International Journal of Hypertension

# Recent Advances and Future Directions in Hypertension

Lead Guest Editor: Jun Cai
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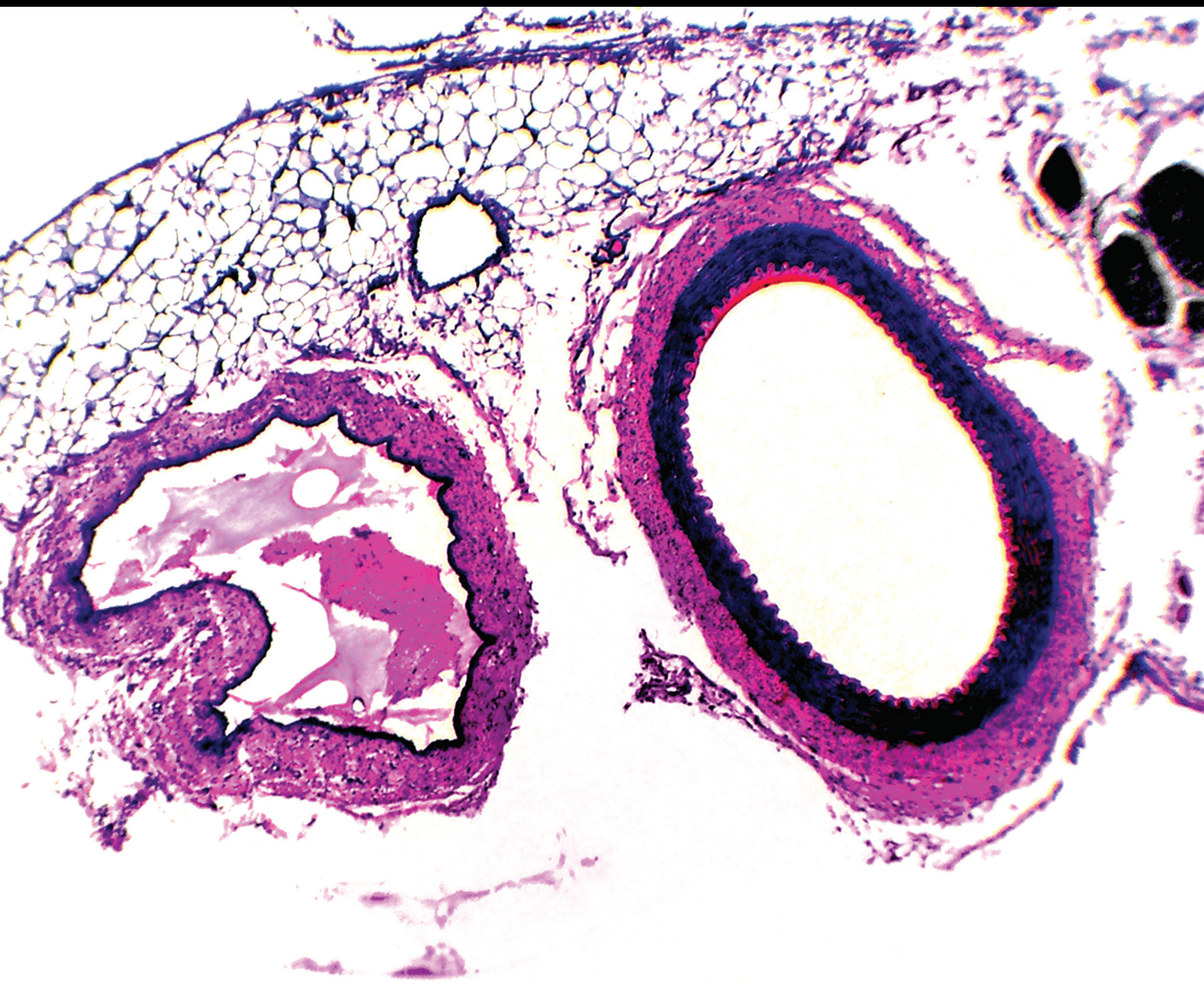

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# Contents

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*Research Article*

# Emergent Anthropometric Indices in Differential Prediction of Prehypertension and Hypertension in Mexican Population: Results according to Age and Sex

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*Background*. Hypertension (HTN) is recognized as a significant public health problem in the world. The objective of this study is to evaluate emergent anthropometric indices as predictors of preHTN and HTN according to age and sex in a sample of Mexican adults. *Methods*. A cross-sectional study was conducted in 1,150 participants aged 18–80 years old. Anthropometric data and blood pressure measurements were analyzed. Comparisons between men and women were carried out by independent analysis. Cutoff points for each emergent anthropometric index were obtained using the values' upper second and third tertiles. Logistic regression models and receiver operating characteristics curve analyses were used to assess the association and the predictive value of several emergent anthropometric indices with the presence of preHTN and HTN. *Results*. The prevalence of preHTN and HTN was 29.74% and 14.35%, respectively. In a logistic regression analysis adjusted by age and sex, the body roundness index (BRI) (OR = 2.08, $p < 0.001$) and conicity index (CI) (OR = 1.37, $p = 0.044$) were associated with preHTN, while CI (OR = 2.47, $p < 0.001$) and waist to height squared ($W/Ht^2$) (OR = 2.19, $p < 0.001$) were associated with HTN. Furthermore, in both sexes, BRI was the main predictor of preHTN (AUC: 0.634 and 0.656, respectively). Particularly, according to sex and age range, the predictive emergent anthropometric indices in men were the body shape index (ABSI) and waist to height cubic ($W/Ht^3$) (AUC = 0.777 and 0.771, respectively), whereas in women, the predictors were CI and ABSI (AUC = 0.737 and 0.729, respectively). In men ≤40 years old, central body fat indices were predictors of preHTN and HTN, but in men >40 years old, the predictor indices were $W/Ht^3$ and $W/Ht^2$. In women ≤40 years, the pulse mass index (PMI) was the best main predictor (AUC = 0.909) of HTN. *Conclusion*. CI, PMI, $W/Ht^3$, $W/Ht^2$, and ABSI could represent differential predictors of preHTN and HTN between men and women according to age range.

## 1. Introduction

Prehypertension (preHTN) and hypertension (HTN) are modifiable risk factors that could lead to mortality by coronary heart disease and ischemic stroke in populations of both sexes [1–4]. In a meta-analysis study, preHTN was related to the carotid intima-media thickness, a predictor of heart disease, stroke, and cardiovascular mortality [5]. Similarly, the presence of HTN is described as a risk factor most significantly correlated with strokes in the world population, as well as a related factor to the increased incidence of stroke in the young population [6].

In Mexico, the prevalence of preHTN reaches from 26.5% to 47.4% [2, 7], while the frequency of HTN is as high as 25.5% and 49.2% [8, 9]. Therefore, early detection of preHTN and HTN can help reduce morbidity and mortality providing timely treatment, management, and prevention of associated comorbidities. Due to the close relation between age, gender, adiposity, preHTN, and HTN [2, 10, 11], the search of anthropometric marker predictors of cardiovascular risk (CVR) such as HTN has revolutionized the field.

Traditional markers such as waist to height ratio (WHtR) have shown higher sensitivity than the body mass index (BMI) and waist circumference (WC) in the evaluation of the CVR [12]. However, emergent markers such as the body roundness index (BRI) have been suggested as an alternative for WHtR [13], because it possesses a predictive capacity for CVD [14, 15], principally for HTN [14, 16, 17]. In addition, the body adiposity index (BAI), abdominal volume index (AVI), body shape index (ABSI), or conicity index (CI) could have a predictive ability for evaluating HTN [16–19], while the ponderal index (PI) could do the same for preHTN [20]. The emergent anthropometric measurements are suggested to assess the risk of morbidity and mortality in the population given the fact that they are simple, inexpensive, and noninvasive tools. However, it is not yet fully clear which emergent anthropometric index may be associated with preHTN and with HTN in Mexican population and whether these vary according to sex and age. The aim of this study is to determine the emergent anthropometric indices as predictors of preHTN and HTN among men and women according to age range in a Mexican population.

## 2. Materials and Methods

*2.1. Design and Study Population.* This study was carried out in 2019 in a general population in the city of Chilpancingo in the state of Guerrero, located in southern Mexico. The study followed a cross-sectional design and was conducted on randomly selected subjects. A total of 1,150 participants (aged 18–80 years old) were included. The group was comprised of women ($n = 852$) and men ($n = 298$). Participants were invited to attend the evaluation sites that had been previously set up by the researchers in health care and educational centres, preferably between 7 and 9:30 a.m., following indications such as fasting and no exercise for at least 8 hours before the test. Eligibility criteria for the present analysis were to be aged between 18 and 80 years old and to live in Chilpancingo. Participants with musculoskeletal disorders or any other medical or physical condition that could make the clinical and anthropometric evaluation impossible were excluded from this study. All participants agreed to be a part of the study by giving their written consent following the considerations of the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the Universidad Autónoma de Guerrero.

*2.2. Data Collection and Anthropometric and Blood Pressure Measurements.* Information on sociodemographic characteristics and lifestyle habits was obtained by a questionnaire. The body composition was evaluated while wearing light clothing and barefooted, using a bioelectrical impedance technique with HBF-514C (Tanita Corporation, OMRON, IL, USA), which allowed to assess weight, body mass index (BMI), body fat percentage, and visceral fat. Height was determined using a portable stadiometer (Seca 240, Hamburg, Germany). The BMI was classified according to the World Health Organization's criteria: normal weight (BMI = 18.5–24.9 kg/m$^2$), overweight (BMI = 25–29.9 kg/m$^2$), and obesity (BMI ≥30 kg/m$^2$) [21]. Waist circumference (WC) was measured at the level of the umbilicus, with the subject standing up. Hip girth was measured at the maximum circumference of the buttocks. The circumference of the left wrist was also measured at the level of the ulna distal of the styloid apophysis process. The circumference of the left arm was measured by identifying the midpoint between the bone protrusion of the acromion and the olecranon, along the nondominant arm, with the elbow flexed at 90°. Once the middle point was identified, the arm was dropped naturally and the ribbon was placed horizontally around the indicated point. The body circumferences were measured twice using a measuring tape with an accuracy of ±0.1 cm (Seca 201, Hamburg, Germany). All measurements were made by trained health personnel.

The pulse and blood pressure were measured twice by trained technicians after a 5-minute seated rest, using the left arm of the participants. Two consecutive measurements were obtained at 5-minute intervals using a baumanometer (HEM-712C, OMRON, IL, USA).

*2.3. Definitions.* Indices such as BMI = weight (kg)/height (m)$^2$, waist to hip ratio (WHR) = WC (cm)/hip (cm), and WHtR = WC (cm)/height (m) are considered traditional anthropometric indices. These were evaluated given that some of them are incorporated in the definition of emergent indices considered in this study, such as: the arm-waist index (AWI), hip-wrist index (HWrI), waist-wrist index (WWrI), waist to hip to height ratio (WHHR), waist to height square (W/Ht$^2$), waist to height cubic (W/Ht$^3$), height cubic to waist cubic (H$^3$/W$^3$), waist-corrected BMI (wBMI), ponderal index (PI), body roundness index (BRI), body adiposity index (BAI), a body shape index (ABSI), conicity index (CI), body fat distribution index (BFDI), abdominal volume index (AVI), and pulse mass index (PMI). The emergent anthropometric indices were derived using the following formulae:

(i) Arm-waist index (AWI, cm): WC (cm)/left arm circumference (cm)

(ii) Hip-wrist index (HWrI, cm): hip circumference (cm)/left wrist circumference (cm) [22].

(iii) Waist-wrist index (WWrI, cm): WC (cm)/left wrist circumference (cm) [22].

(iv) Waist to hip to height ratio (WHHR, m$^{-1}$): WHR/height (m) [23].

(v) Waist to height square (W/Ht$^2$, cm/m$^2$): WC (cm)/height (m)$^2$ [24]

(vi) Waist to height cubic ($W/Ht^3$, $cm/m^3$): WC (cm)/height $(m)^3$ [24]

(vii) Height cubic to waist cubic ($H^3/W^3$, $cm^3/m^3$): height $(m)^3$/WC $(cm)^3$ [24]

(viii) Waist corrected BMI (wBMI, kg/m): [WC (m)] [BMI $(kg/m^2)$] [25].

(ix) Ponderal index (PI): weight (kg)/height$^3$ (cm) [20].

(x) Body roundness index (BRI): $364.2 - 365.5 \times \{1 - [(\text{WC (m)}/2\pi)/(0.5 \times \text{height (m)})^2\}^{0.5}$ [17–19]

(xi) Body adiposity index (BAI): {hip circumference (cm)/height $(m)^{1.5}$} − 18 [18, 20, 23].

(xii) A body shape index (ABSI, $m^{11/6}kg^{-2/3}$): WC (m)/[$BMI^{2/3}$ $(kg/m^2)$] [height$^{1/2}$ (m)] [17, 23].

(xiii) Conicity index (CI, AU): WC (m)/[$0.109\sqrt{}$ [weight (kg)/height (m)] [18, 20].

(xiv) Body fat distribution index (BFDI, m): [WC/height (m)] + [1/height (m)])/WHR [26].

(xv) Abdominal volume index (AVI, L): $\{2 \times \text{WC (cm)}^2 + 0.7\times$ [waist (cm) − hip $(cm)^2]\}/1000$ [27].

(xvi) Pulse mass index (PMI): (pulse) [BMI $(kg/m^2)$]/1.730 [28].

In this study, we defined cutoff values for emergent anthropometric indices to evaluate the association with preHTN and HTN. Values above the second tertile were considered a risk category for BRI (≥4.39), wBMI (≥22.25 $kg/m^2$), and PI (≥16.16). The values above the third tertile were considered as a risk category for WHHR (≥0.60 cm), AWI (≥3.25 cm), HWrI (≥6.52 cm), WWrI (≥5.93 cm), $W/Ht^2$ (≥40.37 $cm/m^2$), $W/Ht^3$ (≥26.40 $cm/m^3$), BAI (≥36.72), ABSI (≥0.103 $m^{11/6}kg^{-2/3}$), CI (≥1.32 UA), BFDI (≥68.23 m), and AVI (≥18.81 L). Meanwhile, for PMI, a value >1 was considered as a risk category [28].

The detection of high blood pressure was defined according to the Seventh Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC7). The following systolic blood pressure (SBP)/diastolic blood pressure (DBP) values were considered and classified: normal blood pressure (SBP/DBP values < 120/80 mmHg), preHTN (SBP/DBP values of 120–139/80–89 mmHg), and HTN (SBP/DBP values ≥ 140/90 mmHg). We also consider those who have antihypertensive treatment as participants with HTN [29].

*2.4. Statistical Analysis.* The statistical analysis of the data was performed using the STATAv.13.0 (StatCorp College Station, TX, USA) and GraphPad Prism v.8.0 software (GraphPad Software, San Diego, CA, USA) for Windows. The categorical variables were compared with the chi-squared test ($X^2$). Descriptive analysis included the estimation of median and percentiles (5th–95th) for non-parametric variables and determining significant differences among the groups using the Mann–Whitney $U$ test. The comparison of median and standard deviation (±) was evaluated using the Student's $t$ test. Comparisons between men and women were carried out by independent analysis. The linear relations between anthropometric indices and blood pressure were determined using Spearman correlation coefficient. The association among traditional and new anthropometric indices and preHTN and HTN was calculated using logistic regression analysis in a model adjusted by age, determining the odds ratio (OR) and 95% confidence interval (95% CI). To determine the predictive value of the emergent anthropometric indices for preHTN and HTN, receiving operating characteristics (ROC) were performed. In all cases, the areas under the curve (AUC) and the level of statistical significance or standard error were calculated. A $p$ value < 0.05 was considered statistically significant.

## 3. Results

A total of 1,150 participants were evaluated. Traditional factors of CVR such as tobacco (16.11% vs. 3.52%; $p < 0.001$) and alcohol (44.97% vs. 17.84%; $p < 0.001$) consumption were more frequent in men than in women. Women were found to be more sedentary compared to men (43.54% vs. 22.15%; $p < 0.001$, respectively). In general, 48.17% presented abdominal obesity, and according to BMI, 43.74% were overweight and 28.17% presented obesity. A total of 29.74% presented preHTN, and 14.35% presented HTN. The summarized data are presented in Table 1. BMI, AWI, CI, and DBP parameters did not show significant differences between men and women.

In this study, we analyzed the linear relation of SBP and DBP with the emergent anthropometric indices. In the total sample, the AVI ($r = 0.40$, $p < 0.001$), BRI ($r = 0.37$, $p < 0.001$), and wBMI ($r = 0.36$, $p < 0.001$) were strongly correlated with SBP, while for DBP those correlated were BRI ($r = 0.36$, $p < 0.001$) and AVI ($r = 0.35$, $p < 0.001$). The HWrI marker was the only one not related to blood pressure. On the other hand, according to sex, in both men and women, the BRI was more strongly correlated with blood pressure (in men, $r = 0.36$, $p < 0.001$ for SBP, and $r = 0.37$, $p < 0.001$ for DBP; and in women $r = 0.42$, $p < 0.001$ for SBP, and $r = 0.37$, $p < 0.001$ for DBP).

The total sample evaluated in this study was arranged in a logistic regression model adjusted by age and sex. The emergent anthropometric indices associated with preHTN were as follows: BRI (OR = 2.08, 95% CI: 1.49–2.91; $p < 0.001$) and CI (OR = 1.37, 95% CI: 1.00–1.86; $p = 0.044$). Meanwhile, for HTN, the main anthropometric indices associated were as follows: CI (OR = 2.47, 95% CI: 1.66–3.69; $p < 0.001$), followed by $W/Ht^2$ (OR = 2.19, 95% CI: 1.45–3.31; $p < 0.001$), AVI (OR = 2.02, 95% CI: 1.36–3.01; $p < 0.001$), and PMI (OR = 1.63, 95% CI: 1.04–2.57; $p = 0.032$).

Nevertheless, the analysis according to sex, adjusted by age, proved that in men BRI (OR = 2.54, 95% CI: 1.41–4.57; $p = 0.002$), PI (OR = 2.49, 95% CI: 1.44–4.31; $p = 0.001$), and $W/Ht^2$ (OR = 2.45, 95% CI: 1.00–6.03; $p = 0.050$) were mainly associated with preHTN. However, only $W/Ht^2$ (OR = 4.46, 95% CI: 1.31–15.17; $p = 0.016$) was associated with HTN (Figures 1(a) and 1(b)). On the other hand, for women, wBMI (OR = .57, 95% CI: 1.04–2.37; $p = 0.032$) and AVI (OR = 1.54, 95% CI: 1.05–2.26; $p = 0.026$) were associated with preHTN, while CI (OR = 2.25, 95% CI: 1.33–3.81;

Table 1: Anthropometrics and clinical characteristics of the study population according to sex.

| Variables | Total ($n = 1150$) | Men ($n = 298$) | Women ($n = 852$) | $p$ value |
|---|---|---|---|---|
| Age (years)[a] | 42 (20–66) | 41 (18–70) | 43 (21–65) | 0.022 |
| Height (m)[a] | 1.55 (1.43–1.74) | 1.67 (1.56–1.80) | 1.52 (1.42–1.64) | <0.001 |
| Weight (kg)[a] | 66.1 (49.3–92.6) | 75.55 (56.7–98.9) | 63.45 (48.4–85.5) | <0.001 |
| WC (cm)[a] | 92 (74–112) | 96 (75–115) | 90 (73–112) | <0.001 |
| BMI ($kg/m^2$)[a] | 27.4 (20.9–36.7) | 27.5 (20.7–34.9) | 27.3 (21–37.1) | 0.80 |
| WHR (cm)[a] | 0.90 (0.80–1.01) | 0.94 (0.82–1.05) | 0.89 (0.79–0.99) | <0.001 |
| WHtR (cm)[a] | 0.58 (0.45–0.73) | 0.57 (0.44–0.69) | 0.59 (0.47–0.74) | <0.001 |
| Body fat (%)[a] | 39.9 (20.7–52.1) | 28.2 (15.1–39.1) | 42.5 (29.8–52.8) | <0.001 |
| Visceral fat (%)[a] | 8 (4–16) | 11 (3–20) | 8 (4–13) | <0.001 |
| *Emergent anthropometric indices* | | | | |
| AWI (cm)[a] | 3.12 (2.70–3.68) | 3.13 (2.71–3.69) | 3.12 (2.70–3.68) | 0.47 |
| HWrI (cm)[a] | 6.29 (5.42–7.34) | 5.91 (5.35–6.68) | 6.42 (5.56–7.42) | <0.001 |
| WWrI (cm)[a] | 5.69 (4.73–6.68) | 5.61 (4.58–6.40) | 5.71 (4.77–6.76) | <0.001 |
| WHHR ($m^{-1}$)[a] | 0.57 (0.49–0.66) | 0.56 (0.47–0.65) | 0.58 (0.50–0.67) | <0.001 |
| $W/Ht^2$ ($cm/m^2$)[a] | 37.46 (28.39–49.79) | 33.88 (25.71–43.01) | 38.83 (29.93–50.63) | <0.001 |
| $W/Ht^3$ ($cm/m^3$)[a] | 23.96 (16.99–34.19) | 20.50 (14.86–27.33) | 25.48 (18.58–35.16) | <0.001 |
| $Ht^3/W^3$ ($cm^3/m^3$)[b] | $5.43 \pm 2.37$ | $5.94 \pm 2.54$ | $5.25 \pm 2.29$ | <0.001 |
| wBMI ($kg/m$)[a] | 25.11 (15.90–40.65) | 26.74 (16.03–40.35) | 24.65 (15.75–40.65) | 0.009 |
| PI[a] | 17.53 (12.99–24.28) | 16.34 (11.95–21.07) | 17.90 (13.31–24.82) | <0.001 |
| BRI[a] | 5.10 (2.63–8.88) | 4.81 (2.35–7.77) | 5.23 (2.83–9.23) | <0.001 |
| BAI[a] | 33.54 (24.76–47.31) | 28.59 (22.05–37.26) | 35.44 (26.90–48.09) | <0.001 |
| ABSI ($m^{11/6}\,kg^{-2/3}$)[a] | 0.100 (0.090–0.111) | 0.101 (0.091–0.110) | 0.100 (0.090–0.111) | 0.031 |
| CI (AU)[a] | 1.28 (1.14–1.42) | 1.29 (1.14–1.42) | 1.28 (1.14–1.43) | 0.06 |
| BFDI (m)[a] | 64.96 (55.76–80.08) | 61.20 (53.30–70.91) | 66.91 (57.31–81.40) | <0.001 |
| AVI (L)[a] | 16.92 (10.95–25.08) | 18.43 (11.40–26.45) | 16.20 (10.65–25.08) | <0.001 |
| PMI[a] | 1.14 (0.79–1.65) | 1.11 (0.78–1.61) | 1.15 (0.80–1.65) | 0.027 |
| *Blood pressure measures* | | | | |
| SBP (mmHg)[a] | 113 (91–152) | 119 (95–151) | 112 (90–152) | <0.001 |
| DBP (mmHg)[a] | 74 (57–94) | 75 (55–93) | 74 (57–94) | 0.83 |
| Blood pressure category[c] | | | | <0.001 |
| Normotensive | 643 (55.91) | 146 (48.99) | 497 (58.33) | |
| Prehypertension | 342 (29.74) | 111 (37.25) | 231 (27.11) | |
| Hypertension | 165 (14.35) | 41 (13.76) | 124 (14.55) | |

ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BMI, body mass index; BRI, body roundness index; CI, conicity index; DBP, diastolic blood pressure; $Ht^3/W^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; SBP, systolic blood pressure; wBMI, waist corrected BMI; WC, waist circumference; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; WHR, waist to hip ratio; $W/Ht^2$, waist to height square; $W/Ht^3$, waist to height cubic; WHtR, waist to height ratio. Data shown represent [a]median and percentile (p5th-p95th), [b]mean and standard deviation and [c]proportions (%). $p$ value <0.05 is statistically significant.

$p = 0.002$), ABSI (OR = 1.87, 95% CI: 1.12–3.14; $p = 0.016$), WHHR (OR = 1.79, 95% CI: 1.06–3.02; $p = 0.028$), and WWrI were associated with HTN (OR = 1.67, 95% CI: 1.01–2.76; $p = 0.045$) (Figures 1(c) and 1(d)).

In Table 2, the analysis using ROC curves adjusted by age in the total sample proved that AVI (AUC = 0.645) and CI (AUC = 0.692) showed a moderate predictive value for preHTN and HTN, respectively. In supplementary Table S1, we observed that VF (AUC = 0.680) and WHtR (AUC = 0.656) had a moderate predictive value for preHTN and HTN, respectively.

In Table 3, the indicator for predicting preHTN in men and women was BRI. However, differential indices for HTN were observed between men and women. The principal predictors for HTN in men were ABSI (AUC = 0.777) and $W/Ht^3$ (AUC = 0.771), while in women the principal predictors for HTN were CI (AUC = 0.737) and ABSI (AUC = 0.729). These emergent indices have shown a better predictive value than traditional parameters such as VF (AUC = 0.674 and 0.681) and WHtR (AUC = 0.661 and 0.635) among men and women (Supplementary Table S1).

When we evaluated the predictive value of the indices for preHTN and HTN according to sex and age range, we proved that in young men (≤40 years old) the predictor of preHTN was AVI (AUC = 0.680). Meanwhile, for HTN, the predictor was BRI (AUC = 0.702). On the other hand, for women in the same age range, the best predictor for preHTN was wBMI (AUC = 0.672), while for HTN it was PMI (AUC = 0.909) (Table 4). In Supplementary Table S2, we observed that WC (AUC = 0.682) shows a similar predictive value for preHTN in comparison with AVI.

Conversely, in men >40 years old, the best predictors of preHTN were $W/Ht^3$ (AUC = 0.670) and $W/Ht^2$ (AUC = 0.667), while for HTN, the best predictors were $W/Ht^3$ (AUC = 0.748) and $W/Ht^2$ (AUC = 0.730). Meanwhile, in women >40 years old, the best predictor of preHTN was CI (AUC = 0.580), while for HTN, the best predictors were ABSI (AUC = 0.685) and CI (AUC = 0.683) (Table 5). $W/Ht^3$

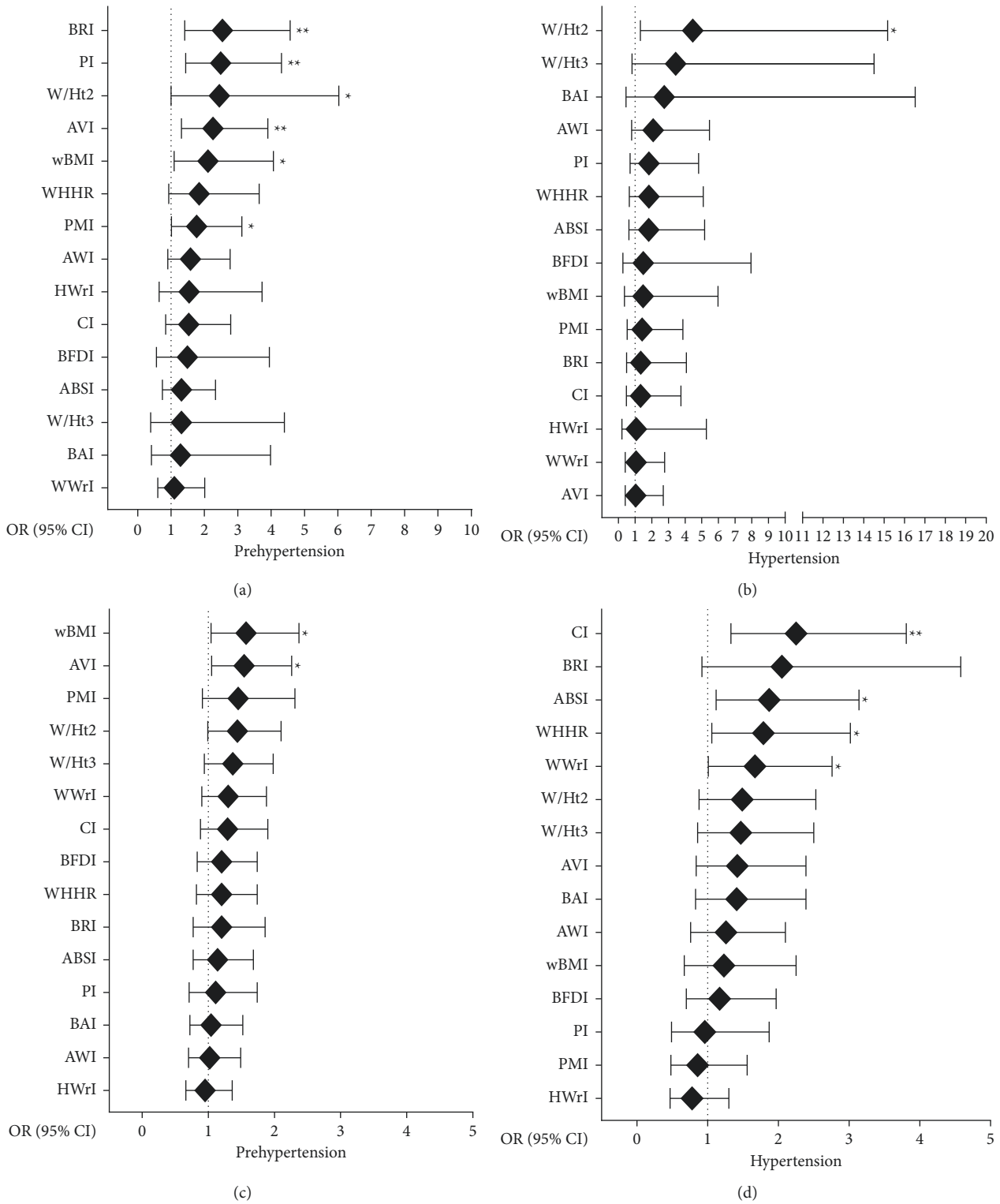


Figure 1: Association of emergent anthropometric indices with preHTN and HTN in men (a, b) and women (c, d). ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BRI, body roundness index; CI, conicity index; $Ht^3/W^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; wBMI, waist corrected BMI; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; $W/Ht^2$, waist to height square; $W/Ht^3$, waist to height cubic. Data shown represent the odds ratio (confidential interval of 95%). Model adjusted by age. $^*p$ value <0.05 and $^{**}p \leq 0.01$ are statistically significant.

Table 2: Predictive value of the emergent anthropometric indices to preHTN and HTN in the total sample.

| Variables | PreHTN (AUC, 95% CI) | Variables | HTN (AUC, 95% CI) |
|---|---|---|---|
| AVI (L) | 0.645 (0.640–0.651)** | CI (UA) | 0.692 (0.686–0.698)** |
| wBMI (kg/m) | 0.641 (0.635–0.646)** | ABSI ($m^{11/6}kg^{-2/3}$) | 0.687 (0.681–0.693)** |
| BRI | 0.634 (0.628–0.639)** | BRI | 0.656 (0.650–0.662)** |
| CI (UA) | 0.616 (0.611–0.622)** | WHHR ($m^{-1}$) | 0.653 (0.647–0.660)** |
| PI | 0.611 (0.605–0.616)** | W/Ht$^2$ (cm/m$^2$) | 0.648 (0.641–0.654)** |
| W/Ht$^2$ (cm/m$^2$) | 0.607 (0.602–0.613)** | W/Ht$^3$ (cm/m$^3$) | 0.634 (0.628–0.641)** |
| WHHR ($m^{-1}$) | 0.600 (0.595–0.606)** | AVI (L) | 0.630 (0.624–0.636)** |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.589 (0.583–0.595)** | AWI (cm) | 0.615 (0.608–0.621)** |
| W/Ht$^3$ (cm/m$^3$) | 0.585 (0.579–0.591)** | WWrI (cm) | 0.602 (0.596–0.608)** |
| WWrI (cm) | 0.582 (0.577–0.588)** | BAI | 0.597 (0.591–0.603)** |
| BFDI (m) | 0.579 (0.573–0.585)** | BFDI (m) | 0.594 (0.588–0.601)** |
| BAI | 0.568 (0.563–0.574)** | wBMI (kg/m) | 0.588 (0.582–0.594)** |
| PMI | 0.559 (0.554–0.565)** | PI | 0.584 (0.577–0.590)** |
| AWI (cm) | 0.551 (0.545–0.557)** | PMI | 0.513 (0.506–0.519)** |
| HWrI (cm) | 0.496 (0.490–0.502)** | HWrI (cm) | 0.499 (0.493–0.506)** |

ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BRI, body roundness index; CI, conicity index; Ht$^3$/W$^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; wBMI, waist corrected BMI; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; W/Ht$^2$, waist to height square; W/Ht$^3$, waist to height cubic. Data shown are the receiver operating characteristic distribution of the areas under curves considering the criterion variables prehypertension (SBP: 120–139 mmHg/DBP: 80–89 mmHg) and hypertension (SBP: ≥140 mmHg/DBP: ≥90 mmHg). Adjusted by age. ** $p$ value ≤0.01.

Table 3: Predictive value of the emergent anthropometric indices of preHTN and HTN according to sex.

| Variables | PreHTN (AUC, 95% CI) | Variables | HTN (AUC, 95% CI) |
|---|---|---|---|
| *Men* | | | |
| BRI | 0.661 (0.650–0.672)** | ABSI ($m^{11/6}kg^{-2/3}$) | 0.777 (0.765–0.788)** |
| W/Ht$^2$ (cm/m$^2$) | 0.653 (0.642–0.664)** | W/Ht$^3$ (cm/m$^3$) | 0.771 (0.759–0.783)** |
| AVI (L) | 0.650 (0.639–0.661)** | W/Ht$^2$ (cm/m$^2$) | 0.767 (0.754–0.779)** |
| PI | 0.648 (0.637–0.658)** | CI (UA) | 0.766 (0.755–0.788)** |
| wBMI (kg/m) | 0.645 (0.634–0.655)** | WHHR ($m^{-1}$) | 0.752 (0.739–0.766)** |
| WHHR ($m^{-1}$) | 0.639 (0.628–0.650)** | BRI | 0.742 (0.729–0.754)** |
| CI (UA) | 0.639 (0.628–0.649)** | BAI | 0.727 (0.714–0.739)** |
| W/Ht$^3$ (cm/m$^3$) | 0.637 (0.626–0.648)** | AWI (cm) | 0.722 (0.709–0.735)** |
| WWrI (cm) | 0.628 (0.617–0.639)** | BFDI (m) | 0.709 (0.697–0.721)** |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.620 (0.609–0.631)** | AVI (L) | 0.673 (0.660–0.685)** |
| BAI | 0.618 (0.607–0.629)** | PI | 0.685 (0.672–0.698)** |
| BFDI (m) | 0.617 (0.606–0.628)** | wBMI (kg/m) | 0.639 (0.626–0.652)** |
| AWI (cm) | 0.608 (0.597–0.619)** | WWrI (cm) | 0.634 (0.619–0.648)** |
| HWrI (cm) | 0.544 (0.533–0.555)** | PMI | 0.487 (0.474–0.501)** |
| PMI | 0.506 (0.495–0.517)** | HWrI (cm) | 0.510 (0.495–0.525)** |
| *Women* | | | |
| BRI | 0.635 (0.628–0.641)** | CI (UA) | 0.737 (0.730–0.744)** |
| AVI (L) | 0.630 (0.623–0.636)** | ABSI ($m^{11/6}kg^{-2/3}$) | 0.729 (0.721–0.736)** |
| W/Ht$^2$ (cm/m$^2$) | 0.628 (0.621–0.634)** | W/Ht$^2$ (cm/m$^2$) | 0.712 (0.705–0.720)** |
| CI (UA) | 0.624 (0.617–0.631)** | W/Ht$^3$ (cm/m$^3$) | 0.709 (0.702–0.717)** |
| wBMI (kg/m) | 0.618 (0.612–0.625)** | BRI | 0.708 (0.701–0.715)** |
| W/Ht$^3$ (cm/m$^3$) | 0.618 (0.611–0.625)** | WHHR ($m^{-1}$) | 0.702 (0.694–0.710)** |
| BFDI (m) | 0.611 (0.604–0.617)** | AVI (L) | 0.678 (0.670–0.685)** |
| BAI | 0.608 (0.601–0.614)** | BAI | 0.669 (0.661–0.677)** |
| WHHR ($m^{-1}$) | 0.603 (0.596–0.610)** | BFDI (m) | 0.653 (0.645–0.661)** |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.600 (0.593–0.607)** | WWrI (cm) | 0.640 (0.632–0.648)** |
| PI | 0.599 (0.593–0.606)** | AWI (cm) | 0.631 (0.622–0.639)** |
| WWrI (cm) | 0.574 (0.567–0.581)** | PI | 0.624 (0.616–0.632)** |
| PMI | 0.545 (0.538–0.552)** | wBMI (kg/m) | 0.623 (0.616–0.631)** |
| AWI (cm) | 0.537 (0.530–0.544)** | PMI | 0.505 (0.496–0.514)** |
| HWrI (cm) | 0.509 (0.502–0.516)** | HWrI (cm) | 0.497 (0.488–0.505)** |

ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BRI, body roundness index; CI, conicity index; Ht$^3$/W$^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; wBMI, waist corrected BMI; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; W/Ht$^2$, waist to height square; W/Ht$^3$, waist to height cubic. Data shown are the receiver operating characteristic distribution of the areas under curves considering the criterion variables prehypertension (SBP: 120–139 mmHg/DBP: 80–89 mmHg) and hypertension (SBP: ≥140 mmHg/DBP: ≥90 mmHg). Adjusted by age. ** $p$ value ≤0.01.

Table 4: Predictive value of the emergent anthropometric indices for preHTN and HTN by gender in ≤40 years old.

| Variables | PreHTN (AUC, 95% CI) | Variables | HTN (AUC, 95% CI) |
|---|---|---|---|
| *Men ≤40 years old* | | | |
| AVI (L) | 0.680 (0.581–0.779)* | BRI | 0.702 (0.605–0.799)* |
| WWrI (cm) | 0.655 (0.555–0.755)* | $W/Ht^2$ ($cm/m^2$) | 0.689 (0.595–0.783)* |
| HWrI (cm) | 0.654 (0.553–0.756)* | wBMI (kg/m) | 0.702 (0.565–0.839) |
| CI (UA) | 0.650 (0.549–0.750)* | PI | 0.683 (0.430–0.935) |
| wBMI (kg/m) | 0.650 (0.546–0.754)† | AVI (L) | 0.679 (0.578–0.780)* |
| BRI | 0.624 (0.518–0.731)† | WHHR ($m^{-1}$) | 0.666 (0.497–0.835) |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.621 (0.514–0.728)† | PMI | 0.640 (0.125–1.000) |
| BFDI (m) | 0.604 (0.499–0.709)* | $W/Ht^3$ ($cm/m^3$) | 0.634 (0.536–0.731)* |
| PI | 0.588 (0.476–0.701) | BFDI (m) | 0.617 (0.473–0.761) |
| AWI (cm) | 0.587 (0.478–0.695)† | BAI | 0.611 (0.452–0.769) |
| $W/Ht^2$ ($cm/m^2$) | 0.568 (0.459–0.677)† | CI (UA) | 0.588 (0.172–1.000) |
| BAI | 0.560 (0.453–0.667)† | AWI (cm) | 0.585 (0.207–0.962) |
| PMI | 0.557 (0.454–0.661)* | ABSI ($m^{11/6}kg^{-2/3}$) | 0.565 (0.061–1.000) |
| $W/Ht^3$ ($cm/m^3$) | 0.540 (0.396–0.612)† | WWrI (cm) | 0.558 (0.047–1.000) |
| WHHR ($m^{-1}$) | 0.467 (0.361–0.573)† | HWrI (cm) | 0.521 (0–1.000) |
| *Women ≤40 years old* | | | |
| wBMI (kg/m) | 0.672 (0.580–0.763)* | PMI | 0.909 (0.797–1.000)† |
| AVI (L) | 0.667 (0.577–0.757)* | BFDI (m) | 0.772 (0.625–0.918) |
| PI | 0.665 (0.572–0.757)* | BAI | 0.761 (0.649–0.873)† |
| BRI | 0.662 (0.569–0.755)* | PI | 0.743 (0.555–0.931) |
| PMI | 0.650 (0.653–0.736)* | BRI | 0.734 (0.530–0.939) |
| BFDI (m) | 0.645 (0.555–0.736)* | wBMI (kg/m) | 0.722 (0.505–0.939) |
| $W/Ht^2$ ($cm/m^2$) | 0.641 (0.545–0.737)* | AVI (L) | 0.718 (0.476–0.961) |
| BAI | 0.635 (0.543–0.727)* | $W/Ht^2$ ($cm/m^2$) | 0.713 (0.546–0.880) |
| WWrI (cm) | 0.631 (0.542–0.719)* | $W/Ht^3$ ($cm/m^3$) | 0.674 (0.511–0.837) |
| $W/Ht^3$ ($cm/m^3$) | 0.624 (0.523–0.724)* | CI (UA) | 0.645 (0.378–0.911) |
| WHHR ($m^{-1}$) | 0.604 (0.499–0.709)† | ABSI ($m^{11/6}kg^{-2/3}$) | 0.576 (0.299–0.854) |
| CI (UA) | 0.602 (0.512–0.693)* | WHHR ($m^{-1}$) | 0.552 (0.283–0.820) |
| HWrI (cm) | 0.570 (0.477–0.663)* | WWrI (cm) | 0.549 (0.275–0.824) |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.568 (0.477–0.659)* | HWrI (cm) | 0.496 (0.262–0.730) |
| AWI (cm) | 0.561 (0.459–0.664)* | AWI (cm) | 0.409 (0.170–0.649) |

ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BRI, body roundness index; CI, conicity index; $Ht^3/W^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; wBMI, waist corrected BMI; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; $W/Ht^2$, waist to height square; $W/Ht^3$, waist to height cubic. Data shown are the receiver operating characteristic distribution of the areas under curves considering the criterion variables prehypertension (SBP: 120–139 mmHg/DBP: 80–89 mmHg) and hypertension (SBP: ≥140 mmHg/DBP: ≥90 mmHg). Adjusted by age. *$p$ value ≤0.05, and †$p$value = 0.05.

appears to represent an emergent index in men >40 years old better than WHtR for preHTN and HTN. While in women >40 years old, the CI and ABSI represent better predictors than VF and WHR (Supplementary Table S2).

## 4. Discussion

The predictive value for preHTN and HTN of sixteen emergent anthropometric indices was demonstrated in this study. The main finding was that the body fat distribution indices had the highest predictive power for preHTN and HTN. However, a differential predictive value of CI, PMI, $W/Ht^3$, $W/Ht^2$, and ABSI was observed for preHTN and HTN between men and women according to age range.

In this study, the prevalence of preHTN is similar to that reported by Guzmán-Guzmán et al. [2] and lower than the one reported by Rodríguez-Reyes et al. [7]. Campos-Nonato et al. [9] reported 49.2% of HTN in Mexican population. Similar data are reported in several countries. The prevalence of HTN in Indian population, US adults, and Shandong province in China is 40.6% [30], 46.1% [31], and 55.1% [32], respectively. On the other hand, Kibria et al. [33] reported comparable data for the preHTN and HTN in the 2016 Nepal Demographic and Health Survey. The principal factors associated with the development of preHTN and HTN were older age, higher BMI index, high levels of total cholesterol and triglycerides, drinking habits [32, 33], and factors related to central obesity and body fat [2].

In Mexican women, traditional anthropometric indices such as the WC and BMI have been considered the better predictors of CVR, whereas the WHR is a better predictor in men [34]. A cross-sectional study of Italian patients from the Department of Preventive Cardiology proved that the emergent anthropometric index wBMI, along with BMI, WC, and WHtR are related to the patterns of adverse cardiac remodelling, increased arterial stiffness, insulin resistance, and an unfavourable lipid profile [25]. In this sense, the traditional anthropometric indices such as WHtR have been considered the best predictors of at least one cardiometabolic disorder, such as HTN, type 2 diabetes (T2D), metabolic syndrome, dyslipidemia, and hyperuricemia in both sexes [15]. Choi et al. [17] found that the WHtR and

Table 5: Predictive value of the emergent anthropometric indices for preHTN and HTN by gender in >40 years old.

| Variables | PreHTN (AUC, 95% CI) | Variables | HTN (AUC, 95% CI) |
|---|---|---|---|
| *Men >40 years old* | | | |
| $W/Ht^3$ ($cm/m^3$) | 0.670 (0.574–0.766)* | $W/Ht^3$ ($cm/m^3$) | 0.748 (0.634–0.862)† |
| $W/Ht^2$ ($cm/m^2$) | 0.667 (0.570–0.763)* | $W/Ht^2$ ($cm/m^2$) | 0.730 (0.610–0.850) |
| WHHR ($m^{-1}$) | 0.659 (0.563–0.755)* | ABSI ($m^{11/6}kg^{-2/3}$) | 0.708 (0.600–0.817)† |
| PI | 0.636 (0.539–0.734)* | BAI | 0.708 (0.592–0.823) |
| BRI | 0.636 (0.538–0.733)* | WHHR ($m^{-1}$) | 0.704 (0.580–0.828) |
| BAI | 0.634 (0.535–0.733)* | CI (UA) | 0.694 (0.579–0.808) |
| BFDI (m) | 0.606 (0.506–0.706)* | BRI | 0.684 (0.560–0.807) |
| wBMI (kg/m) | 0.588 (0.487–0.688)* | BFDI (m) | 0.677 (0.560–0.794) |
| CI (UA) | 0.586 (0.485–0.687)* | AWI (cm) | 0.656 (0.536–0.775) |
| AVI (L) | 0.585 (0.484–0.686)* | PI | 0.639 (0.515–0.764) |
| WWrI (cm) | 0.579 (0.477–0.681)* | AVI (L) | 0.578 (0.455–0.700) |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.564 (0.463–0.666)* | wBMI (kg/m) | 0.552 (0.426–0.678) |
| AWI (cm) | 0.551 (0.449–0.653)* | WWrI (cm) | 0.548 (0.419–0.677) |
| HWrI (cm) | 0.515 (0.413–0.618)* | HWrI (cm) | 0.501 (0.374–0.627) |
| PMI | 0.469 (0.367–0.572)* | PMI | 0.458 (0.338–0.578) |
| *Women >40 years old* | | | |
| CI (UA) | 0.580 (0.521–0.638)* | ABSI ($m^{11/6}kg^{-2/3}$) | 0.685 (0.620–0.749)* |
| AVI (L) | 0.569 (0.511–0.627)* | CI (UA) | 0.683 (0.620–0.746)* |
| BRI | 0.569 (0.511–0.627)* | $W/Ht^3$ ($cm/m^3$) | 0.641 (0.574–0.709)* |
| ABSI ($m^{11/6}kg^{-2/3}$) | 0.564 (0.504–0.623)* | $W/Ht^2$ ($cm/m^2$) | 0.641 (0.574–0.708)* |
| $W/Ht^2$ ($cm/m^2$) | 0.561 (0.503–0.620)* | WHHR ($m^{-1}$) | 0.656 (0.589–0.723)* |
| wBMI (kg/m) | 0.555 (0.496–0.613)* | BRI | 0.636 (0.570–0.702)* |
| WHHR ($m^{-1}$) | 0.554 (0.496–0.612)* | AWI (cm) | 0.608 (0.538–0.677)* |
| $W/Ht^3$ ($cm/m^3$) | 0.552 (0.493–0.611)* | AVI (L) | 0.607 (0.542–0.673)* |
| BFDI (m) | 0.540 (0.481–0.598)* | WWrI (cm) | 0.599 (0.533–0.666)* |
| BAI | 0.536 (0.476–0.595)* | BAI | 0.586 (0.515–0.657)* |
| WWrI (cm) | 0.531 (0.471–0.591)* | BFDI (m) | 0.570 (0.500–0.640)* |
| PI | 0.527 (0.468–0.587)* | wBMI (kg/m) | 0.552 (0.484–0.621)* |
| AWI (cm) | 0.509 (0.449–0.569)* | PI | 0.548 (0.477–0.618)* |
| PMI | 0.504 (0.445–0.563)* | HWrI (cm) | 0.473 (0.402–0.543)* |
| HWrI (cm) | 0.480 (0.420–0.539)* | PMI | 0.468 (0.396–0.540)* |

ABSI, a body shape index; AVI, abdominal volume index; AWI, arm-waist index; BAI, body adiposity index; BFDI, body fat distribution index; BRI, body roundness index; CI, conicity index; $Ht^3/W^3$, height cubic to waist cubic; HWrI, hip-wrist index; PI, ponderal index; PMI, pulse mass index; wBMI, waist corrected BMI; WWrI, waist-wrist index; WHHR, waist to hip to height ratio; $W/Ht^2$, waist to height square; $W/Ht^3$, waist to height cubic. Data shown are the receiver operating characteristic distribution of the areas under curves considering the criterion variables prehypertension (SBP: 120–139 mmHg/DBP: 80–89 mmHg) and hypertension (SBP: ≥140 mmHg/DBP: ≥90 mmHg). Adjusted by age. *$p$*$p$-value ≤0.05, †$p$ value = 0.05.

BRI displayed an equal predictive power for HTN. In this context, Chang et al. [14] reported that emergent anthropometric indices such as ABSI and BRI are associated with HTN. These data are consistent with our study. Moreover, Adegoke et al. [16] reported that indices of central adiposity (AVI, WC, WHtR, and BRI) were the strongest predictors of HTN. For preHTN, the most strongly related indices are WC, BMI, and WHtR, and PI [20, 35]. However, despite the simplicity and economic ease to evaluate these emergent anthropometric indices, not all of them are of common use in population's screening for CVR factors.

This study showed that emergent anthropometric indices such as BRI, as well as CI, $W/Ht^2$, and AVI are associated with the presence of preHTN and HTN. However, CI was consistently correlated with SBP and DBP despite the moderate predictive value in preHTN, while PMI was an emergent index related to HTN, principally in women ≤40 years old. A previous study demonstrated that CI is mostly associated with the development of HTN in men [18], similar to the data shown in our study, whereas in women, CI has been correlated with SBP ($r = 0.29$; $p < 0.01$) and DBP ($r = 0.20$; $p < 0.01$). It has been identified in urban women from Delhi [19] and Nigeria (SBP, $r = 0.114$; $p < 0.01$ and DBP, $r = 0.119$; $p < 0.01$) [16] as well as with SBP ($r = 0.22$; $p < 0.05$) in menopausal women from Iran [36], and with HTN and T2D in women from Brazil [18, 37]. Although it has been proven that CI has a higher predictive value for HTN in women [38] than in adult men [39], it appears to have a limiting predictive value in young populations [40]. These results are in concordance with our findings in women ≥40 years old, in which potentially hormonal changes related to decreasing estrogen levels also contribute to fat gain and redistribution of total body fat toward the central abdominal region, revealing the loss of the cardioprotection status that characterizes the incidence of HTN related to sexual dimorphism [41, 42]. Also, a cross-sectional study in adults from northern Iran determined that CI had a more discriminatory accuracy for 10-year-old cardiovascular events

compared to WC, WHtR, and AVI [43], and for coronary risk [44]. Therefore, future research should evaluate the effect of CI on blood pressure in a variable context of sex and age, ancestry, and nutritional factors in different populations.

In the present study, according to the prediction value, ABSI > $W/Ht^3$>$W/Ht^2$>CI showed predictive ability for HTN, while BRI > $W/Ht^2$>AVI > PI for preHTN in men. In other studies, the emergent indices reported as predictors for HTN in men were BAI > WHHR > ABSI [23], BRI > ABSI [13, 14], AVI > BRI [16], CI > BAI [18], CI [45, 46], and WrC [47], whereas for preHTN it was PI > BAI [20]. The predictive value for ABSI and CI was consistent between populations [14, 17, 38, 39]. However, our study shows that the $W/Ht^3$ and $W/Ht^2$ indices have a potential predictive value for HTN, while that $W/Ht^2$ and PI were consistent markers for preHTN and could be useful for screening impaired blood pressure in the population with similar somatometric characteristics.

Interestingly, in this study, PMI was associated with preHTN and HTN. PMI is considered an emergent CVR marker. Koch et al. [48] reported that a PMI >1 is related to susceptibility to suffering CVD over a period of 5 years. In women with generalized lupus erythematosus, the PMI was considered a predictor of CVD [49]. The relation of PMI on the CVD prognostic can be associated with preHTN and development of HTN mainly in young women. Besides, in women, we found that CI > ABSI > $W/Ht^2$ have predictive power for HTN, while that BRI > AVI > $W/Ht^2$>CI for preHTN. Other emergent anthropometric indices related to adiposity have been consistently reported as predictors of HTN in women of other populations, among them we found that BAI > WHHR > ABSI [23], BRI > ABSI [13, 14], AVI > BRI [16], CI > BAI [18], CI [39, 45, 46, 50], and PI > BAI for preHTN [20]. The predictive value of indices related to central obesity can be explained by several mechanisms, including the biological function of adipokines and cytokines, such as adiponectin, tumor necrosis factor-$\alpha$, and leptin, principally in woman [51] by the stimulation of the renin-angiotensin system, considered one of the essential mechanisms in obesity-related HTN [52].

In this study, we observed that age and being male are biological variables associated with HTN and preHTN and have a differential predictive value for anthropometric indices. It is important to consider that these indicators are easy to measure, noninvasive, and inexpensive, and their clinical value is relevant, so they should be included as routine evaluations in clinics and health campaigns. It is also important to emphasize that the specific use of indices according to sex and age range could increase the screening for risk of preHTN and HTN in populations and could be useful for implementing intervention measures. The limitation of this study was that the measurements of biochemical-metabolic parameters were not included. Furthermore, the cutoff values for risk categories in this study can vary in other populations.

## 5. Conclusions

In conclusions, the body adiposity distribution indices predict preHTN in men and women. Nevertheless, emergent indices such as CI, PMI, $W/Ht^3$, $W/Ht^2$, and ABSI could represent differential predictors of preHTN and HTN according to sex and age range and could be implemented to perform high blood pressure screenings in the population.

## Data Availability

The data used to support the findings of the study can be obtained from the corresponding author.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

I.P.G.-G. conceptualized the study. I.P.G.-G., I.A.G.-P., and O.Z.-G. developed the methodology. O.Z.-G. and I.A.G.-P. helped with software. I.P.G.-G. validated the study. I.A.G.-P. and O.Z.-G. formally analysed the study. O.Z.G., I.A.G.-P., P.D.F., D.J.-M., and I.P.G.-G. investigated the study. I.P.G.-G., I.A.G.-P., and O.Z.-G. wrote and prepared the original draft. I.P.G.-G., O.Z.-G., I.A.G.-P., P.D.-F., D.J.-M., I.P.-R, and C.C.-J. wrote, reviewed, and edited the study. I.P.G.-G. visualized the study. I.P.G.-G. supervised the study. All authors have read and agreed to the published version of the manuscript. Oscar Zaragoza-García and Ilse Adriana Gutiérrez-Pérez these authors contributed equally to this work.

## Supplementary Materials

Supplementary Table 1: Predictive value of the traditional anthropometric indices for preHTN and HTN by the total sample and sex. Supplementary Table 2: Predictive value of the traditional anthropometric indices for preHTN and HTN by gender and age. (*Supplementary Materials*)

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*Review Article*

# The Bidirectional Signal Communication of Microbiota-Gut-Brain Axis in Hypertension

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Hypertension is a critical risk factor of cardiovascular diseases. A new concept of microbiota-gut-brain axis has been established recently, mediating the bidirectional communication between the gut and its microbiome and the brain. Alterations in bidirectional interactions are believed to be involved in the blood pressure regulation. Neuroinflammation and increased sympathetic outflow act as the descending innervation signals from the brain. Increased sympathetic activation plays a recognized role in the genesis of hypertension. The present evidence demonstrates that gut dysbiosis is associated with central nervous system neuroinflammation. However, how the gut influences the brain remains unclear. We reviewed the roles of neuroinflammation and gut microbiota and their interactions in the pathogenesis of hypertension and described the ascending signaling mechanisms behind the microbiota-gut-brain axis in detail. Additionally, the innovative prohypertensive mechanisms of dietary salt through the microbiota-gut-brain axis are summarized. The bidirectional communication mechanisms were proposed for the first time that the descending signals from the brain and the ascending connections from the gut form a vicious circle of hypertension progression, acting as a premise for hypertension therapy.

## 1. Introduction

Researchers estimated mortality from cardiovascular diseases, chronic kidney disease, and diabetes all over the world from 1980 to 2010, and high blood pressure (BP) was the leading risk factor for deaths due to these diseases throughout the analysis period [1]. Therefore, innovative approaches to effectively prevent and manage hypertension are urgently needed. Microbiota-gut-brain axis refers to a bidirectional communication between the gut microbiota (GM) and the brain [2]. Alterations in this bidirectional interactions are believed to be involved in BP regulation, which may provide a new way to treat hypertension in the near future [3].

Cardiovascular brain centers regulate BP by controlling sympathetic and parasympathetic activities. As the sympathetic nervous system innervates multiple organs, it controls key pathophysiological processes in the BP regulation such as vasoconstriction, water-sodium balance, and renin-angiotensin system (RAS) activity and regulates systemic inflammation status by innervating the gut and bone marrow [4]. Neuroinflammation of the central nervous system (CNS) leads to increased sympathetic activation. Recent study highlighted that the alterations of GM composition associated with the neuroinflammation and sympathetic nervous system to mediate BP regulation [5]. The evidence suggests a potential linking axis between the GM and neuroinflammation in the CNS.

Recent basic and clinical findings indicate that gut dysbiosis is a novel causation of hypertension initiation and development. The evidences include (1) reciprocal interactions between the GM and cardiovascular disease risk factors (such as obesity, insulin resistance, and chronic inflammation) [6]; (2) the remarkable alterations of the GM in hypertensive cohorts and experimental models [7–10]; (3) fecal transplantation evidence [8, 11]; (4) antihypertensive properties of intervention strategies to correct gut dysbiosis.

An increased Firmicutes/Bacteroidetes ratio and a significant decrease in microbial richness, diversity, evenness, and short-chain fatty acids (SCFAs)-producing bacteria in

the spontaneously hypertensive rats (SHRs) have been described [12]. Additionally, another study has showed taxonomic and functional changes in the gut microbiome, especially the significant reduction in butyrate-producing bacteria, aberrant gut barrier function, and increased local inflammation in hypertensive patients [13]. Compared to healthy controls, both prehypertensive and hypertensive populations show decreased microbial richness and diversity, distinct metagenomic composition with reduced bacteria associated with healthy status and overgrowth of harmful bacteria, and disease-linked microbial functions [8]. As an efficient method to demonstrate the causal role of the GM in hypertension, fecal transplantation can regulate BP in different animal models [7, 9]. Hypertension could be induced in a normotensive strain (normotensive Wistar–Kyoto (WKY), normotensive OSA) of rats or attenuated in a hypertensive strain [SHRs, hypertensive OSA] of rats by exchanging the GM between the two strains [7, 9]. Also, by fecal transplantation from hypertensive human donors to germ-free mice, high BP was observed to be transferrable through the GM [8].

Salt, as one of the most common prohypertensive factors, added or inherent to food contributes to nearly 99% of the total sodium intake [14]; thus, the effects of dietary salt on the GM and brain need to be elucidated. Recent studies demonstrated that excess salt intake exerts a certain effect on the composition of the GM [15]. Also, dietary salt is approved to cause neuroinflammation and sensitize central sympathetic circuits [14, 16]. However, the role of salt intake on the microbiota-gut-brain axis remains unclear.

The aim of this review is to provide a brief summary of the current knowledge with a focus on neuroinflammation, GM, and their interactions in the pathogenesis of hypertension, as well as the specific signaling mechanisms behind the microbiota-gut-brain axis, and to provide an innovative insight into prohypertensive mechanisms of dietary salt through the microbiota-gut-brain axis.

## 2. Neuroinflammation in Hypertension

The neuroinflammation in cardiovascular brain centers leads to the imbalance of sympathetic/parasympathetic activity, and increased sympathetic activation plays a recognized role in the genesis of hypertension. Increased sympathetic activation affects the target organs which regulate BP, such as the blood vessels, kidney, and heart [4], and also leads to the peripheral and central immune system inflammatory activation by directly stimulating bone marrow [17]. In addition, elevated sympathetic activity in the gut is able to change the components of the GM, contributing to the low-grade inflammation associated with hypertension [18] (Figure 1).

The schematic illustration shows that activated microglia regulate the autonomic nuclei circuits (PVN, NTS, and RVLM) in cardiovascular brain centers and cause neuroinflammation in these brain regions. The neuroinflammation in cardiovascular brain centers leads to the overdrive of the sympathetic system. The sympathetic nervous system innervates multiple organs (peripheral vasculature, kidney, bone marrow, and gut) and controls key pathophysiological process in the onset and progression of hypertension. Gut dysbiosis and central immune system activation in bone marrow associated with the overdrive of the sympathetic system lead to systemic inflammation. The SFO can sense peripheral pro-inflammatory cytokines, project directly to the PVN, and activate microglia, bridging the systemic inflammation and neuroinflammation. Abbreviations are as follows: hypothalamic paraventricular nucleus (PVN), rostral ventrolateral medulla (RVLM), nucleus tractus solitaries (NTS), and subfornical organ (SFO).

*2.1. Neuroinflammation in Cardiovascular Brain Centers.* Cardiovascular brain centers are located in the hypothalamus and brainstem, including several important nuclei such as the hypothalamic paraventricular nucleus (PVN), the rostral ventrolateral medulla, and the nucleus tractus solitaries (NTS). PVN is the predominant autonomic region that accumulates activated microglia exhibiting neuroinflammation in hypertension [19]. These nuclei influence BP by regulating the activity of the autonomic nervous system [20].

The observation that a variety of pro-inflammatory cytokines are upregulated in the cardiovascular brain region of hypertensive animals underscores the link between CNS neuroinflammation and hypertension [18]. Administration of pro-inflammatory factors such as tumor necrosis factor-(TNF)-$\alpha$ or interleukin-(IL)-1$\beta$ into cardiovascular brain centers can increase sympathetic tone, brain RAS activity, and BP, while central down-regulation of these factors has a significant opposite effect [21]. To explore the source of central pro-inflammatory cytokines and the specific cause of neuroinflammation in hypertension, it is important to emphasize the role of activated resident microglia.

*2.2. Activated Microglia in CNS Neuroinflammation.* Microglia are the only resident immune cells in the CNS and are known to participate in both innate and adaptive immune responses to infection and injury. However, activation of microglia can be a two-edged sword. Activated microglia produce many pro-inflammatory mediators—including cytokines, chemokines, reactive oxygen species, and nitric oxide—which contribute to the clearance of pathogen infections, but prolonged or excessive activation may result in pathological neuroinflammation [22]. Activated microglia show a universe of activation states, and M1 ("classical" activation) and M2 ("alternative" activation) represent extremes of this continuum [22].

Microglia can become activated and/or dysregulated in the context of hypertension and can exacerbate hypertension through augmenting neuronal excitation, such as the overdrive of the sympathetic neuron [23, 24]. Ang-II is one of the signals that can activate resident microglia in cardiovascular brain centers. In addition, many other prohypertensive factors have also been proved to be able to activate microglia [25]. This may partially illustrate the reason why microglia is activated in hypertension. Also, gut-derived lipopolysaccharide (LPS) acting as pathogen-associated

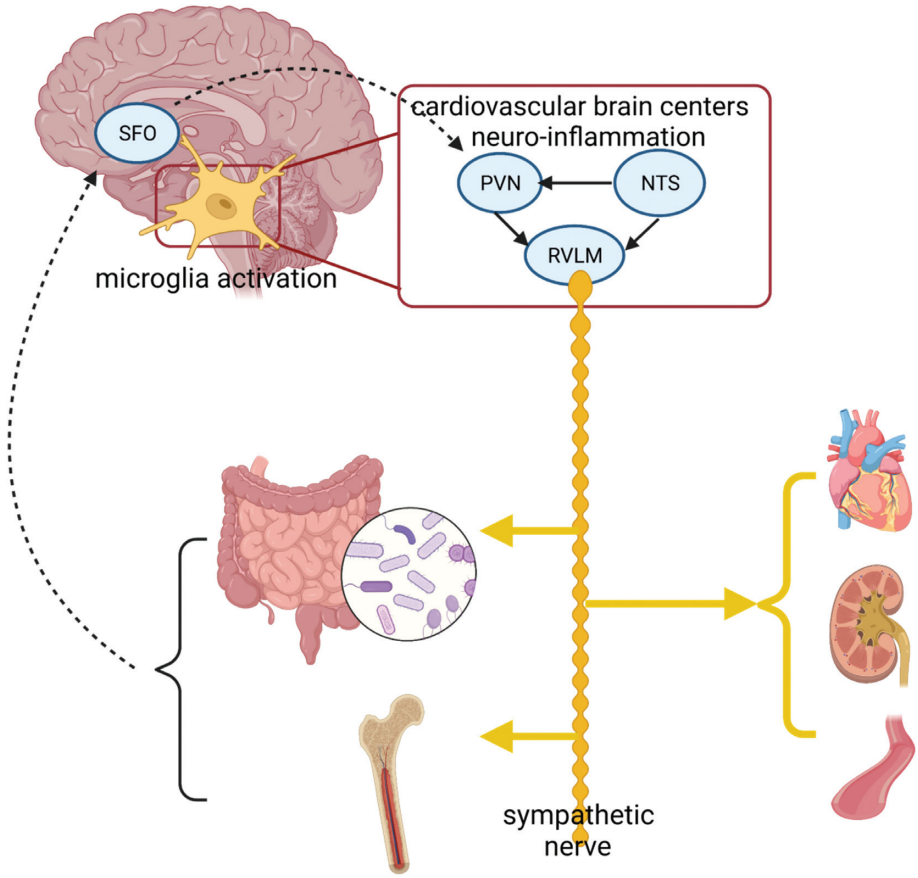


Figure 1: The hypothetic mechanisms of neuroinflammation-mediated bidirectional communication in the microbiota-gut-brain axis.

molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs) on the microglia membrane and activate the local immune response.

Though M1 microglia are thought to be associated with chronic inflammation disease states, the specific activation form of microglia in hypertension has not been determined. Using deoxycorticosterone acetate (DOCA)-salt-treated rat model mimicking sporadic and chronic hypertension, Koizumi et al. showed that microglia juxtaposed to the vessels directly switched to the pro-inflammatory M1 state after 3 weeks, differing from M2-to-M1 class switching in acute ischemic models [24]. However, in the model induced by either angiotensin II (Ang-II) or L-NG-nitro-l-arginine methyl ester (L-NAME), both M1 and M2 markers were upregulated [26]. The interactions among these signaling pathways and the specific molecule mechanisms mediating microglia activation in hypertension remain to be elucidated.

*2.3. Microglial Activation Exacerbates Hypertension.* Microglial activation in established hypertension is detrimental to neural homeostasis and exacerbates the disease [23]. Targeted depletion of microglia in PVN attenuated neuroinflammation and high BP caused by either Ang-II or L-NAME. By contrast, adoptive transfer of preactivated microglia into the brains of normotensive mice prolonged pressor responses [26]. Hypertension leads to cerebrovascular histopathological alterations including structural changes such as hypertrophy, remodeling, stiffening, and vascular regulation insufficiency [27]. Studies have proved that microglial activation preceded the appearance of histopathological abnormalities, thereby underscoring the possible role of microglia in the process of hypertension-induced cerebral vessel damage [24]. Considering these findings, we can conclude that microglial activation is one of the hallmarks and crucial regulating factors in the process of hypertension. As for what causes the activation of microglia, the gut is one of the key factors that cannot be ignored.

## 3. Signaling Mechanisms behind the Microbiota-Gut-Brain Axis

To highlight the complex communication between the gut, its microbiome, and the brain, the concept of the microbiota-gut-brain axis has been proposed [2]. Current evidence suggests that multiple mechanisms may be involved in GM-to-brain signaling and that the brain can in turn alter the GM via the autonomic nervous system [28]. Changes in these bidirectional interactions are believed to be involved in the pathogenesis of hypertension though the evidence is still limited [3]. In the following context, we proposed that enhanced sympathetic tone acts as the signal from the brain innervating multiple target organs of BP regulation, and

both the immune system and the vagus nerve contribute to the ascending connections in the microbiota-gut-brain axis (Figure 2).

The multiple routes of ascending connections between the gut microbiota and the brain are being revealed. Gut dysbiosis in the context of hypertension leads to the imbalance of circulatory anti-and pro-inflammatory mediators and host systemic inflammation. Systemic inflammation can directly or indirectly activate microglia and induce neuroinflammation. The colonic afferent vagus nerve projects to the cardiovascular brain center and is able to transmit a variety of gut signals to the CNS, modulating the important nuclei and their circuits involved in the control of autonomic nervous system activity. Abbreviations are as follows: LPS: lipopolysaccharides, TMAO: trimethylamine-N-oxide, and SCFAs: short-chain fatty acids.

*3.1. Gut Microbiota and Neuroinflammation.* A human individual carries up to 100 trillion resident bacteria, outnumbering the body cells tenfold [29]. The gut is one of the largest endocrine, immune, and neural organs in the body, constituting a huge substantial microbial habitat, and the gut flora has a metabolic activity equal to a virtual organ within an organ [30, 31]. Accumulating evidence has revealed an important role of the GM in the development of hypertension [32].

The GM can establish efficient crosstalk with the rest of the body and influence the host inflammatory status through a number of mediators because a significant part of the metabolites in circulation are derived from the GM [33]. There are experimental data to show that changes of the GM composition are able to influence the neuroinflammation in cardiovascular brain centers, acting as the ascending connection in the microbiota-gut-brain axis [5].

SCFAs are a kind of organic fatty acid with less than six carbon atoms [34]. As the byproducts of bacterial fermentation of nondigestible carbohydrates and resistant starch, the SCFAs acetate, propionate, and butyrate are the most abundant [35, 36]. However, most gut-derived SCFAs are ingested by gut epithelial cells and hepatocytes, with only about 36%, 9%, and 2% of the acetate, propionate, and butyrate, respectively, reaching the systemic circulation to influence target organs and tissues, including the brain [37]. In addition to functioning in the CNS, SCFAs can interact with vagal nerve afferents which project to NTS, arguing for a potential key role of SCFAs in the microbiota-gut-brain axis [36]. Studies have shown that SCFAs are able to decrease BP through the abilities of anti-inflammation and neuroprotection [38]. Given that SCFAs are vital mediators by which the GM regulate the BP, it is reasonable to assume that using SCFAs directly may be a possible intervention of high BP. In the chronic Ang-II infusion hypertensive mouse model, butyrate supplementation could ameliorate high BP, consistent with the hypothesis [13]. Further interventional studies in humans are needed to determine whether there is a cause-and-effect relationship between SCFAs intake and reduced blood pressure.

*3.2. Ascending Connections through the Immune System.* The GM is able to manipulate the inflammatory status of the host through an array of mechanisms. Studies have found that in the context of hypertension: (1) GM-derived proinflammatory mediators increase, including LPS, trimethylamine-N-oxide (TMAO), and sulfate [39–41]; while anti-inflammatory mediators such as SCFAs decrease. The imbalance of anti-inflammatory and proinflammatory mediators in blood circulation leads to host systemic inflammation. (2) The GM can affect the gut epithelium in producing anti-inflammatory gut hormones and neurotransmitters in an indirect way [42]. Compared with the normotensive WKY rats, the SHRs showed a >30% increase in bone marrow and blood inflammatory cells [17]. Under many circumstances, the immune cells and cytokines of peripheral blood circulation can break the "barrier isolation" called the blood-brain barrier (BBB) to act on the brain. LPS plays a recognized role in activating systematic inflammation. In a hypertensive patient cohort, plasma LPS levels and gut-target proinflammatory T helper 17 (Th17) cells were significantly increased [13]. In SHR models, along with the increase in BP, studies observed increased intestinal permeability and decreased tight junction proteins [43]. Furthermore, the hypertensive gut microbiome exhibited higher LPS biosynthesis [10, 44]. Therefore, LPS produced by the GM increases in hypertensive patients as a result of microbiota dysbiosis, and more gut-derived LPS leak into blood circulation due to the increase in intestinal permeability worsen the systemic inflammation.

In humans, the systemic inflammation induced by intravenous injection of LPS activates microglia in the brain and leads to neuroinflammation [45]. Systemic LPS increase results in CNS neuroinflammation mainly through two pathways. As the BBB dysfunction can be found in the early stage or even before the onset of hypertension, systemic LPS can directly cross the aberrant BBB [46]. Microglia express PRRs that recognize various PAMPs including gut-derived LPS [22]. Following the recognition of PAMPs by microglia, PRR-mediated signal transduction induces the classical M1-like activation and innate immune response.

Also, gut-derived LPS can enter the blood circulation and binds to toll-like receptor 4 on innate immune cells, leading to the increase in peripheral proinflammatory cytokines. As a unique brain region that lacks a BBB, the subfornical organ (SFO) is an important brain sensor of peripheral proinflammatory cytokines, mediating their central effects on cardiovascular brain centers [47]. Microinjection of TNF-$\alpha$ or IL-1$\beta$ (mimicking systemically administered proinflammatory cytokines) into the SFO elevated the BP and sympathetic outflow [47]. The SFO projects directly to the PVN, and activates the microglia in the PVN [48]. This is likely why systemic inflammation can influence autonomic brain regions and cardiovascular function.

Along with LPS, trimethylamine-N-oxide (TMAO) is another proinflammatory mediator generated by the GM. Increased circulating levels of TMAO directly activates inflammatory pathways in cells of the vasculature, leading to endothelial cell leukocyte recruitment [39].

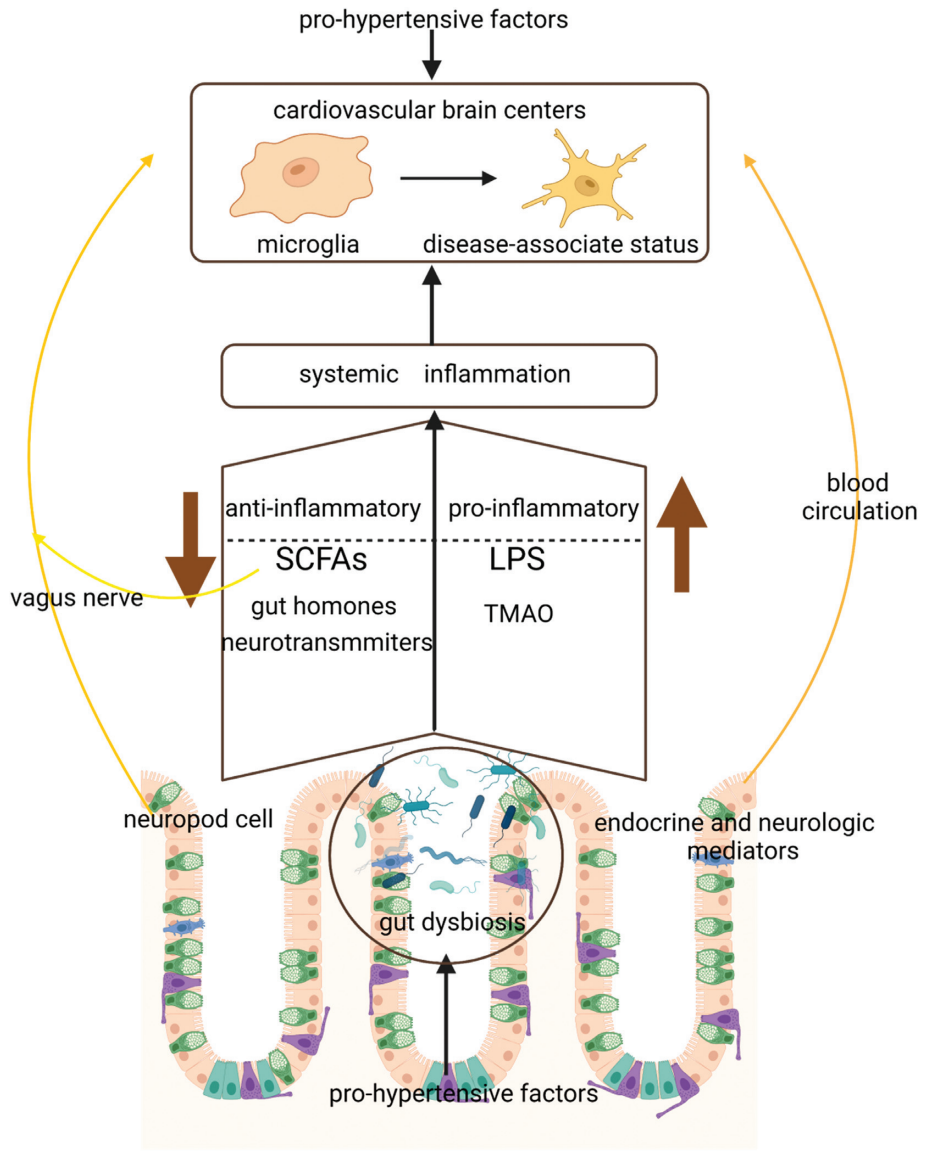


Figure 2: Ascending connections through the immune system and the vagus nerve in the microbiota-gut-brain axis.

SCFAs are able to decrease BP through the abilities of anti-inflammation and neuroprotection [38]. Acetate, propionate, and butyrate are detectable in the human cerebrospinal fluid at physiological concentrations [35]. Studies have shown that sodium butyrate mediates neuroprotection though modifying microglial activation modes [38]. Likewise, the acetate treatment of microglia in primary culture has been shown to reduce inflammatory signaling through downregulation of IL-1$\beta$ and TNF-$\alpha$ expression and p38 MAPK, JNK, and NF-$\kappa$B phosphorylation [49]. Gut-derived SCFAs exert an influence on hosts based on two major pathways: (1) SCFAs enter the target cells mediated by transporters (MCTs and SMCTs) and directly inhibit histone deacetylases (HDACs), consequently regulating the downstream gene expression, and (2) SCFAs bind to G protein-coupled receptors to activate related cellular signal transduction pathways [50–55]. Without G protein-coupled receptor corresponding to SCFAs on the microglial membrane, gut-derived SCFAs influence microglia based on HDAC inhibition. Gut-derived SCFAs acting as HDAC inhibitors exhibit immunosuppressive effects by epigenetically regulating the microglial inflammatory response [38]. Furthermore, reduced circulating butyrate levels caused by impaired transport colonic absorption and reduced responsiveness of the hypothalamic PVN have been found in SHRs [56]. Another research showed that reduction in butyrate-producing bacteria may lead to gut-barrier dysfunction and increase in systemic LPS [13]. SCFAs-producing species can exert the effects of anti-inflammation and neuroprotection by stimulating enteroendocrine cells to produce anti-inflammatory gut hormones, such as glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), and peptide YY (PYY), while some species can directly produce the anti-inflammatory neurotransmitters such as $\gamma$-aminobutyric acid (GABA) and acetylcholine (Ach) [33, 40].

Gut dysbiosis in the context of hypertension leads to the imbalance of circulatory anti- and proinflammatory mediators. Reduced anti-inflammatory mediators result in diminished neuroprotection and anti-inflammation ability. Circulatory LPS increases the level of neuroinflammation through the activation of systemic inflammation and direct recognition of PAMPs by microglia. Thus, the GM levies its effects on cardiovascular brain centers through the immune system, inducing microglial activation and central neuroinflammation.

*3.3. Ascending Connections through the Vagus Nerve.* The colonic afferent vagus nerve projects to the cardiovascular brain center and is able to transmit a variety of gut signals to the CNS, modulating the important nuclei and their circuits involved in the control of autonomic nervous system activity and BP. Specifically, the afferent signal directly projects to the NTS which can modulate the behaviour of the PVN, thus participating in the regulation of sympathetic nerve activity [57]. However, how the afferent vagus nerve can sense the gut signals remains poorly understood.

Electrically excitable sensory cells called the enteroendocrine cells are found dispersed within the gut epithelium, and most enteroendocrine cells communicate indirectly with nerves through hormone secretion but not through a direct synaptic link [58]. Recently, researchers have found a type of gut epithelial cell that forms synapses with vagal neurons and named them the "neuropod cell" [59]. Neuropod cells use glutamate as a neurotransmitter to transduce signals to vagal neurons connecting the gut lumen to the brainstem. Therefore, it can be assumed that specific gut epithelial cells can sense GM signals and transmit them to the cardiovascular brain center by means of nerve and hormone conduction.

In addition, although the vagus nerve cannot contact the GM directly, bacterial metabolites can act on the vagus nerve through the intestinal mucosal barrier. It is recognized that SCFA receptors are expressed in the afferent fibers of the vagus nerve [60]. Administering butyric acid into the colon to increase the concentration by 2-3-fold represents a significant hypotensive effect, and this effect depends on normal function of the afferent colonic vagus nerve and SCFA receptor, GPR41/43 [61]. In summary, SCFAs mediate the communication between the GM and the afferent colonic vagus nerve.

Based on these findings, the ascending connections through the vagus nerve can be transmitted to the brain through the synapses between gut epithelial sensory cells and vagal neurons or through the interaction between SCFAs and the afferent vagus fibers.

## 4. Sodium Salt Intake Influences the Microbiota-Gut-Brain Axis

The intestinal mucosa, loaded with rich immune cells and GM, is the first and main absorption site for excess salt. Diet-induced alterations in the GM have implicated influence on local gut immune systems, especially on T cells [62]. Th17 cells are most abundant at steady state in gut-associated lymphoid tissues, where they accumulate only in the presence of luminal commensal microbiota [63]. High salt intake has been approved to change the GM both in humans and mice, reflecting an increase in Firmicutes, Proteobacteria, and genus *Prevotella* bacteria which were associated with higher BP [15]. More specifically, high salt intake depletes *Lactobacillus murinus* (*L. murinus*) and treatment with *L. murinus* prevented salt-induced aggravation of experimental autoimmune encephalomyelitis and salt-sensitive hypertension by modulating Th17 cells; and also in humans, a moderate high-salt challenge reduced intestinal survival of *Lactobacillus* spp., increased Th17 cells, and increased BP [64]. Another study also linked the excess dietary salt with the GM, inflammation, and hypertension. GM alterations induced by high salt intake are associated with increased costimulatory ligand and IsoLG protein adduct formation in antigen-presenting cells (APCs), which leads to increased intestinal and vascular inflammation and hypertension [65].

Salt is thought to sensitize central sympathetic circuits. Elevations in plasma and cerebrospinal fluid (CSF) Na + enhance sympathetic nerve activity via the RVLM leading to increases in BP [66]. Nonetheless, potential "sensing" mechanisms for Na + existing in the brain have been elucidated using rodent models [67–69]. Central Na + sensing occurs in the circumventricular organs including the organum vasculosum of the lamina terminalis (OVLT) and SFO, which lack an intact BBB [67]. The SFO has been mentioned above as an important brain sensor of peripheral proinflammatory cytokines [47]. This coincidence suggests that both Na+ and inflammatory mediators contribute to neuroinflammation. Like SFO, the OVLT also projects to the PVN, which plays an essential role in regulating sympathetic nerve activation via neuronal projections to the RVLM.

In summary, excess dietary salt can alter the GM and activates gut local and systemic immune systems, and sensitize central sympathetic circuits to elevate BP. The more accurate mechanisms between salt and the microbiota-gut-brain axis need more basic and clinical investigations.

## 5. A Premise for Hypertension Therapy

As the microbiota-gut-brain axis plays an emerging role in hypertension, many studies have explored traditional antihypertensive treatments associated with this crosstalk and GM medication. Despite the breadth of emerging knowledge, current common control and treatment of hypertension are not targeting the overall dysfunctional axis, especially the brain.

Captopril is a classic antihypertensive drug, lowering BP through its suppressive effect on the RAS at both peripheral and central sites. However, recent studies demonstrated that captopril influences the microbiota-gut-brain axis to maintain the sustained antihypertensive effect after withdrawal, exerting significant long lasting influences on GM composition, gut permeability, and pathology as well as brain activity [70]. Similar studies are warranted to validate the translational implications of traditional antihypertensive drugs on the microbiota-gut-brain axis.

Interventions to correct the GM can be seen as an innovative nutritional therapeutic strategy by modulating the microbiota-gut-brain axis to exert the antihypertensive effects, though the effect of decreased CNS inflammation is indirect. Hypertensive OSA rats administered with the probiotic *C. butyricum* or the prebiotic Hylon VII exhibit increased fecal acetate concentration, reduced dysbiosis, and epithelial damage [71]. Blueberries fermented with the tannase-producing bacteria *L. plantarum* DSM 15313 have antihypertensive properties [72]. In elderly people who are initially normotensive, frequent intake of fermented probiotic milk products reduces the risk of developing hypertension [73]. The meta-analysis of nine studies showed that probiotic consumption makes a significant reduction of systolic BP by 3.56 mmHg and diastolic BP by 2.38 mmHg, when compared with the control groups [74]. In the Heart Outcomes Prevention Evaluation (HOPE) study, even modest reduction of systolic BP by 3.3 mm Hg and diastolic BP by 1.4 mmHg led to a significant 22% reduction in relative risk of cardiovascular mortality, myocardial infarction, or stroke [75].

Additionally, lifestyle improvements may be a power approach to ameliorate microbiota-gut-brain axis impairment to induce antihypertensive effects. For example, exercise was associated with improved gut pathology, inflammation, and permeability, enrichment of beneficial bacterial genera, and decreased brain neuroinflammation [76].

## 6. Conclusions

In this review, we focus on the signal communication in microbiota-gut-brain crosstalk associated with hypertension. The descending signal from the CNS is increased sympathetic output. The ascending connections include both the immune system and the vagus nerve. From the existing data, we proposed that hypertensive risk factors (genes, diet, and environment) lead to gut dysbiosis, and this signal transfer from the gut to brain, inducing microglial activation and followed by neuroinflammation. Besides, prohypertensive signals (diet, salt, stress, and Ang-II) perceived in cardiovascular brain centers also activate resident microglia and enhance sympathetic output. The sympathetic nervous system innervates multiple organs and controls key pathophysiological process in the onset and progression of hypertension. The pathological changes of the gut and its microbiome, at least partially caused by increased sympathetic outflow, in turn act on the brain through both immune and neural pathways, forming a vicious circle of hypertension progression. Dietary salt is one of the common prohypertensive factors and influence the microbiota-gut-brain axis in many aspects. Excess dietary salt can alter the GM, activates gut local and systemic immune systems, and sensitize central sympathetic circuits to elevate BP. Limited information is available on how these findings may translate to clinical applications in hypertension involving the microbiota-gut-brain axis, especially targeting the brain neuroinflammation. This new hypothesis is likely to fill fundamental knowledge gaps leading to innovative research, clinical trials, and treatments for hypertension in modulating the microbiota-gut-brain axis.

## Data Availability

All data supporting the conclusions of this review are published papers searched from PubMed. Others can access all the data through the DOIs provided in the references of this review.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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