPH. University of Utah Health Care, Department. of Obstetrics and Gynecology. 30 North 1900 East, Rm 2B200. Salt Lake City, UT 84132. Amir.lueth@hsc.utah.edu 8143236718

Keywords: Allostatic load, cardiovascular disease, pregnancy morbidity, adverse pregnancy outcomes, stress biomarkers

Short title: Allostatic load and postpartum cardiovascular disease

ABSTRACT:

OBJECTIVE

To assess the relationship between allostatic load in early pregnancy and CVD, 2 to 7 years postpartum, and potential pathways contributing to racial disparities in CVDs.

DESIGN

Secondary analysis of an observational cohort study.

SETTING

nuMom2b Heart Health Study.

POPULATION

Pregnant individuals.

METHODS

Our primary exposure was *dichotomous high allostatic load in the first trimester* , defined as four or more out of 12 biomarkers in the "worst" quartile. The primary outcome was new diagnosis of composite CVD, consisting of HTN and or MD (fasting glucose greater than 100 mg/dL or medication for diabetes). Each outcome and allostatic load component was analyzed secondarily. Multivariable logistic regression was used to test the association between high allostatic load and CVD adjusted for potential confounders. Mediation and moderation analyses assessed the role of high allostatic load in racial disparities of CVD.

MAIN OUTCOME MEASURE

Composite CVD.

RESULTS

Among 4,022 individuals, CVD was identified in 1,462 (36.4%); 26.6% had HTN, and had 15.4% MD. High allostatic load was present in 33.0%. After adjustment for covariates, high allostatic load was associated with CVD (aOR 2.0, 1.8-2.3), HTN (2.1, 1.8-2.4), and MD (1.7, 1.5-2.1). There was a reduction in the magnitude of the relationship between race and CVD with the addition of allostatic load. Self-reported race did not significantly moderate the relationship between allostatic load and CVD.

CONCLUSION

High allostatic load is associated with CVD. Allostatic load was a partial mediator between race and CVD. Race did not moderate the relationship between allostatic load and CVD.

INTRODUCTION:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals in the United States (US).[1] Older age, obesity, smoking, use of opioids[2], prior CVD, diabetes, high blood pressure, thromboembolism, and previous adverse pregnancy outcomes (APOs) are risk factors for CVD. Racism and inequities contribute to disparities in birth outcomes and CVD across an individual's life course.[3] In addition, chronic stress, a measure of cumulative wear and tear on the body's adaptive system, can be estimated by allostatic load (AL) and has been associated with increased odds of CVD.[4]

Pregnancy has been described as a window into future maternal health because of the significant anatomical, physiological changes during pregnancy and the association between adverse pregnancy outcomes and subsequent CVD. [5, 7] Chronic stress and allostatic load have been associated with adverse pregnancy outcomes.[8, 9] However, the relationship between chronic stress during pregnancy and subsequent CVD has not been assessed.

Significant racial disparities exist in CVD events among pregnant individuals, and data on racial disparities in CVD outcomes after pregnancy are limited. Chronic stress may, in part, explain racial disparities noted in CVD, with higher rates noted in non-Hispanic Black individuals. [4] Compared to non-Hispanic White individuals, non-Hispanic Black individuals have a higher risk of mortality, myocardial infarction, stroke, pulmonary embolism, and peripartum cardiomyopathy. [10]

We aimed to assess the relationship between allostatic load and CVD-related outcomes. We hypothesize that allostatic load measured in early pregnancy is associated with subsequent maternal CVD-related outcomes. Secondarily, we hypothesize that allostatic load during pregnancy may be a pathway that contributes to racial disparities in subsequent CVD-related outcomes. .

METHODS:

The Nulliparous Pregnancy Outcomes Study: Monitoring mothers-to-be (nuMoM2b) is a geographically diverse, prospective, observational cohort study in which 10,038 nulliparous individuals with singleton pregnancies were enrolled between October 2010 and September 2013. Individuals were eligible for enrollment if they were nulliparous (no prior delivery at 20 weeks or later gestational age), had a viable singleton gestation, had an estimated gestational age of pregnancy between 6^0–13^6 weeks, and intended to deliver at a participating clinical site. The study protocol included three study visits during pregnancy and a final visit at the time of delivery. Maternal characteristics and other covariates were ascertained from baseline clinical assessments, medical record abstraction, and standardized questionnaires by trained personnel. Details of the study procedures have been described elsewhere. [11] Each institutional review board approved the study, and all participants gave written informed consent.

A follow-up study, nuMoM2b-Heart Health Study (HHS), included nuMoM2b participants 2 to 7 years after the nuMoM2b index pregnancy. 4508 HHS participants completed an in-person cardiovascular risk factor

evaluation. HHS participants had not withdrawn from the primary parent study, had pregnancy outcome data available, and agreed to follow-up contact at 6 month intervals beginning at least 6 months after delivery of the index pregnancy. After the in-person study CVD visit, participants agreed to be contacted at an interval of every 12 months. Biometric data, measurements, questionnaires, and bio-specimens were obtained at the in-person nuMoM2b-HHS visit. Further details on the methods of the HHS have been described elsewhere. [12]

This study was a secondary analysis of the nuMoM2b-HHS cohort. We excluded participants for whom the index pregnancy ended in fetal demise < 20 weeks or termination. Participants with missing 1st trimester index pregnancy biomarker measurements, details of APOs, preexisting diabetes, chronic diabetes and other missing delivery details at index pregnancy were excluded from the primary analysis. Chronic hypertension and preexisting diabetes at the index pregnancy, were exclusion criteria from the primary analysis, but were included in analyses of secondary outcomes MD and incident HTN, respectively.

Allostatic load biomarkers were processed from stored urine or serum samples, collected in the first trimester during the nuMoM2b index pregnancy. Samples were stored at -80°C at a central core biorepository. Assays were completed at the HHS core laboratory (Lundquist Institute, Torrance, CA) using standard protocols on a Beckman AU480.

This study's definition of allostatic load modifies the NHANES[13, 14] commonly used risk biomarkers by adding triglycerides, insulin and glucose. Based on available data and assays, allostatic load was defined using: clinically-measured (systolic blood pressure (SBP) diastolic blood pressure (DBP), and body mass index (BMI) (kg/m2)), serum-measured (cholesterol (mg/dL), low-density lipoprotein (LDL) (mg/dL), high-density lipoprotein (HDL) (mg/dL), high sensitivity C-reactive protein (hsCRP) (mg/dL), triglycerides (mg/dL), insulin (ulU/mL), and glucose (mg/dL)) and urine-measured (creatinine (mg/dL) and albumin (mg/dL)). Numerous variations and definitions of allostatic load that have been used, and one is not clearly superior to another [14]. We decided to use biomarkers that were available in our dataset and had been used in other definitions of allostatic load commonly utilized in studies of health disparities. These biomarkers exemplify organ and tissue damage within the following physiological systems: cardiovascular, inflammation, metabolic, and immune.[14-16]

A high allostatic load score was defined as four or more out of 12 biomarkers in the worst quartile; the 'worst' quartile was lowest for HDL and albumin and highest for the rest. [17] For each biomarker, if values were at or above the worst quartile (high risk), that biomarker received a value score of "1." Values not in the worst quartile were characterized as "low risk" and given a value score of "0". [13] The total allostatic load score was summed for an allostatic load index ranging from 0 to 12. Low allostatic load was reported as an allostatic load index of 4 or less, and high allostatic load was an allostatic load index of more than 4 since this threshold has been discriminatory. [17]

The study's primary outcome, a composite CVD-related outcome, consisted of hypertension (HTN), and metabolic disorder (MD) newly diagnosed in the 2 to 7 years after the index pregnancy. The diagnostic threshold for HTN was based on confirmed elevated or high clinical measurements of blood pressure (SBP [?] 120 mm Hg, DBP [?] 80 mm Hg) or antihypertensive medication use. The diagnostic threshold for MD consisted of diabetes as diagnosed by a health care provider, fasting glucose levels >= 100 mg/dL, or medication use for glucose control. Individually, HTN and MD were assessed as secondary outcomes and were chosen due to their strong associations with CVD risk and mortality.[12] Definitions for these outcomes were standard and previously reported in detail. [18]

Obstetric, medical history, clinical features of pregnancy, maternal demographic, and health behavior characteristics, all measured during the index pregnancy, were evaluated as risk factors for CVD. Obstetric and medical history included: gravida, prior miscarriages, and previous abdominal surgery. Clinical features of pregnancy included bleeding in the first trimester. Maternal demographic and health behavior characteristics included maternal age, education, smoking, federal poverty level, and health insurance status. We report time between index pregnancy and HHS visit.

Non-Hispanic black race has been associated with chronic stress and allostatic load. [32] Thus, although race is a social construct, we evaluated it as a proxy for social experience, systematic, racism, and other unmeasured social determinants of health that potentially manifest through chronic stress. Outcomes were compared between people of self-reported non-Hispanic Black race, and non-Hispanic White, Hispanic, Asian, Native American, Native Hawaiian, Multiracial, and additional racial backgrounds. It was not possible to analyze some groups separately due to small numbers.

Risk factors associated with the composite outcome were identified by testing differences in percentages with chi-square between individuals with and without composite outcome. Unadjusted and adjusted odds ratios (ORs) and 95% confidence interval (CIs) were calculated from bi-variable logistic regression models between individuals with and without composite outcome.

Our primary analysis assessed the association between allostatic load and composite outcome. Unadjusted odds ratios (ORs) and 95% confidence interval (CIs) for the association of high allostatic load with composite outcome were calculated from bi-variable logistic regression models. As secondary outcomes, we evaluated each component of composite outcome in a separate model using a similar methodology. For multivariable modeling of composite outcome, maternal age, smoking status, gravidity, the time between index pregnancy, bleeding at the first trimester, and health insurance status were chosen either *a priori* based on reported associations[19, 20] or were risk factors with an association with the outcome of P-value <0.10. The same covariates were used in the HTN model with the addition of preexisting diabetes and in the MD model with the addition of chronic hypertension. As an additional exploratory analysis, we modeled each of the twelve individual allostatic load component with three outcomes for a total of 36 comparisons. A sensitivity analysis of the primary outcome was performed excluding blood pressure and insulin from the allostatic load definition, and similarly for each secondary outcome allostatic load was redefined excluding blood pressure and insulin separately.

To test whether allostatic load is a pathway that contributes to racial disparities in CVDs, we conducted a four-step mediation analysis to test whether allostatic load is a mediator of the relationship between self-reported race and composite outcome. We first examined the association of maternal race on composite outcome (path c, Figure 2).[21-23] Second, we examined the impact of maternal race on allostatic load (path a, Figure 2). [21-23] Third, we report the association between allostatic load with composite outcome (path b, Figure 2). [21-23] In the final step, we assessed whether the race-composite outcome relationship was mediated by allostatic load (path c', Figure 2). We conducted a sensitivity analysis of the mediation examining the association between allostatic load and composite outcome, limiting the analytical population to individuals of non-Hispanic Black and non-Hispanic White race and ethnicity. This was repeated for secondary outcomes.

As an exploratory analysis, we tested whether there's an effect modification by race between allostatic load and composite outcome. In unadjusted and adjusted models of composite outcome, we tested for an interaction between race (non-Hispanic Black vs. "Non-Hispanic White, Hispanic, Asian, Native American, and Native Hawaiian, multiracial and additional racial backgrounds".) and high allostatic load. A significant interaction would demonstrate a difference in the association between high allostatic load and CVD outcomes for people of non-Hispanic Black race compared to people of "Non-Hispanic White, Hispanic, Asian, Native American, and Native Hawaiian, multiracial and additional racial backgrounds". (i.e., moderation). We conducted a sensitivity analysis of the exploratory moderation examining the association, limiting the analytical population to individuals of non-Hispanic Black and non-Hispanic White race and ethnicity. This was repeated for secondary outcomes.

Data analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). All tests were performed at a significance level of $p < 0.05$, and all single degrees of freedom tests were 2-sided.

RESULTS:

The primary analysis included a total of 4,022 pregnant individuals (Figure 1). High allostatic load was identified in 33.0% (n=1327) of individuals. Maternal age, race, gravidity, prior miscarriage, prior bleeding at the first trimester, and insurance status were associated with high allostatic load (Table 1)

The composite outcome was identified in 36.4% (n=1,462) individuals; 1079 (26.6%) had HTN, and 636 (15.4%) had MD. The time between index pregnancy and HHS, maternal age, race, education, gravidity of 3 or more, smoking status, and government health insurance were associated with CVD outcomes, while other maternal characteristics were not (Tables S1, S2, and S3). High allostatic load (OR= 2.1; 95% CI: 1.8-2.4) was significantly associated with composite outcome. After adjustment for the time between index pregnancy and HHS, maternal age, race, education, smoking status, gravidity, smoking status, bleeding in the first trimester, prior adverse pregnancy outcomes, and government health insurance status, allostatic load remained significantly associated with composite outcome (aOR 2.0, 1.8-2.3), (Table 2).

Associations persisted in the analysis of both components of composite outcome. In bi-variable analysis, a high allostatic load was associated with HTN (OR= 2.1; 95% CI: 1.8-2.4) and MD (OR= 1.9; 95% CI: 1.6-2.2). In an adjusted model, HTN and MD remained significantly associated with high allostatic load (aOR= 2.1; 95% CI: 1.8-2.4), and (aOR= 1.7; 95% CI: 1.5-2.1), respectively. Results were similar in the sensitivity analysis, where we included prior APOs: composite outcome (aOR = 1.9; 95% CI: 1.6-2.2), HTN (aOR = 1.9, 95% CI: 1.6-2.2), and MD (aOR = 1.8, 95% CI: 1.5-2.1) (Table 2).

In the exploratory analyses, the individual components of allostatic load: BMI, DBP, SBP, triglycerides, HDL, creatinine, and CRP, were significantly associated with composite outcome, HTN, and MD while others were not. In addition, glucose was associated with composite outcome and MD, LDL was associated with composite outcome, and HTN and total cholesterol were associated with composite outcome (Table S4). In a sensitivity analysis, an allostatic load score excluding both DBP and SBP remained significantly associated with composite outcome (aOR = 1.9, 95% CI: 1.6-2.2), HTN (aOR = 1.7, 95% CI: 1.5-2.0). Similarly, an allostatic load index excluding insulin remained significantly associated with MD (aOR = 1.9, 95% CI: 1.6-2.3) (Table S7).

High allostatic load was a partial mediator in the association between race and composite outcome, but not the individual components HTN or MD (Table 3). In greater detail, first, we established a significant association between race and composite outcome (path c, Table 3), race and high allostatic load (path a, Table 3), and high allostatic load and composite outcome (path b, Table 3). The magnitude of the relationship between race and composite outcome in the presence of high allostatic load was modestly smaller (path c' vs. path c, Table 3). For composite outcome components, HTN and MD, a significant association between race and each outcome was present (path c). The association between race and high allostatic load is significant (path a). The association between allostatic load and each component of CVD outcomes was significant (path b). However, we did not see a reduction in the magnitude of the relationship between race and each component of the composite outcome with the addition of high allostatic load. Thus, high allostatic load was not demonstrated to mediate the association between race and HTN or MD (Table 3). In a sensitivity mediation analysis where we restricted the population to examine the association of allostatic load and CVD between non-Hispanic Black and non-Hispanic White individuals, results were similar in magnitude, significance, and interpretation (Table S5).

In the exploratory analysis testing whether race moderates the relationship between allostatic load and composite outcome, the association between allostatic load and CVD outcomes) was not significantly different for non-Hispanic Black compared to "Non-Hispanic White, Hispanic, Asian, Native American, Native Hawaiian, multiracial and additional racial backgrounds". The interaction test (difference in the association of high allostatic load and CVD outcomes by race) was not significant for any outcome in either unadjusted or adjusted modeling. (Table 4), as such, race was not a significant moderator of the relationship between allostatic load and composite outcome. In a sensitivity moderation analysis where we restricted the population to examine the difference in association of allostatic load and CVD outcomes between non-Hispanic Black and non-Hispanic White individuals, results were similar in magnitude, significance, and interpretation (Table S6).

DISCUSSION:

In this prospective cohort study, high allostatic load in early pregnancy was associated with subsequent

composite outcome 2 to 7 years after delivery. After adjustment for covariates, high allostatic load was significantly associated with composite outcome, HTN, and MD. Results were similar in sensitivity analysis, where we adjusted for prior APOs. The components of allostatic load most strongly associated with CVD outcomes in exploratory analyses were BMI, SBP, DBP, and CRP. These data support growing evidence that cumulative stress is associated with subsequent CVD-related outcomes.

Others also have noted allostatic load as a risk factor for increased risk of contemporaneous coronary artery disease, ischemic heart disease, and peripheral arterial disease. [24-27] Similarly, individuals with type 2 diabetes, elevated blood pressure and worse glycemic control have higher allostatic load. [24-27]Again, these studies assessed contemporaneous allostatic load.[33]

Generally, subclinical higher levels of blood pressure and glucose metabolism are associated with subsequent HTN and MD.[28] As such blood pressure and metabolic parameters were individually associated with subsequent CVD and high allostatic load remained significantly associated with subsequent CVD, even when we excluded blood pressure and insulin from the allostatic load index for the composite, HTN and MD.

Self-reported race has been included as a proxy for social experience, systematic and interpersonal racism, and other unmeasured social determinants of health. As such allostatic load has been strongly associated with the non-Hispanic Black race in several studies.[29, 30] Black individuals reporting greater perceived racial discrimination had a higher allostatic load. [31]However, one study noted that this was somewhat mitigated by additional educational attainment. [32] We found that non-Hispanic Black race was associated with high allostatic load and CVD outcomes. The addition of allostatic load only partially mediated the relationship between race and CVD outcomes in our study and not between race and each component of the composite outcome as such these associations were not significantly different by race.

Our study has several limitations. Our cohort lacks some generalizability since it was limited to nulliparous individuals who could access tertiary medical care centers and had the means to participate in a complex longitudinal study. This analysis was restricted to individuals in a follow-up study, introducing potential bias in the cohort. Also, we only evaluated allostatic load during the first trimester of the index pregnancy. Thus, we could not assess the trajectory relationship between allostatic load later in pregnancy or allostatic load and CVD outcomes longitudinally. Also, we could not assess the impact of subsequent pregnancies between the index pregnancy and HHS in person visit 2-7 years postpartum. Although we assessed a 12-factor index and individual components of allostatic load, we did not assess other combination, including additional metabolic and cardiovascular indicators that make up a broader allostatic load index, which may be more robust for evaluating allostatic load and CVD.[33]

This study had notable strengths. We utilized a large, well-characterized prospective cohort with standardized data collection by trained research personnel. Outcomes used rigorous definitions, and physicians adjudicated uncertain cases. [11]Importantly, our population was geographically, racially, and ethnically diverse and is somewhat representative of the US population. Another strength is that each allostatic load biomarker component was weighted equally, a scientifically sound approach. Evidence suggests no significant difference between empirical and clinical cut-off assessments. [34]

In summary, early pregnancy high allostatic load is associated with composite maternal CVD outcomes 2-7 years postpartum, particularly HTN and MD. High allostatic load early in pregnancy could indicate increased risk for subsequent HTN and MD. High allostatic load modestly mediated the association between self-reported race and composite outcome, but not individual components of the composite outcome. Discovery of early pregnancy biomarkers that are associated with increase long-term CVD risk might have impact on public health. Thus, pathways contributing to allostatic load such as stress and inflammation should be investigated as therapeutic targets intended to decrease CVD.

Financial Disclosure

The authors did not report any potential conflicts of interest.

Contribution to authorship:

Amir Lueth, MPH: Responsible for the conception, methodology, and hypothesis, planning, programing statistical codes, carrying out formal analysis, and writing up the manuscript.

Amanda A. Allshouse: Responsible for checking analysis and reviewing the final version of the manuscript.

Nathan M. Blue: Responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

William A. Grobman: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Lisa D. Levine: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Janet Catov: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

George Saade: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Lynn M. Yee: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Fernando A. Wilson: Responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Maureen Murtaugh: Responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Noel Merz: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Judith Chung: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Mitali Ray: Responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Christina Scifres: One of the nuMoM2b PI who was responsible for providing comments, feedback on all sections of the manuscript and reviewing the final version of the manuscript.

Robert M. Silver: One of the nuMoM2b PI who was responsible for providing critical and final comments on the hypothesis, plan and discussion section of the manuscript.

Details of patients consent: All participants gave written informed consent.

Sources of Funding

This study is supported by 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; and U10-HL120018. U10 HD063036, RTI International; U10 HD063072, Case Western Reserve University; U10 HD063047, Columbia University; U10 HD063037, Indiana University; U10 HD063041, University of Pittsburgh; U10 HD063020, Northwestern University; U10 HD063046, University of California Irvine; U10 HD063048, University of Pennsylvania; and U10 HD063053, University of Utah. In addition, support was provided by respective Clinical and Translational Science Institutes to Indiana University (UL1TR001108) and University of California Irvine (UL1TR000153).

Each site's local governing Institutional Review Board(s) approved the nuMoM2b protocol and procedures.

ClinicalTrials.gov Registration number NCT02231398

References:

1. Ramlakhan, K.P., Johnson, M.R. & Roos-Hesselink, J.W. Pregnancy, and cardiovascular disease. Nat Rev Cardiol 17, 718–731 (2020).
2. Courchesne NS, Smith LR, Zúñiga ML, et al. Association of alcohol and other substance-related diagnoses with severe maternal morbidity. Alcohol Clin Exp Res. 2021;45(9):1829-1839. doi:10.1111/acer.14671
3. Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. Lancet. 2017;389(10077):1453-1463. doi:10.1016/S0140-6736(17)30569-X
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021;143(8):e254-e743. doi:10.1161/CIR.0000000000000950
5. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016;27(2):89-94. doi:10.5830/CVJA-2016-021
6. Smith GN, Saade G. SMFM White Paper: Pregnancy as a Window to Future Health. Accessed December 17, 2019. https://www.smfm.org/publications/141- smfm-white-paper-pregnancy-as-a-window-to-future-health
7. Enkhmaa D, Wall D, Mehta PK, et al. Preeclampsia and Vascular Function: A Window to Future Cardiovascular Disease Risk. J Women's Health 2002. 2016;25(3):284-291. doi:10.1089/jwh.2015.5414
8. Hux VJ, Catov JM, Roberts JM. Allostatic load in women with a history of low birth weight infants: the national health and nutrition examination survey. J Women's Health (Larchmt). 2014;23(12):1039-1045. doi:10.1089/jwh.2013.4572
9. Hux VJ, Roberts JM. A potential role for allostatic load in preeclampsia. Matern Child Health J. 2015;19(3):591-597. doi:10.1007/s10995-014-1543-7
10. Gad MM, Elgendy IY, Mahmoud AN, et al. Disparities in Cardiovascular Disease Outcomes Among Pregnant and Postpartum Women. J Am Heart Assoc. 2021;10(1):e017832. doi:10.1161/JAHA.120.017832
11. Haas DM, Parker CB, Wing DA, et al. A description of the methods of the Nulliparous Pregnancy Outcomes Study: monitoring mothers-to-be (nuMoM2b). *American Journal of Obstetrics and Gynecology* . 2015; 212(4). doi:10.1016/j.ajog.2015.01.019.
12. Haas DM, Ehrenthal DB, Koch MA, et al. Pregnancy as a Window to Future Cardiovascular Health: Design and Implementation of the nuMoM2b Heart Health Study. Am J Epidemiol. 2016;183(6):519-530. doi:10.1093/aje/kwv309
13. Hux VJ, Catov JM, Roberts JM. Allostatic load in women with a history of low birth weight infants: the national health and nutrition examination survey. J Women's Health (Larchmt). 2014;23(12):1039-1045. doi:10.1089/jwh.2013.4572
14. Duong MT, Bingham BA, Aldana PC, Chung ST, Sumner AE. Variation in the Calculation of Allostatic Load Score: 21 Examples from NHANES. J Racial Ethn Health Disparities. 2017;4(3):455-461. doi:10.1007/s40615-016-0246-8
15. Jones SA, Challis JR. Steroid, corticotrophin-releasing hormone, ACTH, and prostaglandin interactions in the amnion and placenta of early pregnancy in man. J Endocrinol. Apr; 1990 125(1):153–159.
16. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and Allostatic Load. Ann N Y Acad Sci. 1999;896:30–47.
17. Frei R, Haile SR, Mutsch M, Rohrmann S. Relationship of Serum Vitamin D Concentrations and Allostatic Load as a Measure of Cumulative Biological Risk among the US Population: A Cross-Sectional Study. PLoS One. 2015;10(10):e0139217. Published 2015 October 9. doi:10.1371/journal.pone.0139217
18. Haas DM, Parker CB, Marsh DJ, et al. Association of Adverse Pregnancy Outcomes With Hypertension 2 to 7 Years Postpartum. *J Am Heart Assoc* . 2019;8(19):e013092. doi:10.1161/JAHA.119.013092
19. income, stress and C-reactive protein among parous women: implications for preterm birth disparity

research. J Natl Med Assoc 2008;100(5):540–6.
20. Dunkel Schetter C, Tanner L. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr Opin Psychiatry. 2012;25(2):141-148. doi:10.1097/YCO.0b013e3283503680
21. MacKinnon DP, Valente MJ. Mediation from multilevel to structural equation modeling. Ann Nutr Metab. 2014;65(2-3):198-204. doi:10.1159/000362505
22. Baron R.M., Kenny D.A. The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. J. Personal. Soc. Psychol. 1986;51:1173–1182. doi: 10.1037/0022-3514.51.6.1173.
23. Rijnhart JJM, Twisk JWR, Eekhout I, Heymans MW. Comparison of logistic-regression based methods for simple mediation analysis with a dichotomous outcome variable. BMC Med Res Methodol. 2019;19(1):19. Published 2019 January 21. doi:10.1186/s12874-018-0654-z
24. Guidi J, Lucente M, Sonino N, Fava GA. Allostatic Load and Its Impact on Health: A Systematic Review. Psychother Psychosom. 2021;90(1):11-27. doi:10.1159/000510696
25. Parikh NI, Gonzalez JM, Anderson CAM, 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(18):e902-e916. doi:10.1161/CIR.0000000000000961
26. Bellamy L, Casas J, Hingorani A D, Williams D J. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis BMJ 2007; 335 :974 doi:10.1136/bmj.39335.385301.B
27. Bellamy L, Casas J, Hingorani A D, Williams D J. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis BMJ 2007; 335 :974 doi:10.1136/bmj.39335.385301.B
28. Männistö T, Mendola P, Vääräsmäki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127(6):681-690. doi:10.1161/CIRCULATIONAHA.112.128751
29. Chyu L, Upchurch DM. A Longitudinal Analysis of Allostatic Load among a Multi-Ethnic Sample of Midlife Women: Findings from the Study of Women's Health Across the Nation. Women's Health Issues. 2018;28(3):258-266. doi:10.1016/j.whi.2017.11.002
30. Memiah P, Biadgilign S, Kuhlman J, et al. Allostatic Load, Single, and Dual Chronic Conditions: Evidence from the National Health and Nutrition Examination Survey [published online ahead of print, 2021 Dec 15]. Metab Syndr Relat Disord. 2021;10.1089/met.2021.0008. doi:10.1089/met.2021.0008
31. Cuevas AG, Wang K, Williams DR, Mattei J, Tucker KL, Falcon LM. The Association Between Perceived Discrimination and Allostatic Load in the Boston Puerto Rican Health Study. Psychosom Med. 2019;81(7):659-667. doi:10.1097/PSY.0000000000000715
32. Allen AM, Thomas MD, Michaels EK, et al. Racial discrimination, educational attainment, and biological dysregulation among midlife African American women. Psychoneuroendocrinology. 2019;99:225-235. doi:10.1016/j.psyneuen.2018.09.001
33. Gillespie SL, Anderson CM, Zhao S, Tan Y, Kline D, Brock G, et al. Allostatic load in the association of depressive symptoms with incident coronary heart disease: The Jackson Heart Study. Psychoneuroendocrinology. 2019 Nov;109:104369.
34. Prior L. Allostatic Load and Exposure Histories of Disadvantage. Int J Environ Res Public Health. 2021;18(14):7222. Published 2021 July 6. doi:10.3390/ijerph18147222

Table 1: Demographic and clinical characteristics of individuals with high and low allostatic loads.

Variables	Study cohort N (%) N = 4,022	High Allostatic Load [?] 4 N = 1327	Low Allostatic Load < 4 N = 2695	P-value
Time elapsed from index pregnancy	3.2 ±0.9	3.2±0.9	3.2±0.9	0.393

Variables	Study cohort N (%) N = 4,022	High Allostatic Load [?] 4 N = 1327	Low Allostatic Load < 4 N = 2695	P-value
Maternal Age >= 35	378 (9.4)	142 (10.7)	236 (9.0)	0.047
Race (Non-Hispanic Black)	495 (12.3)	181 (13.6)	314 (11.7)	0.071
Education (Some college or less)	1506 (37.4)	568 (42.8)	938 (34.8)	<0.001
Gravidity >= 3	248 (6.2)	94 (7.1)	154 (5.7)	0.089
Smoking	625 (15.6)	235 (17.7)	390 (14.5)	0.008
Alcohol Use (ever)	2509 (62.4)	800 (60.3)	1709 (63.4)	0.054
Prior Miscarriage	599 (14.9)	222 (16.7)	377 (14.0)	0.021
Prior Abdominal Surgery	408 (10.1)	149 (11.2)	259 (9.6)	0.110
Prior Bleeding at First Trimester	272 (6.8)	108 (8.1)	164 (6.1)	0.015
[?] 200% of federal poverty level	1013 (30.3)	354 (32.2)	659 (29.4)	0.094
Government Health Insurance	1066 (26.6)	353 (26.8)	713 (26.6)	0.894

Data are expressed as binary variables and as n (column %)

Table 2: Adjusted logistic regression estimating the association between cardiovascular related outcomes and allostatic load score.

	High Allostatic Load Score [?] 4	Low Allostatic Load Score < 4	Odds Ratio
Cardiovascular related Event (2 to 7yrs)	n/N (%)	n/N (%)	Unadjusted
Composite Outcome	635/1327(48.0)	827/2695(30.7)	2.1 (1.8-2.4)
New Hypertension	496/1354(36.6)	583/2707(21.5)	2.1 (1.8-2.4)
Metabolic disorder	296/1408(21.0)	340/2715 (12.5)	1.9 (1.6-2.2)

*Model 1: Odds ratios and Cis are reported using logistic regression after adjusting for covariates (maternal age, education level, gravida, smoking status, bleeding at first trimester, health insurance status, and elapsed time since index pregnancy).

**Model 1: Odds ratios and Cis are reported using logistic regression after adjusting for covariates from model 1 and prior APOs (preterm delivery, small for gestational age, stillbirth, and hypertensive disorders of pregnancy).

Composite outcome: (N=4,022): Odds ratios and CIs were reported using logistic regression after adjusting for covariates in model 1 and model 2.

Hypertension outcome (N= 4,061): Odds ratios and CIs are reported from logistic regression after adjusting for covariates in model 1, model 2 and preexisting diabetes.

Metabolic disorder outcome (N= 4,123): Odds ratios and CIs are reported using logistic regression after adjusting for covariates from model 1, model 2 and chronic hypertension.

Table 3: Mediation analysis assessing allostatic load as a mediator of the association between race and cardiovascular related outcomes.

Outcome	Total Effect:			Direct Effect:
	Step 1 (path c)	Step 2 (path a)	Step 3 (path b)	Step 4 (path c')
1. composite outcome	1.4 (1.1-1.6)	1.2 (1.0-1.5)	2.1 (1.8-2.4)	1.3 (1.1-1.6)
2. New HTN	1.4 (1.2-1.7)	1.2 (1.0-1.5)	2.1 (1.8-2.4)	1.4 (1.1-1.7)
3. MD	1.2 (1.0-1.6)	1.3 (1.1-1.6)	1.9 (1.6-2.2)	1.2 (0.9-1.5)

Abbreviations: AL, allostatic load; HTN, hypertension; MD, metabolic disorder. Data are expressed as n(column %) or Odds Ratio and 95% CI as indicat

Grey cells indicate significant differences.

Table 4: Moderation of race in the association between cardiovascular related outcomes and high allostatic load ([?] 4), unadjusted and adjusted logistic regression model estimates.

	Black N = 495	Non-Hispanic White and additional race and ethnicities N = 3,527	P value
Composite outcome	212 (42.8)	1250 (35.4)	
uOR (95%CI)	1.8 (1.3-2.7)	2.1 (1.8-2.4)	0.555
aOR (95%CI)	1.8 (1.2-2.6)	2.1 (1.8-2.4)	0.457
New Hypertension	166 (33.1)	913 (25.7)	
uOR (95%CI)	1.8 (1.3-2.7)	2.1 (1.8-2.5)	0.483
aOR (95%CI)	1.7 (1.2-2.6)	2.1 (1.8-2.5)	0.326
Metabolic disorder	94 (17.9)	542 (15.1)	
uOR (95%CI)	2.1 (1.3-3.3)	1.8 (1.5-2.2)	0.534
aOR (95%CI)	2.2 (1.4-3.4)	1.7 (1.5-2.1)	0.396

Abbreviations: uOR, unadjusted odds ratios; aOR, adjusted odds ratio; CI, confidence interval; *Adjusted Odds ratios and CIs were reported using unconditional logistic regression after adjusting for maternal age, the time elapsed since index pregnancy, education level, gravida, smoking status, bleeding at first trimester, health insurance status.

Data are expressed as binary variables and as n (column %); n = proportion of individuals with outcomes in each racial category.

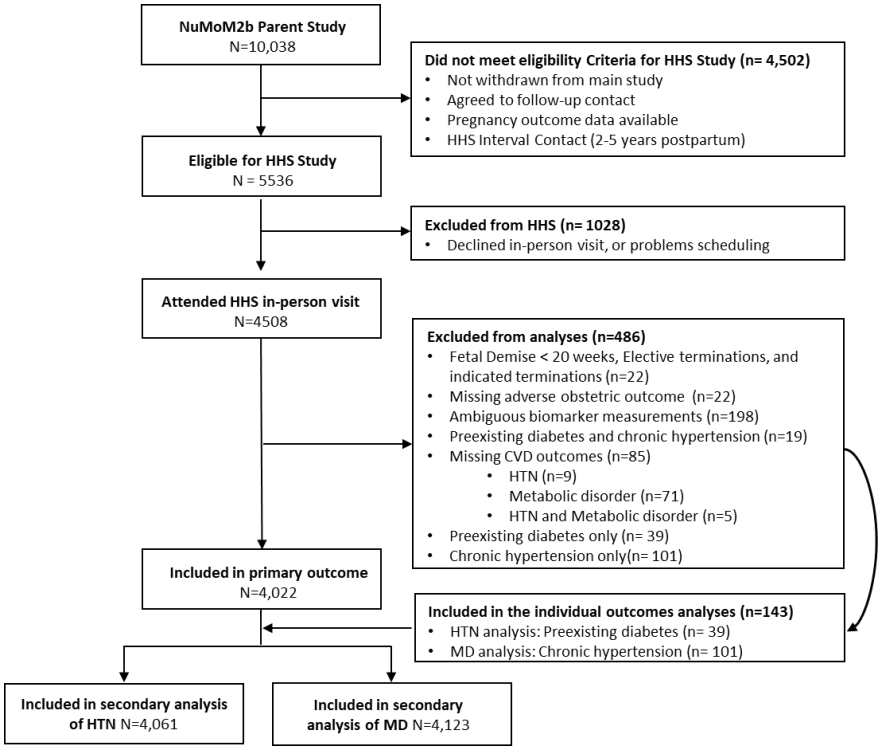
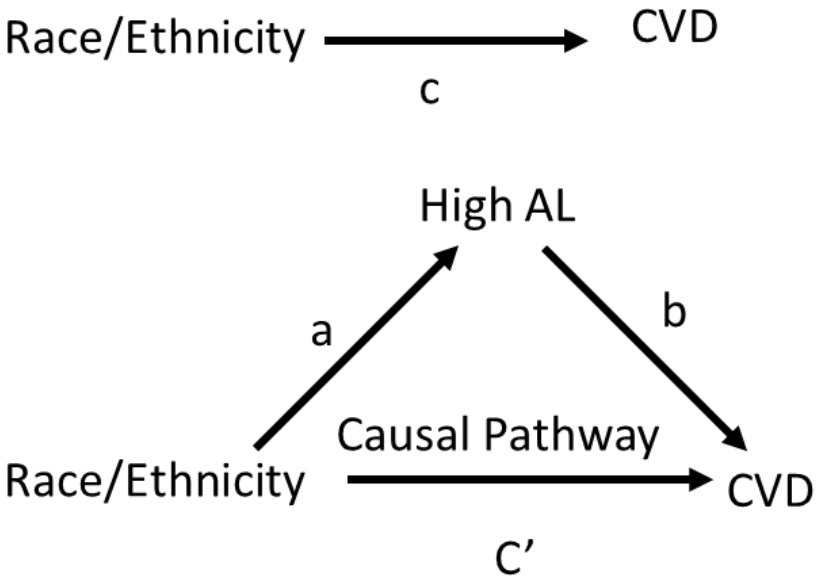


Figure 1. Flow diagram of the study participant included in the analysis.

Abbreviations: HTN, hypertension; MD, metabolic disorder; CVD, cardiovascular disease; NuMoM2b, Nulliparous Pregnancy Outcomes Study Monitoring

Figure 2. Causal Diagram



Abbreviations: CVD, cardiovascular disease; AL, allostatic load

Step 1 (Path c) = Association of maternal race on adverse CVD outcomes (race predicting CVD)

Step 2 (Path a) = Association of maternal race on high allostatic load (race predicting high allostatic load)

Step 3 (path b and c') = Association of maternal race on adverse CVD outcomes mediated by or adjusted for high allostatic load (race and high allostatic load predicting CVD)

Supplementary Tables:

Table S1. Demographic and clinical characteristics of with and without composite outcomes.

Variables	HH Study N (%) N = 4,022	Composite Outcome N (%) N = 1,462	No Composite
Time elapsed from index pregnancy	3.2 ±0.9	3.2 ±0.9	3.2 ±0.9
Maternal Age >= 35	378 (9.4)	159 (10.9)	219 (8.6)
Race (Non-Hispanic Black)	495 (12.3)	212 (14.5)	283 (11.1)
Education (Some college or less)	1506 (37.4)	592 (40.5)	914 (35.7)
Gravidity >= 3	248 (6.2)	107 (7.3)	141 (5.5)
Smoking	625 (15.6)	282 (19.3)	343 (13.4)
Alcohol Use (ever)	2509 (62.4)	902 (61.7)	1607 (72.8)
Prior Miscarriage	599 (14.9)	232 (15.9)	367 (14.3)
Prior Abdominal Surgery	408 (10.1)	151 (10.3)	257 (10.0)
Prior Bleeding at First Trimester	272 (6.8)	106 (7.3)	166 (6.5)
200% of the federal poverty level	1013 (30.3)	410 (34.0)	603 (28.2)
Government Health Insurance	1066 (26.6)	428 (29.4)	638 (25.0)

Data are expressed as binary variables and as n (column %)

Table S2: Demographic and clinical characteristics of individuals with and without new hypertension.

Variables	HH-Study N (%) N = 4,061	New HTN N (%) N = 1,079	No New HTN N (%) N
Time elapsed from index pregnancy	3.2 ±0.9	3.2 ±0.9	3.2 ±0.9
Maternal Age >= 35	381 (9.4)	121 (11.2)	260 (8.7)
Race (Non-Hispanic Black)	502 (12.4)	166 (15.4)	336 (11.3)
Education (Some college or less)	1526 (37.6)	423 (39.2)	1103 (37.0)
Gravidity >= 3	253 (6.2)	90 (8.3)	163 (5.5)
Smoking	635 (15.6)	205 (19.0)	430 (14.4)
Alcohol Use (ever)	2531 (62.3)	664 (61.5)	1867 (62.6)
Prior Miscarriage	607 (15.0)	173 (16.0)	434 (14.6)
Prior Abdominal Surgery	413 (10.2)	117 (10.3)	296 (9.9)
Prior Bleeding at First Trimester	276 (6.8)	77 (7.1)	199 (6.7)
200% of federal poverty level	1024 (30.4)	292 (32.5)	732 (29.6)
Government Health Insurance	1081 (26.8)	302 (28.2)	779 (26.2)
Preexisting Diabetes	39 (1.0)	15 (1.4)	24 (0.8)

Abbreviations: HTN, hypertension; HH, heart health study

Data are expressed as binary variables and as n (column %)

Table S3: Demographic and clinical characteristics of individuals with and without the metabolic disorder.

Variables	HH-Study N (%) N = 4,123	Metabolic Disorder N (%) N = 636	No Metabolic Di
Time elapsed from index pregnancy	3.2 ±.9	3.0±0.8	3.2±0.9
Maternal Age >= 35	395 (9.6)	76 (12.0)	319 (9.2)
Race (Non-Hispanic Black)	525 (12.7)	94 (14.8)	431 (12.4)
Education (Some college or less)	1558 (37.8)	272 (42.8)	1286 (36.9)
Gravidity >= 3	258 (6.3)	39 (6.1)	219 (6.3)
Smoking	654 (15.9)	133 (20.9)	521 (15.0)
Alcohol Use (ever)	2572 (62.4)	397 (72.4)	2175 (62.4)
Prior Miscarriage	621 (15.1)	108 (17.0)	513 (14.7)
Prior Abdominal Surgery	412 (10.0)	67 (10.5)	345 (9.9)
Prior Bleeding at First Trimester	284 (6.9)	51 (8.0)	233 (6.7)
200% of federal poverty level	1042 (30.5)	186 (36.7)	856 (29.4)
Government Health Insurance	1109 (27.0)	213 (33.5)	896 (25.8)
Chronic Hypertension	101 (2.5)	36 (6.7)	65 (1.9)

Data are expressed as binary variables and as n (column %)

Table S4: Adjusted logistic regression estimating the association between cardiovascular related outcomes and allostatic load components.

	Composite Outcome N (%) (N = 1,462)	New Hypertension N (%) (N = 1,079)	Metabolic disorder N
High AL	635 (43.4)	496 (46.0)	296 (46.5)
Unadjusted	2.1 (1.8-2.4)	2.0 (1.8-2.3)	1.9 (1.6-2.2)
Adjusted	1.9 (1.7-2.2)	1.9 (1.7-2.2)	1.8 (1.5-2.1)
BMI	495 (33.9)	367 (34.0)	258 (40.6)
Unadjusted	2.5 (2.1-2.9)	2.1 (1.8-2.5)	2.5 (2.1-3.0)
Adjusted	2.2 (1.9-2.7)	1.9 (1.6-2.2)	2.2 (1.9-2.7)
DBP	534 (36.5)	437 (40.5)	213 (33.5)
Unadjusted	2.2 (1.9-2.5)	2.5 (2.1-2.8)	1.4 (1.2-1.7)
Adjusted	2.1 (1.8-2.5)	2.3 (1.9-2.7)	1.4 (1.2-1.7)
SBP	509 (34.8)	415 (38.5)	214 (33.6)
Unadjusted	2.2 (1.9-2.5)	2.4 (2.0-2.8)	1.5(1.3-1.8)
Adjusted	1.9 (1.6-2.3)	2.2 (1.9-2.5)	1.4 (1.2-1.7)
CRP	248 (16.9)	190 (17.6)	124 (19.5)
Unadjusted	1.9 (1.6-2.3)	1.8 (1.5-2.2)	1.9 (1.5-2.3)
Adjusted	1.8 (1.4-2.2)	1.7 (1.4-2.1)	1.8 (1.4-2.2)
Triglycerides	424 (29.0)	326 (30.2)	201 (31.6)
Unadjusted	1.4 (1.2-1.6)	1.4 (1.2-1.7)	1.5 (1.2-1.7)
Adjusted	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.5 (1.2-1.8)
Glucose	407 (27.8)	295 (27.3)	214 (33.7)
Unadjusted	1.3 (1.1-1.5)	1.1 (1.0-1.3)	1.6 (1.4-1.9)
Adjusted	1.3 (1.1-1.5)	1.1 (0.9-1.3)	1.6 (1.3-2.0)
HDL	399 (27.3)	303 (28.1)	185 (29.1)
Unadjusted	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.3 (1.1-1.6)
Adjusted	1.1 (1.0-1.4)	1.3 (1.1-1.5)	1.2 (1.0-1.4)
LDL	374 (25.6)	282 (26.1)	162 (25.5)
Unadjusted	1.1 (1.0-1.3)	1.0 (1.0-1.3)	1.1 (0.9-1.3)
Adjusted	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (0.9-1.3)
Total Cholesterol	370 (24.3)	273 (25.3)	157 (24.7)
Unadjusted	1.1 (0.9-1.2)	1.1 (0.9-1.2)	1.0 (0.8-1.2)

	Composite Outcome N (%) (N = 1,462)	New Hypertension N (%) (N = 1,079)	Metabolic disorder N
Adjusted	1.1 (1.0-1.3)	1.0 (0.9-1.2)	1.1 (0.9-1.3)
Insulin	373 (25.5)	291 (27.0)	180 (28.3)
Unadjusted	1.1 (1.0-1.3)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
Adjusted	1.0 (0.8-1.2)	1.1 (0.9-1.3)	1.1 (0.9-1.4)
Creatinine	399 (27.3)	289 (26.8)	183 (29.0)
Unadjusted	1.3 (1.1-1.6)	1.2 (1.0-1.4)	1.3 (1.1-1.5)
Adjusted	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
Albumin	347 (23.7)	255 (23.6)	147 (23.1)
Unadjusted	0.9 (0.8-1.0)	0.9 (0.8-1.1)	0.9 (0.7-1.1)
Adjusted	0.9 (0.8-1.1)	1.0 (0.8-1.2)	1.0 (0.8-1.2)

Abbreviations: AL, allstatic load; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; CRP,c-reactive protein; HDL high –

Data are expressed as binary variables and as n (column %); n = proportion of individuals with "worst" or highest quartile.

*Adjusted analyses: Odds ratios and CIs were reported using unconditional logistic regression after adjusting for maternal age, education level, gravida, smoking status, bleeding at first trimester, health insurance status, preterm delivery, small for gestational age, stillbirth, hypertensive disorders of pregnancy and elapsed time since index pregnancy.

Grey cells indicate significant differences.

Table S5: Mediation analysis assessing allostatic load as a mediator of the association between race (non-Hispanic Black vs. non-Hispanic White) and cardiovascular related outcomes.

Outcome	Total Effect:			Direct Effect:
	Step 1 (path c)	Step 2 (path a)	Step 3 (path b)	Step 4 (path c')
1. composite outcome	1.4 (1.2-1.7)	1.2 (1.0-1.5)	2.1 (1.8-2.4)	1.3 (1.1-1.6)
2. New HTN	1.4 (1.2-1.7)	1.3 (1.0-1.5)	2.1 (1.8-2.4)	1.4 (1.1-1.7)
3. MD	1.4 (1.1-1.8)	1.3 (1.1-1.6)	1.9 (1.6-2.2)	1.2 (0.9-1.5)

Abbreviations:HTN, hypertension; MD, metabolic disorder. Data are expressed as n(column %) or Odds Ratio and 95% CI as indicated.

Grey cells indicate significant differences.

Table S6: Moderation of race (non-Hispanic Black vs. non-Hispanic White) in the association between cardiovascular related outcomes and high allostatic load ([?] 4), unadjusted and adjusted logistic regression model estimates.

	Non-Hispanic Black N = 495	Non-Hispanic White N = 2,577	P value
Composite outcome	212 (42.8)	893 (34.6)	
uOR (95%CI)	1.9 (1.3-2.7)	2.4 (2.0-2.8)	0.250
aOR (95%CI)	1.8 (1.2-2.6)	2.3 (2.0-2.7)	0.175
New Hypertension	166 (33.1)	672 (25.8)	
uOR (95%CI)	1.8 (1.3-2.7)	2.4 (2.0-2.9)	0.241
aOR (95%CI)	1.7 (1.2-2.5)	2.4 (2.0-2.8)	0.155
Metabolic disorder	94 (17.9)	359 (13.7)	
uOR (95%CI)	2.1 (1.3-3.3)	1.9 (1.5-2.4)	0.652
aOR (95%CI)	2.2 (1.4-3.4)	1.8 (1.5-2.3)	0.572

Abbreviations: uOR, unadjusted odds ratios; aOR, adjusted odds ratio; CI, confidence interval; *Adjusted Odds ratios and CIs were reported using unconditional logistic regression after adjusting for maternal age, the time elapsed since index pregnancy, education level, gravida, smoking status, bleeding at first trimester, health insurance status.

Data are expressed as binary variables and as n (column %); n = proportion of individuals with outcomes in each racial category.

Table S7: Adjusted logistic regression estimating the association between individual components of cardiovascular related outcomes and allostatic load score.

	High Allostatic Load AL [?] 4	**Low Allostatic Load AL < 4**	**Odds Rat**
Cardiovascular Event (2 to 7yrs)	**n/N (%)**	**n/N (%)**	**Unadjust**
Composite Outcome***	345/702 (49.1)	1117/3320 (33.6)	1.9 (1.6-2.2
New Hypertensionˆ	333/934 (35.6)	746/3127 (23.9)	1.7 (1.5-2.1
Metabolic disorder#	270/1213 (22.3)	366/2910 (12.6)	2.0 (1.7-2.4

* Model 1: Odds ratios and Cis are reported using logistic regression after adjusting for covariates (maternal age, education level, gravida, smoking status, bleeding at first trimester, health insurance status, and elapsed time since index pregnancy)

** Model 2: Odds ratios and Cis are reported using logistic regression after adjusting for covariates from model 1 and (prior APOs (preterm delivery, small for gestational age, stillbirth, and hypertensive disorders of pregnancy).

*** Composite outcome does not include insulin and blood pressure in the allostatic load index: Odds ratios and CIs are reported from logistic regression after adjusting for covariates in model 1 and preexisting diabetes.

allostatic load index: Odds ratios and CIs are reported from logistic regression after adjusting for covariates in model 1, model 2and preexisting diabetes.

Metabolic disorder outcome does not include insulin in the allostatic load index: Odds ratios and CIs are reported using logistic regression after adjusting for covariates from model 1, model 2 and chronic hypertension.