Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Sex-Divergent Blood Pressure Associations With Multiorgan System Metabolic Stress—Brief Report

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BACKGROUND: Women experience excess cardiovascular risk compared with men in the setting of similar metabolic disease burden. We aimed to examine sex differences in the vascular response to various forms of metabolic stress.

METHODS: We conducted an observational study of 4299 adult participants (52% women, aged 59±13 years) of the National Health and Nutrition Examination Survey 2017 to 2018 cohort and 110 225 adult outpatients (55% women, aged 64±16 years) from the Cedars-Sinai Medical Center in 2019. We used natural splines to examine the association of systemic and organ-specific measures of metabolic stress including body mass index, hemoglobin A1c, hepatic FIB-4 (Fibrosis-4) score, and CKD-EPI estimated glomerular filtration rate with systolic blood pressure (SBP). Piecewise linear models were generated using normal value thresholds (body mass index <25 kg/m^2, hemoglobin A1c <5.7%, FIB-4 <1.3, and estimated glomerular filtration rate ≥90 mL/min), which approximated observed spline break points. The primary outcome was an increase in SBP in association with increase in each metabolic measure.

RESULTS: Women compared with men demonstrated larger magnitudes and an earlier onset of increase in SBP per increment increase across all metabolic stress measures. The slope of SBP increase per increment of each metabolic measure was greater for women than men particularly for metabolic measures within the normal range, with slope differences of 1.86 mm Hg per kg/m^2 of body mass index, 12.48 mm Hg per %hemoglobin A1c, 6.87 mm Hg per FIB-4 unit, and 0.44 mm Hg per mL/min decrement of estimated glomerular filtration rate in the National Health and Nutrition Examination Survey cohort (*P* difference <0.05 for all). Overall results were consistent in the Cedars-Sinai Medical Center cohort.

CONCLUSIONS: Women exhibited greater SBP alteration in the setting of multiple types of metabolic stress, particularly in periods representing the transition from metabolic health to disease. These findings suggest potential benefit of early metabolic health interventions as part of efforts to mitigate vascular risks in both women and men.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: heart disease risk factors ■ metabolic diseases ■ outpatients ■ risk factors ■ sex characteristics

Decades of clinical trial and observational study data have consistently shown that women experience greater cardiovascular disease risk than men in the setting of obesity, insulin resistance, and type 2 diabetes.[1,2] The reasons for this persistent sex disparity remain unclear. While theoretically attributable to more frequent clustering of metabolic traits in women than men, the excess risk in women is seen to persist even after adjustment for these factors.[3,4] Intriguingly, recent studies have suggested the vascular response to similar doses of chronic metabolic stress may be more pronounced in females than males over the life course.[5,6] Given that aggregate metabolic stress may arise from disease involving ≥1 distinct organ systems, including the liver and kidney, it is possible that associated excess vascular risk is not only sex biased but also predominantly related to a particular metabolic organ system or systemic process. To investigate this possibility, which would inform treatment

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
CSMC	Cedars-Sinai Medical Center
eGFR	estimated glomerular filtration rate
HbA1c	hemoglobin A1c
NHANES	National Health and Nutrition Examination Survey
SBP	systolic blood pressure

approaches, we examined sex-specific systolic blood pressure (SBP) relations with graded severity of organ-specific and systemic measures of metabolic stress.

Highlights

- Women compared with men consistently exhibited a larger magnitude of increased systolic blood pressure per unit for all metabolic stress types.
- Blood pressure increases in women were most significant in the preclinical ranges of metabolic stress markers, before overt organ-specific or systemic disease (ie, obesity, diabetes, liver fibrosis, and chronic kidney disease).
- The greater vascular sensitivity to metabolic stress in women is not organ specific and may represent an early precursor to observed sex differences in cardiovascular outcomes.

MATERIALS AND METHODS

Data Sharing Statement

We conducted our primary analyses using adult participant data from the NHANES 2017 to 2018 cohort, representing the most recent complete prepandemic NHANES data set available. The NHANES data were acquired from and are available to the scientific community through https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. Our external validation data consisted of data from Cedars-Sinai Medical Center (CSMC) and are available upon reasonable request. Requests for deidentified data may be directed to biodatacore@cshs.org and will be reviewed by the Office of Research Administration at CSMC before issuance of data sharing agreements, which are designed to ensure patient and participant confidentiality.

Ethical Approval of Studies and Informed Consent

The NHANES protocol for 2017 to 2018 was approved under protocol number 2018-01 and continuation of protocol number 2011-17. The Cedars-Sinai data were approved by the Cedars-Sinai Institutional Review Board under STUDY00000603.

Availability of Data

To focus on adults at risk of subclinical cardiovascular disease, we limited the population to adults aged ≥35 years, with SBP between 100 and 180 mm Hg. We excluded individuals <35 years of age, given the smaller sample size available for this age group and thus limited generalizability of findings. We selected widely accessible systemic and organ-based measures of metabolic stress including body mass index (BMI), hemoglobin A1c (HbA1c), FIB-4 (Fibrosis-4; a marker of subclinical hepatic disease commonly assessed in the setting of steatotic liver disease),[7] and estimated glomerular filtration rate (eGFR) calculated using the 2021 CKD-EPI formula.[8] For participants reporting antihypertensive medication use, we added 10 mm Hg to on-treatment SBP measures as done in prior similar studies.[9,10] We used natural splines to examine SBP in relation to each metabolic stress measure, with 4 knots and 95% CIs, excluding outliers beyond the <2.5% and >97.5% range to avoid extreme deviations in the spline end points. We then used piecewise linear splines with a single knot to examine the relations above and below the normal value thresholds (BMI of 25 kg/m^2, HbA1c of 5.7%, FIB-4 of 1.3, and eGFR of 90 mL/min), comparing the slopes between women and men for each linear segment using the *P* value of the interaction terms. Measures of SBP increase are presented in the splines as the difference in SBP (ie, SBP shift) from the sex-specific normal healthy (ie, physiological) thresholds (110 mm Hg for women and 120 mm Hg for men) previously established from multicohort epidemiological reference data.[11] We conducted secondary analyses that included iteratively adjusting for comorbidities and use of lipid-lowering or blood pressure–lowering medications and stratifying analyses by median age and by menopausal status given the well-established previously described sex differences in early adulthood SBP measures.[12,13]

For external validation cohort analyses, we curated outpatient data from CSMC, a large urban academic medical center, between January 1, 2019, and December 31, 2019; we included data from all ambulatory patients with a recorded outpatient blood pressure and laboratory draw involving a complete blood count and comprehensive metabolic panel. If available, HbA1c measures were collected. If multiple measurements were recorded, the average value (for SBP or laboratory measure) was considered representative for that year. Demographic data including race and ethnicity were self-reported during visits, and comorbidities were obtained from the electronic health record via the *International Classification of Diseases, Tenth Revision*, codes (Table S1). Similar to the NHANES cohort, in the CSMC cohort, 10 mm Hg was added to SBP for the use of antihypertensive medications, as assessed by prescribed medications within the electronic health record during the time of SBP measurement. Ethical approval was obtained for both cohorts: the NHANES protocol for 2017 to 2018 was approved under protocol number 2018-01 and continuation of protocol number 2011-17. Cedars-Sinai data were approved by the Cedars-Sinai Institutional Review Board under STUDY00000603. Analyses were conducted using R v4.3.1 and STATA-SE 14; a 2-tailed $P<0.05$ was considered significant.

RESULTS

Our NHANES community-based sample included 4299 unique adult participants (52% women; mean age, 59±13 years). Self-reported comorbidities included 46% with

history of hypertension, 43% receiving antihypertensive medications, 43% with hyperlipidemia, 20% with diabetes, and 6% with coronary artery disease. The CSMC patient-based sample included 110 225 unique adult patients (55% women; mean age, 64±16 years; Table S2). Documented comorbidities included hypertension in 40% of patients, antihypertensive use in 39%, hyperlipidemia in 46%, diabetes in 14%, and coronary artery disease in 2.7%.

Overall, women exhibited a greater magnitude of increased SBP in association with increase in each measure of metabolic stress (Figure). We found that empirically generated data from our spline analyses identified inflection points approximating standardized thresholds for each metabolic stress measure, perhaps, in part, due to interventions tending to be more frequently applied at or beyond these thresholds in general clinical practice; nonetheless, sex differences were seen consistently across the range of metabolic stress measures. Expectedly, the rate of SBP increase was the highest in a period of presumed transition from metabolic health to metabolic disease, prior to when any given measure exceeded the normal range. Notably, the slope of SBP increase in this preclinical period was significantly higher for women than men across all metabolic stress measures in the primary NHANES cohort (Figure; Table), with prominent sex differences seen for BMI (β [SE] was 1.39 [0.37] in women and −0.47 [0.36] in men), HbA1c (20.15 [2.26] in women and 7.67 [1.99] in men), FIB-4 (21.28 [1.95] in women and 14.41 [1.89] in men), and eGFR (0.59 [0.06] in women and 0.15 [0.06] in men; *P* sex difference <0.05 for all). In the ranges consistent with overt metabolic disease, elevations in SBP with increasing measures of metabolic stress were generally less steep with attenuated sex differences, although the sex differences remained significant for FIB-4 (Figure; Table). These patterns were similar in analyses with and without accounting for potential effects of antihypertensive treatment, using a variety of methods for adjustment (Table S3A and S3B; Figure S1) and in models adjusting for age, hypertension, diabetes, smoking, family history of premature coronary artery disease, congestive heart failure, coronary artery disease, stroke, lipid-lowering medication use, or antihypertensive medication use (Table S4A through S4J). Analyses stratified by median age and menopausal status reveal generally similar findings with the results of some comparative analyses appearing to be attenuated by the smaller sample sizes of subgroups stratified by both age and sex (Table S4K and S4L). Results were similar in secondary analyses considering varying thresholds for metabolic stress measures (Table S5) and in analyses considering metabolic measures as continuous variables without thresholds (Table S6). In the CSMC patient cohort, the same analyses revealed steeper SBP slopes for women than men across both normal and abnormal ranges of HbA1c, FIB-4, and eGFR; the only exception to this trend was the observation of parallel SBP slopes (ie, no sex difference) seen for both the normal and abnormal ranges of BMI (Figure; Table).

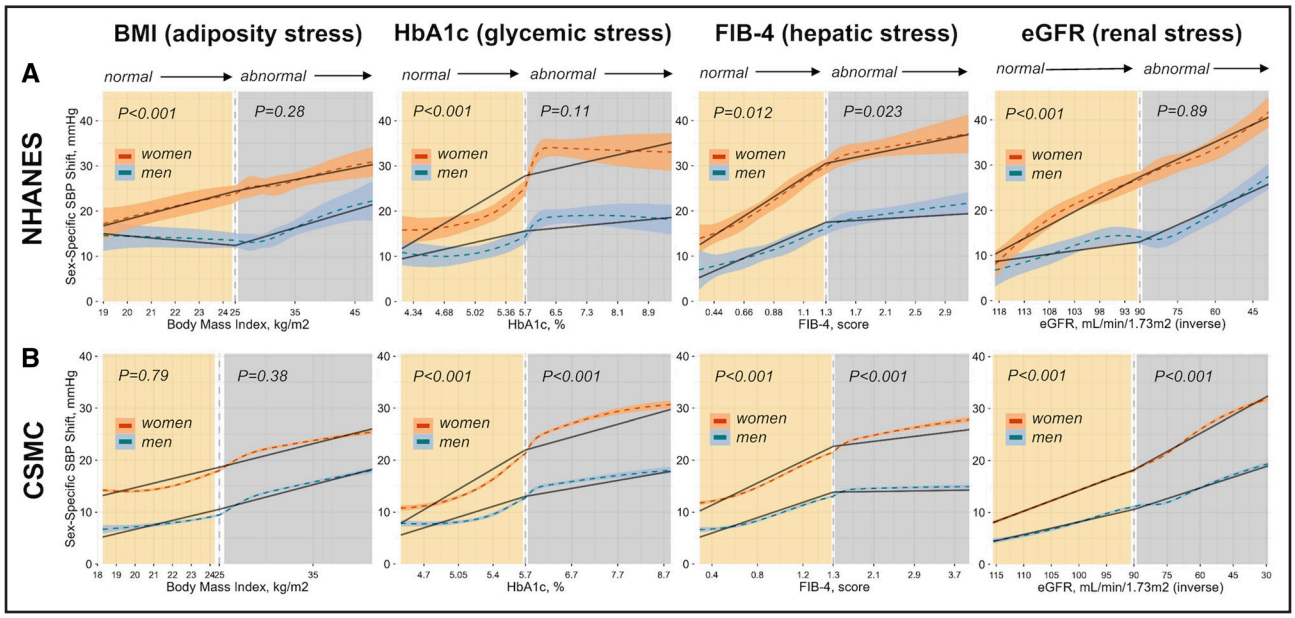

Figure. Multiorgan system metabolic stress measures in relation to vascular health, by sex.
P values are shown for the sex difference in the segmented slope of rise in systolic blood pressure (SBP), serving as a measure of vascular health, across each measure of metabolic stress categorized as within the normal or with the abnormal range for each measure. SBP is adjusted for antihypertensive use by adding 10 mm Hg to all measurements with concurrent antihypertensive therapy. Women demonstrate both earlier onset and greater vascular sensitivity to accumulation of metabolic stress of various types, as reflected by a significantly steeper initial rise in SBP from sex-specific normal healthy (ie, physiological) thresholds (110 mm Hg for women and 120 mm Hg for men) previously established from multicohort epidemiological reference data. BMI indicates body mass index; CSMC, Cedars-Sinai Medical Center; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; and NHANES, National Health and Nutrition Examination Survey.

Table. Associations of Metabolic Stress Measures With Systolic Blood Pressure, by Sex

Metabolic stress measure (normal value threshold)	Community-based NHANES cohort sample (n=4299)						Ambulatory patient-based CSMC cohort sample (n=109 225)					
	Within-sex piecewise linear regression coefficients				Between-sex comparisons		Within-sex piecewise linear regression coefficients				Between-sex comparisons	
	Women (n=2214)		Men (n=2085)		Normal range	Abnormal range	Women (n=60 823)		Men (n=48 402)		Normal range	Abnormal range
	Normal range slope est. (SE)	Abnormal range slope est. (SE)	Normal range slope est. (SE)	Abnormal range slope est. (SE)	*P* diff in slope in women vs men	*P* diff in slope in women vs men	Normal range slope est. (SE)	Abnormal range slope est. (SE)	Normal range slope est. (SE)	Abnormal range slope est. (SE)	*P* diff in slope in women vs men	*P* diff in slope in women vs men
BMI (<25 vs ≥25)	1.39 (0.37)*	0.26 (0.08)*	−0.47 (0.36)	0.39 (0.09)*	<0.001*	0.28	0.88 (0.04)*	0.45 (0.01)*	0.86 (0.06)*	0.47 (0.02)*	0.79	0.38
HbA1c (<5.7 vs ≥5.7)	20.15 (2.26)*	1.93 (0.54)*	7.67 (1.99)*	0.79 (0.46)	<0.001*	0.11	15.71 (0.35)*	2.47 (0.12)*	8.28 (0.38)*	1.53 (0.10)*	<0.001*	<0.001*
FIB-4 (<1.3 vs ≥1.3)	21.28 (1.95)*	3.33 (0.98)*	14.41 (1.89)*	0.99 (0.44)*	0.012*	0.023*	14.16 (0.23)*	1.20 (0.08)*	9.87 (0.25)*	0.15 (0.06)*	<0.001*	<0.001*
eGFR (≥90 vs ≤90) per unit decrease	0.59 (0.06)*	0.26 (0.04)*	0.15 (0.06)*	0.25 (0.04)*	<0.001*	0.89	0.40 (0.01)*	0.23 (0.00)*	0.24 (0.01)*	0.14 (0.00)*	<0.001*	<0.001*

Linear piecewise regression coefficients represent the slope of association between a given metabolic stress measure and increase in SBP above and below the normal value thresholds, by sex. SBP is adjusted for antihypertensive use by adding 10 mm Hg to all measurements with concurrent antihypertensive therapy. *P* values are estimated for differences between piecewise linear regression slopes for women and men, separated into normal or abnormal range regression segments for each metabolic measure and in both the NHANES community cohort and the CSMC clinical cohort sample. Women exhibit steeper slope associations of metabolic stress measures with SBP than men, particularly when assessed within the normal range of values for a given metabolic measure. BMI indicates body mass index; CSMC, Cedars-Sinai Medical Center; diff, difference; eGFR, estimated glomerular filtration rate; est., estimate; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

*$P<0.05$, levels of statistical significance.

DISCUSSION

In 2 large independent cohorts of ambulatory adults, we found that women compared with men consistently demonstrated a larger magnitude and an earlier onset of vascular sensitivity in the setting of metabolic disease stress of varying types, including both systemic and organ-specific sources of metabolic stress. Sex differences in the slope of SBP increase were especially pronounced in relation to increasing levels of metabolic stress within the normal range, suggesting a greater sensitivity in women during the transition from metabolic health to metabolic disease. Given that recent publications have highlighted inherently different age-related trajectories in blood pressure across genetic risk and between women and men,[13] we adjusted for age and other cardiovascular comorbidities, finding that the pattern remained primarily consistent. In age-stratified analyses, the trends largely remained significant in the subgroup aged ≤60 years, further supporting that the differences in SBP response are pronounced in younger women compared with younger men. In our large-sized ambulatory patient cohort, sex differences in slope of SBP elevation persisted across both normal and abnormal metabolic stress measurement values suggesting that women retain a greater vascular sensitivity to systemic and organ-specific stress from the earliest through the latest stages of metabolic disease. These results are consistent with prior longitudinal studies demonstrating that women compared with men exhibit generally steeper trajectories in SBP elevation over time,[14] particularly in the setting of greater total burden of cardiometabolic risk factors.[5] Our analyses extend from prior work by examining potential variation in sex differential SBP elevations in relation to distinct organ-specific measures of metabolic stress. In particular, we included measures of metabolic liver and of metabolic kidney stress, given increasing recognition of their contributions to cardiovascular disease.[15] Our results not only revealed consistency of sex-divergent SBP elevations across organ-specific measures but also parallel sex-specific excess in SBP elevations in relation to a rise in metabolic measures even within the normal range. Overall, our findings suggest that efforts to mitigate vascular disease risk in women should consider targeting a wide spectrum of metabolic stressors and that such targeting should begin early on in younger populations and well before the onset of clinically evident metabolic disease.

Our study limitations included the inability to examine more detailed measures of vascular health or metabolic stress beyond the measures that were readily available across both our community and our ambulatory patient cohorts. For instance, nutritional intake patterns can substantially impact metabolic health and warrant investigation in future studies. In addition, precision of our results may have been affected by circadian and other factors influencing variation in nonstandardized acquisition of SBP measures. While using several methods to account for potential effects of antihypertensive treatment, lack of granular data on type and number of medications

per individual precluded the ability to account for variations in on-treatment effects. Additionally, adjustments for covariates were performed iteratively instead of as a single model due to joint missingness, which may affect the results. The use of clinical data in the CSMC cohort is subject to selection bias given that collected data imply health care contact and referral for testing. We also recognize that while the use of standardized clinical thresholds for continuous measures in our analyses may facilitate interpretability, varying thresholds may be more appropriate for certain subpopulations (eg, application of race-specific BMI cutoffs[16] or age- and sex-based eGFR cutoffs[17]). Thus, while empirically generated data from the spline analyses also suggested inflection points approximating standardized thresholds of risk, these results should be interpreted in context and include consideration of the demographic characteristics of our study samples. The cross-sectional study design also precludes causal inference, and results should be interpreted as observed associations. Notably, for associations of metabolic stress measures with SBP, bidirectional or reverse causation is biologically plausible albeit much more so for some measures (eg, eGFR) than for others (eg, HbA1c and FIB-4). Future prospective and longitudinal studies are needed to clarify temporality and directionality of our observed associations, and additional studies are needed to similarly examine related markers such as diastolic blood pressure and pulse pressure.

In conclusion, we found support for vascular sensitivity in the setting of even the mildest forms of preclinical metabolic stress; notably, this vascular sensitivity was not specific to any given systemic or organ-derived metabolic stress. Moreover, the finding was especially pronounced in women compared with men and so may represent an important precursor to sex differences in cardiovascular outcomes. Notwithstanding the need for further work to examine underlying mechanisms and directionality, these results underscore the importance of ongoing endeavors to involve metabolic interventions as part of efforts to mitigate vascular risks in both women and men.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figure S1
Major Resources Table

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