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Sex-Divergent Blood Pressure Associations with Multi-Organ System Metabolic Stress

Alan C. Kwan, MD[1], **Minhao Wang, MPH**[1], **Hongwei Ji, MD**[2], **Brian Claggett, PhD**[3], **David Ouyang, MD**[1], **Hirsh Trivedi, MD**[4], **Sonia Sharma, PhD**[5], **John Shyy, PhD**[6], **Amanda Velazquez, MD**[7], **Joseph E. Ebinger, MD**[1], **Susan Cheng, MD, MPH**[1]

[1]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

[2]Tsinghua Medicine, Tsinghua University, Beijing, China

[3]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts

[4]Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[5]La Jolla Institute for Immunology, La Jolla, CA, USA.

[6]Division of Cardiology, Department of Medicine, University of California, San Diego, La Jolla, CA, USA.

[7]Departments of Surgery and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Abstract

Background.—Women experience excess cardiovascular risk compared to 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 4,299 adult participants 52% women, aged 59±13 years) of the National Health and Nutrition Examination Survey (NHANES) 2017–2018 cohort and 110,225 adult outpatients (55% women, aged 64±16 years) from Cedars-Sinai Medical Center (CSMC) in 2019. We used natural splines to examine the association of systemic and organ-specific measures of metabolic stress including body mass index (BMI), hemoglobin A1c (HbA1c), hepatic FIB-4 score, and CKD-EPI estimated glomerular filtration rate (eGFR) with systolic blood pressure (SBP). Piecewise linear models were generated using normal value thresholds (BMI <25 kg/m^2, HbA1c <5.7%, FIB-4 <1.3, and eGFR ≥90 ml/min), which approximated observed spline breakpoints. The primary outcome was increase in SBP in association with increase in each metabolic measure.

Correspondence. Alan Kwan, MD, Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. alan.kwan@cshs.org.

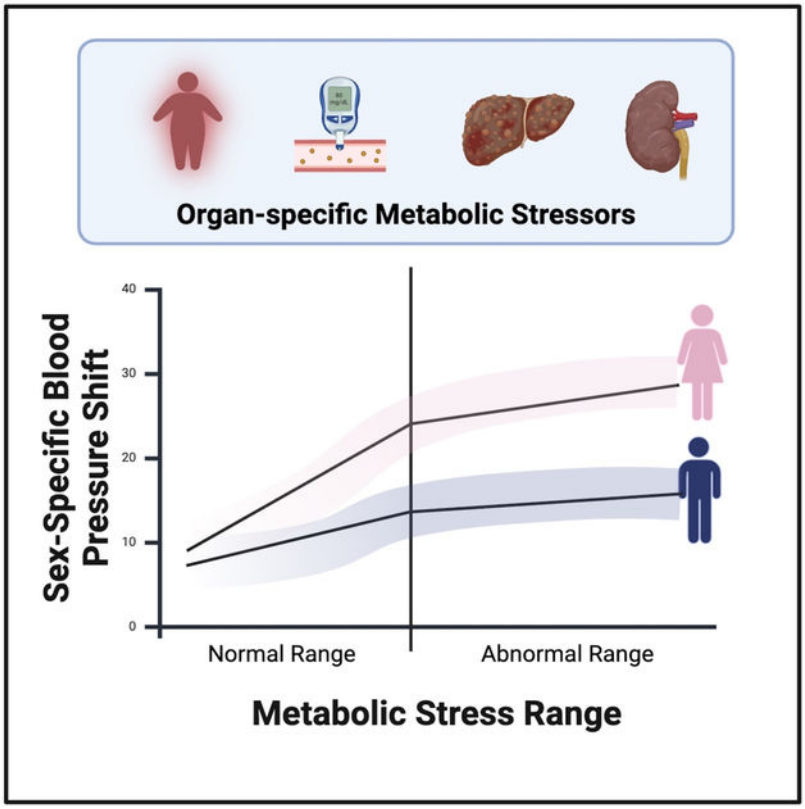
Disclosures. No relevant disclosures.

Ethical Approval of Studies and Informed Consent. The NHANES protocol for 2017–2018 was approved under Protocol #2018–01 and Continuation of Protocol #2011–17. Cedars-Sinai data was approved by Cedars-Sinai Institutional Review Board under STUDY00000603.

Results.—Women compared to 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 mmHg per kg/m2 of BMI, 12.48 mmHg per %HbA1c, 6.87 mmHg per FIB-4 unit, and 0.44 mmHg per ml/min decrement of eGFR in the NHANES cohort (P difference <0.05 for all). Overall results were consistent in the CSMC 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.

Graphical Abstract:



Introduction

Decades of clinical trial and observational study data have consistently shown that women experience greater cardiovascular disease (CVD) 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 one or more 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 approaches, we examined sex-specific systolic blood pressure (SBP) relations with graded severity of organ-specific and systemic measures of metabolic stress.

Methods

Availability of Data.

We conducted our primary analyses using adult participant data from the National Health and Nutrition Examination Survey (NHANES) 2017–2018 cohort, representing the most recent complete pre-pandemic NHANES dataset 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 de-identified data may be directed to biodatacore@cshs.org and will be reviewed by the Office of Research Administration at CSMC prior to issuance of data sharing agreements, which are designed to ensure patient and participant confidentiality.

To focus on adults at risk of subclinical CVD, we limited the population to adults age ≥35 years, with systolic blood pressure (SBP) between 100 mmHg and 180 mmHg. We excluded individuals younger than age 35, 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 (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 anti-hypertensive medication use, we added 10 mmHg 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% confidence intervals, excluding outliers beyond the <2.5% and >97.5% range to avoid extreme deviations in the spline endpoints. We then used piecewise linear splines with a single knot to examine the relations above and below normal value thresholds (BMI of 25 kg/m^2, HbA1c of 5.7%, FIB-4 of 1.3, and GFR 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 (i.e. SBP shift) from the sex-specific normal healthy (i.e. physiologic) thresholds (110 mmHg for women, 120 mmHg for men) previously established from multi-cohort epidemiologic 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 as well as 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 Cedars-Sinai Medical Center, 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 *ICD-10* codes (Table S1). Similar to the NHANES cohort, in the CSMC cohort, 10 mmHg was added to SBP for 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 2017–2018 was approved under Protocol #2018–01 and Continuation of Protocol #2011–17. Cedars-Sinai data was approved by Cedars-Sinai Institutional Review Board under STUDY00000603. Analyses were conducted using R v4.3.1, and STATA-SE 14; a two-tailed $P<0.05$ was considered significant.

Results

Our NHANES community-based sample included 4,299 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 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 pre-clinical period was significantly higher for women than men across all metabolic stress measures in the primary NHANES cohort (Figure and Table), with prominent sex differences seen for BMI (β [SE] was 1.39 [0.37] in women, −0.47 [0.36] in men), HbA1c (20.15 [2.26] in women, 7.67 [1.99] in men), FIB-4 (21.28 [1.95] in women, 14.41 [1.89] in men), and eGFR (0.59 [0.06] in women, 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 and 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 b and 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 anti-hypertensive medication use (Tables S4a–j). 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 samples sizes of subgroups stratified by both age and sex (Tables S4k–l). 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 (i.e. no sex difference) seen for both the normal and abnormal ranges of BMI (Figure and Table).

Discussion

In two large independent cohorts of ambulatory adults, we found that women compared to 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 as well as 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 or younger, further supporting that the differences in SBP response are pronounced in younger women compared to 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 to 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 CVD.[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 prior to 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 non-standardized 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 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 results. The use of clinical data in the CSMC cohort is subject to selection bias given that collected data imply healthcare contact and referral for testing. We also recognize that while use of standardized clinical thresholds for continuous measures in our analyses may facilitate interpretability, varying thresholds may be more appropriate for certain subpopulations (e.g. 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 (e.g. eGFR) than for others (e.g. HbA1c, 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 pre-clinical 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 to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding.

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Data Sharing Statement.

The NHANES data were acquired from and are available to the scientific community through https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. Data was accessed on 4/1/2024 through R Package nhanesA. The internal data that support the findings of this study are available on request from the corresponding author.

ABBREVIATIONS AND ACRONYMS

BMI	Body mass index
CSMC	Cedars-Sinai Medical Center
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HbA1c	Hemoglobin A1c
NHANES	National Health and Nutrition Examination Survey
SBP	Systolic blood pressure

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Highlights

- Women compared to 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 pre-clinical ranges of metabolic stress markers, prior to overt organ-specific or systemic disease (i.e., obesity, diabetes, liver fibrosis, 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

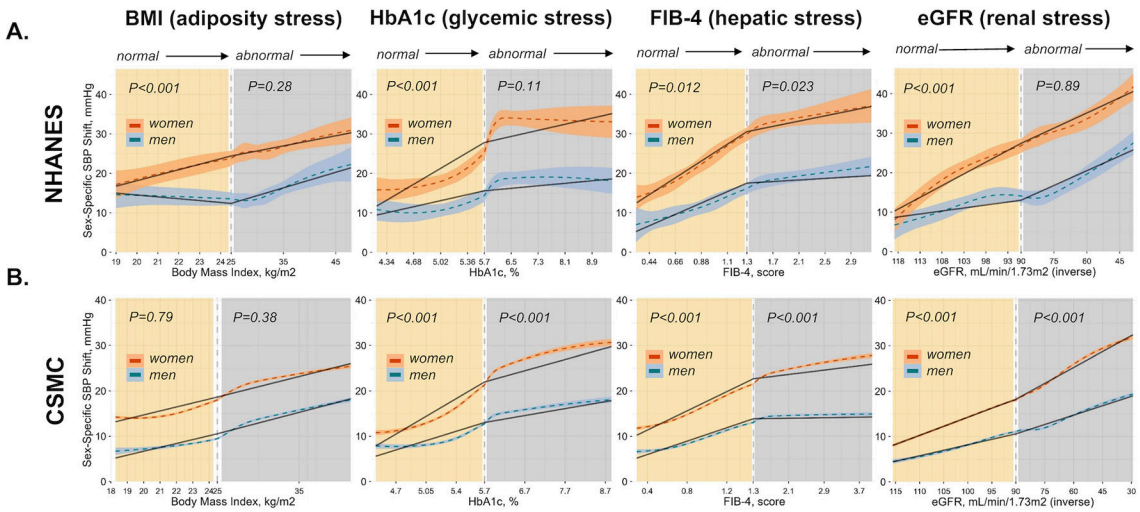

Figure. Multi-organ system metabolic stress measures in relation to vascular health, by sex.

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 mmHg 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 (i.e. physiologic) thresholds (110 mmHg for women, 120 mmHg for men) previously established from multi-cohort epidemiologic reference data. NHANES: National Health and Nutrition Examination Survey; CSMC: Cedars-Sinai Medical Center; BMI: Body mass index; HbA1c: Hemoglobin A1c; eGFR: Estimated glomerular filtration rate.

Table.

Associations of metabolic stress measures with systolic blood pressure, by sex.

Metabolic stress measure (normal value threshold)	Community-Based NHANES Cohort Sample (N=4,299)						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=2,214)		Men (N=2,085)		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**
GFR (≥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 systolic blood pressure (SBP) above and below the normal value thresholds, by sex. SBP is adjusted for antihypertensive use by adding 10 mmHg 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 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 measures. Bold face denotes P<0.05 levels of statistical significance. NHANES: National Health and Nutrition Examination Survey; CSMC: Cedars-Sinai Medical Center; BMI: Body mass index; HbA1c: Hemoglobin A1c; eGFR: Estimated glomerular filtration rate.