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PARENTAL CARDIOMETABOLIC BURDEN AND EARLY VASCULAR RISK PHENOTYPE IN YOUNG ADULTS WITH PREHYPERTENSION

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Abstract

Background: Prehypertension in young adults may represent an early stage of cardiovascular risk rather than a benign intermediate blood pressure category. Familial cardiometabolic predisposition, adiposity, cardiac workload, autonomic modulation, and vascular biomarkers may contribute to this early risk phenotype. The present study was designed to characterize the early vascular risk phenotype of young adults with prehypertension compared with age-matched normotensive controls, and to examine whether parental history of type 2 diabetes mellitus and hypertension is associated with prehypertensive status and selected cardiometabolic risk markers.

Methods: This age-matched case–control study included 113 young adults, comprising 66 prehypertensive subjects and 47 normotensive controls. Anthropometric indices, body composition, haemodynamic parameters, heart rate variability, endothelial/angiogenic and oxidative stress biomarkers, lipid profile, and parental history of type 2 diabetes mellitus and hypertension were assessed. Between-group comparisons were performed using appropriate parametric or non-parametric tests. Age- and sex-adjusted regression models were used to evaluate independent associations. Logistic regression was performed to assess the association of parental cardiometabolic history with prehypertension.

Results: Prehypertensive subjects had significantly higher BMI, waist circumference, waist–hip ratio, body fat percentage, visceral fat, heart rate, mean arterial pressure, and rate pressure product compared with normotensive controls. VEGF and resistin concentrations were also higher among prehypertensive subjects. VEGF remained significantly associated with prehypertension after adjustment for age, sex, and BMI. Heart rate variability and lipid parameters did not show robust group differences after correction for multiple testing. Any parental history of type 2 diabetes mellitus was associated with approximately four-fold higher odds of prehypertension after adjustment for age and sex. Parental cardiometabolic burden score was also independently associated with prehypertensive status, while parental hypertension showed a positive but borderline association.

Conclusion: Young adults with prehypertension demonstrate an adverse early cardiovascular risk phenotype characterized by increased adiposity, higher cardiac workload, elevated VEGF and resistin, and greater familial cardiometabolic burden. Parental type 2 diabetes mellitus and cumulative parental cardiometabolic burden may help identify young individuals at increased risk for early blood pressure dysregulation.

KEYWORDS: Prehypertension, parental history, type 2 diabetes mellitus, hypertension, adiposity, visceral fat, rate pressure product, VEGF, resistin.

INTRODUCTION

Prehypertension, originally defined by the Seventh Report of the Joint National Committee as systolic blood pressure between 120–139 mmHg and/or diastolic blood pressure between 80–89 mmHg, represents an intermediate blood pressure phenotype between normotension and established hypertension (1). Although historically considered a “borderline” state, accumulating evidence suggests that prehypertension is not clinically relevant. In the Framingham Heart Study, high-normal blood pressure was associated with an increased risk of cardiovascular disease compared with optimal blood pressure (2). Subsequent meta-analyses have confirmed that prehypertension is associated with greater risk of incident cardiovascular disease, stroke, myocardial infarction, and cardiovascular mortality, with risk increasing across the higher range of prehypertensive blood pressure values (3,4). The relevance of prehypertension is particularly important in young adults, in whom early vascular risk may remain clinically silent for years before progression to overt hypertension or manifest cardiovascular disease. Recent nationally representative Indian data showed a rising burden of prehypertension among young individuals aged 15–24 years, with high body mass index strongly associated with both prehypertension and hypertension (5). This is concerning because early adulthood represents a critical window during which modifiable cardiovascular risk factors, if identified, may be targeted before irreversible vascular remodeling and end-organ damage occur. Adiposity is a central determinant of elevated blood pressure and early cardiometabolic risk. Earlier reports have demonstrated a continuous positive association of body mass index, abdominal adiposity, and weight gain with incident

hypertension (6). In addition, waist circumference may capture cardiovascular risk more strongly than body mass index alone, reflecting the contribution of central adiposity to hypertension, dyslipidaemia, insulin resistance, and low-grade inflammation (7). Therefore, assessment of both generalized and central adiposity is essential when characterizing the early risk phenotype of prehypertensive individuals.

Familial cardiometabolic history may further identify individuals who are biologically predisposed to early vascular risk. Longitudinal data from a previous study demonstrated that offspring of parents with type 2 diabetes mellitus had greater generalized and truncal adiposity, adverse lipid profiles, higher insulin resistance, and higher systolic and diastolic blood pressure from childhood to young adulthood (8). Similarly, parental histories of hypertension, diabetes, and dyslipidemia have been associated with clustering of cardiometabolic disorders in offspring (9). A recent meta-analysis also showed that young adults with a family history of hypertension have higher systolic and diastolic blood pressure and less favorable heart rate variability indices, suggesting early autonomic involvement even before overt disease (10). These findings support the concept that parental type 2 diabetes mellitus and hypertension may act not merely as historical risk factors, but as markers of inherited and shared environmental susceptibility to early cardiometabolic dysregulation.

Autonomic imbalance is another plausible mechanism linking prehypertension to future cardiovascular risk. Heart rate variability provides a non-invasive assessment of cardiac autonomic modulation and reflects the dynamic interaction between sympathetic and parasympathetic influences on the sinus node (11). Reduced heart rate variability has been reported across the blood pressure spectrum and is associated with hypertension and adverse cardiovascular risk profiles (12). In young persons with a familial predisposition to hypertension, lower RMSSD, SDNN and high-frequency power, along with higher low-frequency power and LF/HF ratio, suggest reduced vagal modulation and relative sympathetic predominance (10). Thus, heart rate variability may provide insight into early functional alterations preceding established hypertension. Beyond hemodynamic and autonomic changes, endothelial dysfunction and altered vascular repair mechanisms may contribute to the transition from prehypertension to sustained hypertension. Prehypertension has been associated with impaired endothelial repair capacity of early endothelial progenitor cells, supporting the view that vascular dysfunction may be present before the development of overt hypertension (13). Biomarkers related to endothelial function, angiogenesis, inflammation, and oxidative stress may therefore help characterize the biological phenotype of prehypertension. Vascular endothelial growth factor is of particular interest because plasma and platelet-derived VEGF levels have been reported to be increased in hypertension and to decrease after antihypertensive treatment (14). Resistin, an adipocytokine linked to inflammation and vascular dysfunction, has also been associated with incident hypertension among non-diabetic women (15). Together, these observations suggest that prehypertension may reflect a broader vascular and inflammatory phenotype rather than isolated elevation of blood pressure.

Despite increasing evidence on the cardiovascular implications of prehypertension, relatively few studies have simultaneously examined adiposity, hemodynamic load, autonomic function, endothelial/angiogenic biomarkers, oxidative stress markers, lipid parameters, and parental cardiometabolic history in young adults. This integrated approach is important because prehypertension in early adulthood may represent the convergence of inherited susceptibility, excess adiposity, autonomic dysregulation, endothelial activation, and increased cardiac workload. Therefore, the present study was designed to characterize the early vascular risk phenotype of young adults with prehypertension compared with age-matched normotensive controls, and to examine whether parental history of type 2 diabetes mellitus and hypertension is associated with prehypertensive status and selected cardiometabolic risk markers.

METHODOLOGY

Study setting and population

This study was conducted among students of Sri Venkateswara Medical College, Tirupati. The study population consisted of apparently healthy students of Sri Venkateswara Medical College, Tirupati. Participants were classified into two groups based on resting systolic and diastolic blood pressure, according to the JNC 7 criteria for prehypertension.

Inclusion criteria

Normotensive controls

Apparently healthy subjects with systolic blood pressure between 100–119 mmHg and diastolic blood pressure between 60–79 mmHg were included in the normotensive group.

Prehypertensive subjects

Apparently healthy subjects with systolic blood pressure between 120–139 mmHg and/or diastolic blood pressure between 80–89 mmHg were included in the prehypertensive group.

Exclusion criteria

Subjects were excluded if they were receiving any medication or had a history of diabetes mellitus, hypertension, endocrine disorders, kidney disease, or any other known systemic illness. Subjects with established hypertension or those already receiving antihypertensive medication were also excluded.

Ethical considerations

The study was conducted after obtaining clearance from the Institutional Ethics Committee of Sri Venkateswara Medical College, Tirupati. Written informed consent was obtained from all participants before enrolment. All study procedures were performed in accordance with institutional ethical standards and the principles of human research ethics.

Pre-assessment preparation
Participants were instructed to refrain from heavy physical activity for 24 hours before testing and to avoid alcohol and caffeinated beverages for 12 hours before the measurements. On arrival at the research laboratory, participants were asked to void urine and were then seated comfortably in a quiet environment to acclimatize to the laboratory setting. Baseline and anthropometric measurements were recorded before heart rate variability assessment.

Anthropometric and body composition assessment
Anthropometric parameters including height, weight, waist circumference and hip circumference were recorded using standard procedures. Body mass index was calculated as weight in kilograms divided by the square of height in metres. Waist–hip ratio was calculated as waist circumference divided by hip circumference.
Body composition analysis was performed using OMRON HBF 500 which works on the principle of bioimpedance assay in the Multidisciplinary Research Unit of Sri Venkateswara Medical College, Tirupati.

Blood pressure and haemodynamic assessment
Heart rate and auscultatory blood pressure were recorded after the participant had been sitting calmly for 10 minutes. Blood pressure was measured using the auscultatory method. Three successive recordings were obtained, ensuring an optimum difference of not more than 4 mmHg between recordings for both systolic and diastolic blood pressure. The mean of the three recordings was used for analysis(12).

Heart rate variability assessment
HRV recording was performed in the Multidisciplinary Research Unit of Sri Venkateswara Medical College, Tirupati under standardized resting conditions. After baseline measurements, participants were placed in the supine position with eyes closed and were asked to remain relaxed. Lead II electrocardiogram was recorded for 10 minutes at a sampling rate of 2000 samples/second, with spontaneous breathing maintained between 12–18 breaths/minute. HRV acquisition and analysis were performed in accordance with the recommendations of the Task Force on heart rate variability (11). RR intervals were extracted from the ECG signal using recordings with optimum amplitude and sharp R-wave identification. After exclusion of artefacts and ectopic beats, a stationary 256-second RR interval segment was selected for analysis. HRV analysis was performed using Kubios HRV Version 2.0 software developed by the Biosignal Analysis and Medical Imaging Group, Finland. For frequency-domain analysis, the RR series was resampled at 4 Hz. The mean and trend were removed, a Hann window was applied, and the 1024-point data series was transformed using Fast Fourier Transformation. Frequency-domain indices including total power, normalized low-frequency power, normalized high-frequency power and LF/HF ratio were calculated. The following HRV parameters were analyzed:
Time-domain indices: mean RR, SDNN, mean heart rate, RMSSD, NN50 and pNN50.
Geometric indices: RR triangular index and TINN.
Frequency-domain indices: VLF power, LF power, HF power, total power, LF percentage, HF percentage, LF normalized units, HF normalized units and LF/HF ratio.

Blood sample collection and biochemical analysis
After physiological recordings, 5 ml of venous blood was collected from each participant under aseptic precautions. The samples were processed and stored appropriately until biochemical analysis. Laboratory processing of biochemical parameters was performed at the Multidisciplinary Research Unit. The following biomarkers were analysed: vascular cell adhesion molecule, endothelin-1, thiobarbituric acid reactive substances, total antioxidant status/equivalent, vascular endothelial growth factor, resistin and soluble E-selectin. Lipid profile parameters included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol, TC/TGL ratio, TC/HDL ratio and LDL/HDL ratio. Lipid parameters were analysed as an exploratory subset because complete lipid data were not available for all participants.

Assessment of parental cardiometabolic history
Parental history of type 2 diabetes mellitus and hypertension was obtained from each participant using a structured questionnaire. Separate information was recorded for father's history of type 2 diabetes mellitus, father's history of hypertension, mother's history of type 2 diabetes mellitus and mother's history of hypertension.

Statistical analysis
Statistical analysis was performed using R for windows 4.6.0. Continuous variables were assessed for distributional pattern using visual inspection and normality testing. Normally distributed variables were summarized as mean ± standard deviation, whereas skewed variables were summarized as median and interquartile range. Categorical variables were presented as frequency and percentage. Between-group comparisons were performed between normotensive controls and prehypertensive subjects. Normally distributed continuous variables were compared using independent-samples t-test. Skewed continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using chi-square test or Fisher's exact test, as appropriate. Age- and sex-adjusted linear regression models were used to examine the independent association between prehypertensive status and selected cardiometabolic, hemodynamic, autonomic, endothelial, oxidative stress and lipid parameters. For skewed outcomes, logarithmic transformation was applied before regression analysis where appropriate. Results from adjusted linear models were expressed as regression coefficients with 95% confidence intervals and p-values. To evaluate whether parental cardiometabolic history was associated with prehypertension, binary logistic regression was performed with prehypertensive status as the dependent variable. The main predictors were any parental T2DM, any parental hypertension and parental cardiometabolic burden score. Models were

adjusted for age and sex. Additional sensitivity models were performed with further adjustment for BMI to assess whether associations were independent of generalized adiposity. A two-sided p-value <0.05 was considered statistically significant for primary analyses.

RESULTS

A total of 113 young adults were included in the analysis, comprising 47 normotensive controls and 66 prehypertensive subjects. Anthropometric, blood pressure, haemodynamic, and parental history variables were available for all participants.

Baseline characteristics

The two groups were comparable in age. The median age was 19.0 years in both controls and prehypertensive subjects, with no statistically significant difference between groups ($p = 0.259$). Male sex was more frequent among prehypertensive subjects than controls, although this difference did not reach conventional statistical significance: 44/66, 66.7% vs 22/47, 46.8%, respectively ($p = 0.052$). Prehypertensive subjects had significantly higher body weight, BMI, body surface area, waist circumference, waist–hip ratio, and visceral fat compared with controls. Median body weight was 63.50 kg [56.32, 75.12] in prehypertensive subjects compared with 52.60 kg [47.30, 60.05] in controls ($p < 0.001$; $q < 0.001$). BMI was also higher in prehypertensive subjects (24.23 ± 3.90 kg/m²) than in controls (20.87 ± 3.99 kg/m²; $p < 0.001$; $q < 0.001$). Waist circumference was significantly greater in prehypertensives (80.96 ± 6.76 cm) than controls (75.29 ± 8.93 cm; $p < 0.001$; $q = 0.002$), and WHR was higher in the prehypertensive group (0.82 ± 0.05) compared with controls (0.77 ± 0.06; $p < 0.001$; $q < 0.001$). Median visceral fat was approximately two-fold higher among prehypertensive subjects (6.00 [4.50, 9.25]) compared with controls (3.00 [1.88, 5.00]; $p < 0.001$; $q < 0.001$). Hip circumference and unadjusted body fat percentage did not differ significantly between groups.

Parental cardiometabolic history

Parental cardiometabolic history was more common among prehypertensive subjects. Any parental history of T2DM was present in 23/66 prehypertensive subjects, 34.8%, compared with 6/47 controls, 12.8% ($p = 0.009$; $q = 0.072$). Any parental history of hypertension was present in 21/66 prehypertensive subjects, 31.8%, compared with 7/47 controls, 14.9% ($p = 0.048$; $q = 0.114$). The parental cardiometabolic burden score was higher in the prehypertensive group, with a median of 0 [0, 2] compared with 0 [0, 0] in controls ($p = 0.013$).

Hemodynamic and cardiac workload parameters

As expected from the study group definition, systolic and diastolic blood pressure were significantly higher in the prehypertensive group. Median SBP was 124.00 mmHg [122.00, 128.00] in prehypertensive subjects compared with 112.00 mmHg [110.00, 118.00] in controls ($p < 0.001$; $q < 0.001$). DBP was 83.79 ± 3.48 mmHg in prehypertensive subjects compared with 73.83 ± 4.29 mmHg in controls ($p < 0.001$; $q < 0.001$). MAP was also higher in prehypertensives (96.67 mmHg [94.67, 100.00]) than controls (86.67 mmHg [84.67, 90.00]; $p < 0.001$; $q < 0.001$). Prehypertensive subjects also demonstrated higher resting heart rate and rate pressure product. Resting heart rate was 87.73 ± 4.01 beats/min in the prehypertensive group and 79.11 ± 3.62 beats/min in controls ($p < 0.001$; $q < 0.001$). Rate pressure product was markedly higher in prehypertensives (10915.61 ± 617.45) compared with controls (8879.19 ± 611.11; $p < 0.001$; $q < 0.001$), indicating greater myocardial workload.

Heart rate variability parameters

Heart rate variability indices did not show robust between-group differences. Time-domain indices including SDNN, RMSSD, NN50, pNN50, mean RR, mean HR, RR triangular index, and TINN were not significantly different between prehypertensive subjects and controls after correction for multiple testing. Frequency-domain indices including LF power, HF power, VLF power, total power, LF%, HF%, LFnu, HFnu, and LF/HF ratio also did not differ significantly between groups.

Endothelial, angiogenic, inflammatory, and oxidative stress biomarkers

Among the biomarker variables, VEGF and resistin were higher among prehypertensive subjects. Median VEGF was 1245.20 [785.09, 5438.24] in the prehypertensive group compared with 136.29 [78.09, 4013.13] in controls ($p < 0.001$; $q = 0.002$). Median resistin was also higher in prehypertensives (822.54 [522.99, 2360.66]) compared with controls (318.80 [122.50, 1885.68]; $p = 0.014$; $q = 0.049$). Endothelin-1 showed a nominally higher level in the prehypertensive group (132.83 [35.41, 279.61]) compared with controls (38.45 [25.61, 221.70]; $p = 0.041$), but this did not remain significant after false discovery rate correction ($q = 0.123$). VCAM, TBARS, total antioxidant status/equivalent, and soluble E-selectin did not differ significantly between groups.

Lipid profile

Lipid data were available for only 29 participants and were therefore analysed as an exploratory subset. There were no statistically significant differences between controls and prehypertensive subjects in total cholesterol, HDL, LDL, triglycerides, VLDL, TC/TGL ratio, TC/HDL ratio, or LDL/HDL ratio.

Age- and sex-adjusted group differences

In age- and sex-adjusted linear regression models, prehypertensive status remained significantly associated with multiple adverse cardiovascular risk markers. Prehypertensive subjects had higher BMI, with an adjusted mean difference of 3.82 kg/m² compared with controls (95% CI 2.36 to 5.27; $p < 0.001$; $q < 0.001$). Waist circumference was higher by 6.26 cm (95% CI 3.05 to 9.47; $p < 0.001$; $q < 0.001$), and WHR was higher by 0.05 (95% CI 0.03 to 0.07; $p < 0.001$; $q < 0.001$). Visceral fat remained significantly higher in prehypertensives, with a geometric mean ratio of 2.14 compared with controls (95% CI 1.59 to 2.89; $p < 0.001$; $q < 0.001$). Body fat percentage was also higher after adjustment, with an adjusted mean difference of 3.28 percentage points (95% CI 0.86 to 5.71; $p = 0.008$; $q = 0.028$). Haemodynamic and cardiac workload differences also remained highly significant after age and sex adjustment. Prehypertensive subjects had higher heart rate by 8.65 beats/min (95% CI 7.14 to 10.17; $p < 0.001$; $q < 0.001$) and higher rate pressure product by 2027.42 units (95% CI 1776.96 to 2277.88; $p < 0.001$; $q < 0.001$). Adjusted differences in SBP, DBP, and MAP also remained significant, consistent with the classification criteria. In adjusted biomarker models, VEGF remained strongly associated with prehypertensive status. The geometric mean VEGF level was 5.36-fold higher in prehypertensive subjects than controls (95% CI 2.51 to 11.45; $p < 0.001$; $q < 0.001$). Resistin was also higher, with a geometric mean ratio of 2.34 (95% CI 1.24 to 4.38; $p = 0.008$; $q = 0.028$).

BMI-adjusted sensitivity analysis

Sensitivity models additionally adjusted for BMI were performed to assess whether biomarker differences were independent of generalized adiposity. VEGF remained significantly higher in prehypertensive subjects after adjustment for age, sex, and BMI, with a geometric mean ratio of 5.67 (95% CI 2.17 to 14.83; $p < 0.001$; $q = 0.003$). Resistin remained nominally higher after BMI adjustment, with a geometric mean ratio of 2.46 (95% CI 1.25 to 4.85; $p = 0.009$), but this association was borderline after correction for multiple testing ($q = 0.052$). ET-1 was nominally associated with prehypertensive status after BMI adjustment, but this did not remain significant after FDR correction. Other biomarker, HRV, and lipid variables did not show robust BMI-adjusted associations.

Association of parental cardiometabolic history with prehypertension

Age- and sex-adjusted logistic regression showed that parental T2DM was significantly associated with prehypertensive status. Participants with any parental history of T2DM had approximately four-fold higher odds of being prehypertensive compared with participants without parental T2DM (OR 4.11; 95% CI 1.46 to 11.58; $p = 0.008$). Any parental hypertension showed a positive but borderline association with prehypertension (OR 2.53; 95% CI 0.95 to 6.76; $p = 0.064$). The parental cardiometabolic burden score was also associated with prehypertension; each one-unit increase in the burden score was associated with nearly two-fold higher odds of prehypertension (OR 1.99; 95% CI 1.15 to 3.44; $p = 0.013$).

In BMI-adjusted sensitivity models, the associations between parental history and prehypertension persisted. Any parental T2DM was associated with higher odds of prehypertension (OR 5.80; 95% CI 1.79 to 18.78; $p = 0.003$), and any parental hypertension also became statistically significant (OR 3.36; 95% CI 1.14 to 9.92; $p = 0.028$). The parental cardiometabolic burden score remained independently associated with prehypertension after BMI adjustment (OR 2.41; 95% CI 1.29 to 4.47; $p = 0.006$).

Association of parental history with selected cardiovascular risk markers

Exploratory models were used to assess whether parental cardiometabolic history was associated with selected cardiovascular risk markers after adjustment for group, age, and sex. Any parental T2DM was nominally associated with higher heart rate and higher rate pressure product. Participants with parental T2DM had an adjusted heart rate difference of 2.88 beats/min (95% CI 0.69 to 5.08; $p = 0.010$) and an adjusted rate pressure product difference of 558.87 units (95% CI 98.33 to 1019.42; $p = 0.017$). Similarly, parental cardiometabolic burden score was nominally associated with higher heart rate and rate pressure product. However, these parental-outcome associations did not remain significant after false discovery rate correction and should therefore be interpreted as exploratory.

Interaction analyses

Exploratory interaction models assessed whether parental T2DM or parental hypertension modified the association between prehypertensive status and selected outcomes. Most interaction terms were not statistically significant after correction for multiple testing. One interaction between prehypertensive status and any parental T2DM was observed for RMSSD, with an interaction difference of 23.42 ms (95% CI 9.43 to 37.41; $p = 0.001$; $q = 0.020$). Given the exploratory nature of the interaction analysis and the absence of robust overall HRV group differences.

Table 1. Baseline, adiposity and parental characteristics

Characteristic	Control (n=47)	Prehypertensive (n=66)	Presentation	Test	P value
Age	19.00 [18.00, 19.00]	19.00 [18.00, 19.00]	Median [IQR]	Mann–Whitney U	0.259
Height (cms)	162.43 ± 8.70	164.07 ± 7.94	Mean ± SD	Welch t-test	0.308
Weight	52.60 [47.30, 60.05]	63.50 [56.32, 75.12]	Median [IQR]	Mann–Whitney U	<0.001
BMI	20.87 ± 3.99	24.23 ± 3.90	Mean ± SD	Welch t-test	<0.001
BSA	1.57 ± 0.16	1.71 ± 0.17	Mean ± SD	Welch t-test	<0.001
Waist	75.29 ± 8.93	80.96 ± 6.76	Mean ± SD	Welch t-test	<0.001

Hip	98.02 ± 12.64	98.43 ± 9.26	Mean ± SD	Welch t-test	0.850
WHR	0.77 ± 0.06	0.82 ± 0.05	Mean ± SD	Welch t-test	<0.001
Body Fat	25.45 ± 9.40	25.55 ± 8.02	Mean ± SD	Welch t-test	0.953
V. Fat	3.00 [1.88, 5.00]	6.00 [4.50, 9.25]	Median [IQR]	Mann–Whitney U	<0.001
Male sex	22/47 (46.8%)	44/66 (66.7%)	n/N (%)	Fisher exact	0.052
Any parental T2DM	6/47 (12.8%)	23/66 (34.8%)	n/N (%)	Fisher exact	0.009
Any parental HTN	7/47 (14.9%)	21/66 (31.8%)	n/N (%)	Fisher exact	0.048
Parental cardiometabolic burden score	0 [0, 0]	0 [0, 2]	Median [IQR]	Mann–Whitney U	0.013

Table 2. Age- and sex-adjusted group differences in key outcomes

Variable	N_model	Transformation	Effect_type	Effect (95% CI)	P value
RPP	104	None	Adjusted mean difference (PreHTN-Control)	2027.42 (1776.96, 2277.88)	<0.001
MAP	113	None	Adjusted mean difference (PreHTN-Control)	10.59 (9.26, 11.92)	<0.001
SBP	113	None	Adjusted mean difference (PreHTN-Control)	11.79 (10.14, 13.44)	<0.001
DBP	113	None	Adjusted mean difference (PreHTN-Control)	10.00 (8.50, 11.49)	<0.001
HR	113	None	Adjusted mean difference (PreHTN-Control)	8.65 (7.14, 10.17)	<0.001
BMI	113	None	Adjusted mean difference (PreHTN-Control)	3.82 (2.36, 5.27)	<0.001
V. Fat	95	Natural log	Geometric mean ratio (PreHTN/Control)	2.14 (1.59, 2.89)	<0.001
WHR	113	None	Adjusted mean difference (PreHTN-Control)	0.05 (0.03, 0.07)	<0.001
VEGF C	82	Natural log	Geometric mean ratio (PreHTN/Control)	5.36 (2.51, 11.45)	<0.001
Waist	113	None	Adjusted mean difference (PreHTN-Control)	6.26 (3.05, 9.47)	<0.001
Body Fat	105	None	Adjusted mean difference (PreHTN-Control)	3.28 (0.86, 5.71)	0.008
Resistin c	83	Natural log	Geometric mean ratio (PreHTN/Control)	2.34 (1.24, 4.38)	0.008

Table 3. Parental cardiometabolic history as predictor of prehypertension

Model	Predictor	OR (95% CI)	P value
Separate Model: any parental T2DM + age + sex	AnyParent_T2DM	4.11 (1.46, 11.58)	0.008
Separate Model: any parental HTN + age + sex	AnyParent_HTN	2.53 (0.95, 6.76)	0.064
Separate Model: parental burden + age + sex	Parent_Burden	1.99 (1.15, 3.44)	0.013
Sensitivity: any parental T2DM + age + sex + BMI	AnyParent_T2DM	5.80 (1.79, 18.78)	0.003
Sensitivity: any parental HTN + age + sex + BMI	AnyParent_HTN	3.36 (1.14, 9.92)	0.028
Sensitivity: parental burden + age + sex + BMI	Parent_Burden	2.41 (1.29, 4.47)	0.006

Table 4. BMI-adjusted sensitivity models for selected non-adiposity outcomes

Variable	N_model	Transformation	Effect_type	Effect (95% CI)	P value
VEGF C	82	Natural log	Geometric mean ratio (PreHTN/Control)	5.67 (2.17, 14.83)	<0.001
RESISTIN c	83	Natural log	Geometric mean ratio (PreHTN/Control)	2.46 (1.25, 4.85)	0.009
ET 1 C	83	Natural log	Geometric mean ratio (PreHTN/Control)	1.99 (1.02, 3.88)	0.043

sE selectin C	83	Natural log	Geometric mean ratio (PreHTN/Control)	1.82 (0.87, 3.81)	0.114
TE C	83	None	Adjusted mean difference (PreHTN-Control)	11.27 (-7.52, 30.06)	0.240
VCAM C	83	Natural log	Geometric mean ratio (PreHTN/Control)	1.41 (0.68, 2.90)	0.358
TBARS C	83	Natural log	Geometric mean ratio (PreHTN/Control)	1.17 (0.62, 2.22)	0.622
HR	113	None	Adjusted mean difference (PreHTN-Control)	8.81 (7.08, 10.53)	<0.001
RPP	104	None	Adjusted mean difference (PreHTN-Control)	1945.99 (1660.59, 2231.40)	<0.001

DISCUSSION

The present study demonstrates that young adults with prehypertension exhibit a broader adverse cardiovascular risk phenotype, extending beyond modest elevation of systolic and diastolic blood pressure. Compared with age-matched normotensive controls, prehypertensive subjects had higher generalized and central adiposity, greater visceral fat, increased resting heart rate, markedly higher rate pressure product, and elevated VEGF and resistin concentrations. In addition, parental T2DM and cumulative parental cardiometabolic burden were independently associated with prehypertensive status. These findings support the concept that prehypertension in young adults is not merely an isolated blood pressure category but may represent an early integrated phenotype of adiposity-related, haemodynamic, vascular, inflammatory, and familial cardiometabolic risk. The clinical relevance of prehypertension has been established in large population-based studies and meta-analyses. In the Framingham Heart Study, high-normal blood pressure was associated with increased cardiovascular disease risk compared with optimal blood pressure (2). Previous studies has further shown that prehypertension is associated with higher incidence of cardiovascular disease, coronary heart disease and stroke, with risk present even in lower-range prehypertension and increasing further in high-range prehypertension (3,4). The present findings are consistent with these observations and suggest that measurable adverse biological alterations may already be present in young prehypertensive individuals before the development of established hypertension. A major finding of this study was the strong association between prehypertension and adiposity. Prehypertensive subjects had significantly higher BMI, waist circumference, waist–hip ratio, body fat percentage and visceral fat. Importantly, these differences persisted after age and sex adjustment. This is biologically plausible because adiposity contributes to blood pressure elevation through multiple mechanisms, including increased sympathetic drive, activation of the renin–angiotensin–aldosterone system, insulin resistance, renal sodium retention, vascular inflammation and endothelial dysfunction. A meta-analysis of prospective studies reported that each 5-unit increment in BMI was associated with a 50% higher risk of incident hypertension, while waist circumference and waist–hip ratio were also positively associated with hypertension risk (16). Therefore, the higher central and visceral adiposity observed in prehypertensive subjects may represent a key upstream contributor to early blood pressure dysregulation.

The higher heart rate and rate pressure product observed in the prehypertensive group are also clinically meaningful. Rate pressure product, calculated as heart rate multiplied by systolic blood pressure, is widely used as an indirect index of myocardial oxygen demand and cardiac workload (17). In the present study, the increase in rate pressure product was marked and remained significant after age and sex adjustment, suggesting that even young prehypertensive individuals may experience higher resting myocardial workload. This finding strengthens the interpretation that prehypertension is associated not only with vascular pressure load but also with increased hemodynamic stress on the heart. Over time, such persistent hemodynamics load may contribute to early cardiac remodeling, especially when combined with adiposity and familial cardiometabolic susceptibility.

One of the most important observations in the present study was the association between parental cardiometabolic history and prehypertension. Participants with any parental history of T2DM had approximately four-fold higher odds of prehypertension after adjustment for age and sex, while parental cardiometabolic burden score was also significantly associated with prehypertensive status. These findings are consistent with previous evidence that parental histories of hypertension, diabetes and dyslipidemia are associated with clustering of cardiometabolic risk factors in offspring (9). The present study extends this concept by showing that parental T2DM and cumulative parental burden are already associated with prehypertension in young adults. This may reflect shared genetic susceptibility, shared lifestyle and dietary patterns, epigenetic influences, early-life metabolic programming, or a combination of these factors. The stronger association observed for parental T2DM than parental hypertension is particularly noteworthy. Offspring of parents with T2DM may inherit or acquire a broader metabolic risk profile, including insulin resistance, adiposity, endothelial dysfunction and low-grade inflammation, all of which can contribute to early blood pressure elevation. The Bogalusa Heart Study previously showed that offspring of parents with T2DM had adverse longitudinal changes in insulin resistance-related risk variables from childhood to young adulthood (9). In our study, parental T2DM remained associated with prehypertension even after BMI adjustment, suggesting that familial diabetic history may contribute to prehypertensive status through pathways not fully explained by generalized adiposity alone. This makes parental T2DM a potentially useful clinical marker for identifying young individuals who may benefit from early cardiometabolic screening. The biomarker findings provide further support for early vascular and inflammatory involvement in prehypertension. VEGF was substantially higher among prehypertensive subjects and remained significant even after additional adjustment for BMI, indicating that the association was not explained solely by adiposity. VEGF is a key regulator of angiogenesis, endothelial activation and

vascular permeability. Previous work has reported increased plasma and platelet-derived VEGF in hypertension, with reduction after antihypertensive therapy (14). In addition, impaired endothelial repair capacity of early endothelial progenitor cells has been demonstrated in prehypertension, suggesting that vascular repair mechanisms may be altered before the onset of established hypertension (13). The elevated VEGF observed in the present study may therefore represent compensatory angiogenic signaling, endothelial activation, or early vascular stress in prehypertensive individuals.

Resistin was also higher in prehypertensive subjects. Resistin is an adipocytokine linked to inflammation, insulin resistance and vascular dysfunction. In a prospective study of non-diabetic women, higher plasma resistin levels were independently associated with increased risk of incident hypertension (15). The present finding of elevated resistin in young prehypertensive individuals is therefore consistent with a role for inflammatory adipokine signalling in early blood pressure elevation. However, after BMI adjustment, the association with resistin was attenuated after correction for multiple comparisons, suggesting that part of the resistin difference may be mediated or confounded by adiposity. This supports the interpretation that resistin may lie within an adiposity–inflammation–blood pressure pathway rather than acting as a fully independent marker.

In contrast to the adiposity, haemodynamic and biomarker findings, HRV indices did not show robust group differences after correction for multiple testing. Prior studies have shown that hypertension is associated with reduced HRV, and a meta-analysis in young adults reported that family history of hypertension is associated with higher blood pressure, lower RMSSD, SDNN and HF power, and higher LF/HF ratio (10,12). The absence of a strong HRV signal in the present study may be due to the relatively young age of participants, modest sample size, variability in HRV measurements, incomplete HRV data, or the possibility that autonomic changes are subtle and not uniformly present at the prehypertensive stage.
The lipid findings were also not robust, but this should mainly be interpreted in the context of data availability. Lipid profile data were available only for a small subset of participants, limiting statistical power and increasing uncertainty. Therefore, the absence of significant lipid differences should not be taken as evidence that lipid abnormalities are absent in prehypertension. Future studies with complete lipid assessment, insulin resistance markers and dietary/lifestyle data would be better positioned to evaluate whether dyslipidaemia contributes to the prehypertensive phenotype in this population. The strengths of this study was, it focused on young adults, a group in whom early detection of vascular risk may have substantial preventive value. We have evaluated prehypertension using a multidimensional approach, incorporating anthropometry, adiposity, haemodynamics, HRV, biomarkers, lipids and parental cardiometabolic history. The analysis included age- and sex-adjusted models, BMI-adjusted sensitivity models, and correction for multiple comparisons, thereby reducing the risk of overinterpreting isolated unadjusted findings.

There are few limitations also should also be acknowledged. The case–control design limits causal inference; therefore, the observed associations should not be interpreted as proof that adiposity, parental T2DM, VEGF or resistin cause prehypertension. The sample size was modest, particularly for biomarker, HRV and lipid subset analyses. Parental history was based on reported history and may be affected by recall bias or underdiagnosis in parents. Ambulatory blood pressure monitoring was not available, so white-coat or masked hypertension could not be fully excluded. The study also lacked detailed assessment of diet, physical activity, insulin resistance, sleep, stress, socioeconomic factors and genetic markers, all of which may influence blood pressure and cardiometabolic risk. Finally, although VEGF and resistin were significantly associated with prehypertension, the cross-sectional nature of the data prevents determination of whether these biomarker changes precede, accompany or follow blood pressure elevation.

Despite these limitations, the findings have important clinical and research implications. Young adults with prehypertension should not be assessed only by blood pressure values. Instead, evaluation of adiposity, central obesity, visceral fat, resting heart rate, cardiac workload and family history may help identify individuals with a more adverse early risk phenotype. Parental T2DM and cumulative parental cardiometabolic burden appear particularly relevant and may provide simple, low-cost tools for early risk stratification. The persistence of higher VEGF after BMI adjustment also raises the possibility that endothelial or angiogenic alterations may be present early in the prehypertensive state and could be explored further in longitudinal studies.

CONCLUSION

Young adults with prehypertension demonstrated a distinct early cardiovascular risk phenotype characterized by higher adiposity, increased cardiac workload, elevated VEGF and resistin, and greater familial cardiometabolic burden. Parental T2DM and cumulative parental cardiometabolic burden were independently associated with prehypertensive status, suggesting that familial metabolic susceptibility may contribute to early blood pressure dysregulation. These findings support early identification and preventive intervention in young adults with prehypertension, especially when accompanied by central adiposity and positive parental cardiometabolic history.

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Conflict of interest
Nil

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560-72.
2. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001;345(18):1291-7.
3. Huang Y, Wang S, Cai X, Mai W, Hu Y, Tang H, et al. Prehypertension and incidence of cardiovascular disease: a meta-analysis. BMC Med. 2013;11:177.
4. Guo X, Zhang X, Guo L, Li Z, Zheng L, Yu S, et al. Association between pre-hypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Curr Hypertens Rep. 2013;15(6):703-16.
5. Khan ZA, Qureshi U, Khan T, Goel S. Change in the prevalence of prehypertension and hypertension among young Indians aged 15-24 years between 2015-16 and 2019-21: insights from nationally representative surveys. PLoS One. 2025;20(4):e0319274.
6. Jayedi A, Rashidy-Pour A, Khorshidi M, Shab-Bidar S. Body mass index, abdominal adiposity, weight gain and risk of developing hypertension: a systematic review and dose-response meta-analysis of more than 2.3 million participants. Obes Rev. 2018;19(5):654-67.
7. Menke A, Muntner P, Wildman RP, Reynolds K, He J. Measures of adiposity and cardiovascular disease risk factors. Obesity (Silver Spring). 2007;15(3):785-95.
8. Srinivasan SR, Frontini MG, Berenson GS; Bogalusa Heart Study. Longitudinal changes in risk variables of insulin resistance syndrome from childhood to young adulthood in offspring of parents with type 2 diabetes: the Bogalusa Heart Study. Metabolism. 2003;52(4):443-50.
9. Wada K, Tamakoshi K, Yatsuya H, Otsuka R, Murata C, Zhang H, et al. Association between parental histories of hypertension, diabetes and dyslipidemia and the clustering of these disorders in offspring. Prev Med. 2006;42(5):358-63.
10. Queiroz MG, Prado AGK, Alves-Santos ET, Araújo JA, Damazo AS, Cambri LT. Influence of family history of hypertension on blood pressure and heart rate variability in young adults: a meta-analysis. Blood Press Monit. 2022;27(4):259-71.
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93(5):1043-65.
12. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities study. Hypertension. 2003;42(6):1106-11.
13. Giannotti G, Doerries C, Mocharla PS, Mueller MF, Bahlmann FH, Horvath T, et al. Impaired endothelial repair capacity of early endothelial progenitor cells in prehypertension: relation to endothelial dysfunction. Hypertension. 2010;55(6):1389-97.
14. Nadar SK, Blann AD, Lip GYH. Plasma and platelet-derived vascular endothelial growth factor and angiopoietin-1 in hypertension: effects of antihypertensive therapy. J Intern Med. 2004;256(4):331-7.
15. Zhang L, Curhan GC, Forman JP. Plasma resistin levels associate with risk for hypertension among nondiabetic women. J Am Soc Nephrol. 2010;21(7):1185-91.
16. Zhou W, Shi Y, Li YQ, Ping Z, Wang C, Liu X, et al. Body mass index, abdominal fatness, and hypertension incidence: a dose-response meta-analysis of prospective studies. J Hum Hypertens. 2018;32(5):321-33.
17. White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. Am J Hypertens. 1999;12(2 Pt 2):50S-55S.