

Effect of chronic angiotensin system inhibitor treatment on cardiovascular adaptations to exercise training in adults with metabolic syndrome

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Abstract

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are commonly prescribed alongside exercise to manage hypertension in individuals with metabolic syndrome (MetS). However, whether chronic renin–angiotensin system (RAAS) inhibition modifies exercise-induced physiological adaptations remains unclear. In this prospective parallel-group study, 62 sedentary adults with MetS completed a 16-week supervised high-intensity interval training (HIIT) program. Participants were either chronically treated with ACEi or ARBs (antihypertensive medication group, AHM, $n = 27$) or not receiving pharmacological treatment (CONTROL, $n = 35$). Primary outcomes included changes in resting and exercise blood pressure (BP), MetS components, and cardiorespiratory fitness (CRF). Both groups showed significant improvements over time in cardiometabolic health (MetS Z-score: AHM -0.22 ± 0.42 ; CONTROL -0.30 ± 0.33 ; $p < 0.001$) and CRF (VO_{2MAX} : AHM 3.9 ± 2.1 ; CONTROL 5.0 ± 3.1 mL·kg⁻¹·min⁻¹; $p = 0.003$), with no significant time $\times$ group interactions (all $p > 0.05$). Resting blood pressure decreased similarly in both groups (mean arterial pressure [MAP]: AHM -4.2 ± 8.7 ; CONTROL -6.5 ± 6.3 mmHg; $p = 0.005$; interaction $p > 0.05$). Exercise blood pressure responses also improved, with significant time effects for maximal MAP ($p = 0.008$) and submaximal diastolic BP ($p = 0.047$), without between-group differences (interaction $p > 0.05$). Chronic treatment with ACEi or ARBs does not appear to attenuate improvements in cardiometabolic health, BP, or CRF by 16 weeks of supervised HIIT in adults with MetS. These findings suggest that RAAS inhibition is compatible with structured exercise training, supporting HIIT as an effective adjunct therapy in individuals receiving antihypertensive medication. However, the absence of significant interactions should be interpreted in the context of limited power to detect small-to-moderate differences.

What is known about the topic

- Hypertension and metabolic syndrome (MetS) are major cardiovascular risk factors commonly managed with antihypertensive drugs and exercise.
- ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) target the renin–angiotensin system and are first-line therapies in hypertension.
- High-intensity interval training (HIIT) improves blood pressure (BP), cardiorespiratory fitness (CRF), and metabolic health in MetS.

What this study adds

- Chronic ACEi/ARB therapy does not attenuate adaptations to 16 weeks of supervised HIIT in adults with MetS.
- HIIT produced similar reductions in BP and improvements in CRF (~ 18 – 22% VO_{2MAX} increase) in medicated and non-medicated participants.
- Exercise-induced cardiometabolic benefits are preserved despite long-term RAAS inhibition, supporting combined therapy in clinical practice.

INTRODUCTION

Hypertension remains one of the most prevalent modifiable risk factors for cardiovascular disease (CVD)¹. Despite the widespread use of antihypertensive medications (AHM), their global burden continues to rise, affecting nearly one-third of adults². Current guidelines recommend lifestyle interventions as first-line therapy; however, long-term adherence is often suboptimal, and pharmacological treatment is frequently initiated early in high-risk individuals owing to concerns about target organ damage³. Consequently, clinical management commonly combines pharmacotherapy with structured exercise interventions.

Global use of AHM has increased substantially over the past decade, and angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers, and thiazide/thiazide-like diuretics are widely recommended as first-line therapies⁴. ACEi and ARBs act by inhibiting the renin–angiotensin–aldosterone system (RAAS), a key regulator of vascular tone, blood volume, and systemic vascular resistance⁵, and provide additional cardiovascular benefits, including improved endothelial function and reduced myocardial remodeling⁶. In parallel, exercise training is a cornerstone of hypertension management⁷, with robust evidence supporting its blood pressure (BP)-lowering effects⁸, mediated in part by reductions in sympathetic activity and modulation of RAAS signaling⁹.

Emerging evidence suggests that combining AHM with high-intensity interval training (HIIT) may produce additive or synergistic effects on BP reduction. HIIT can further reduce ambulatory BP beyond pharmacotherapy in hypertensive individuals with metabolic syndrome (MetS)¹⁰, and exercise-induced reductions in systolic BP may approach those achieved with pharmacological interventions under certain conditions although comparisons remain limited by the heterogeneity across studies¹¹. Higher cardiorespiratory fitness (CRF) is also consistently associated with lower BP and reduced cardiovascular risk¹², and improvements in CRF appear to be preserved during ACEi therapy¹³. However, whether chronic RAAS inhibition modifies the magnitude of exercise-induced cardiometabolic and hemodynamic adaptations remains unclear.

Therefore, this study examined the effects of chronic ACEi or ARBs therapy on cardiometabolic and hemodynamic adaptations to a 16-week supervised HIIT program in adults with MetS. We hypothesized that RAAS inhibition would not attenuate training-induced improvements in blood pressure, cardiorespiratory fitness, or metabolic health.

METHODS

Subjects. Sixty-two middle-aged volunteers (51 ± 12 years; 29 women and 33 men) with overweight and obesity (i.e., body mass index [BMI], $32.2 \pm 4.3 \text{ kg}\cdot\text{m}^{-2}$) with MetS criteria¹⁴ completed the study. Participants were previously sedentary as assessed by the 7-day IPAQ (International Physical Activity Questionnaire) with less than $150 \text{ min}\cdot\text{wk}^{-1}$ of moderate-intensity activity. Exclusion criteria included untreated cardiovascular or renal disease, any condition associated with exercise intolerance, and the use of any pharmacological therapy targeting MetS components other than ACEi or ARBs. Upon questioning at

the onset of the intervention, subjects reported a stable body weight ($\pm 1\%$) over the 4 months preceding the survey. All subjects provided written, witnessed, and informed consent under a protocol approved by the local Virgen de la Salud Hospital Ethics Committee of Toledo (reference #170) and in accordance with the Declaration of Helsinki. This is a substudy of a larger clinical trial assessing the effects of medication and exercise interactions in individuals with MetS (ClinicalTrials.gov Identifier: NCT03019796).

Experimental design. This prospective parallel-group intervention study examined the effects of exercise training in participants either treated or untreated with RAAS inhibitors (ACEi or ARBs). Participants were allocated using a non-randomized block design based on medication treatment. Recruitment, screening, intervention, and all assessments were conducted in the sequence outlined in Fig. 1. Twenty-seven individuals with MetS receiving chronic antihypertensive therapy with ACEi or ARBs for more than six months constituted the antihypertensive medication group (AHM). Thirty-five individuals with MetS who had never received chronic pharmacologic treatment served as the control group (CONTROL; Table 1).

Table 1
Medication use.

Medication	AHM (n = 27)	CONTROL (n = 35)
Antihypertensive medication	27 (100%)	-
ACEi	12 (44%)	-
Enalapril	11 (41%)	-
Imidapril	1 (4%)	-
ARBs	15 (56%)	-
Candesartan	1 (4%)	-
Irbesartan	6 (22%)	-
Losartan	4 (15%)	-
Telmisartan	1 (4%)	-
Valsartan	3 (11%)	-
Cholesterol lowering	-	-
Triglyceride lowering	-	-
Glucose lowering	-	-
Data are presented as the number of subjects taking each medication, expressed as absolute frequency (n) and proportion (%). Abbreviations: ACEi , angiotensin-converting enzyme inhibitors; and ARBs , angiotensin receptor blockers.		

Intervention. All participants completed a 16-week supervised aerobic training program, performed three times per week (Monday, Wednesday, and Friday), consisting of high-intensity interval training (HIIT) on stationary cycle ergometers (Tomahawk S-Series, Nürnberg, Germany). Participants were required to

attend at least 90% of sessions to be included in the analysis. Each session began with a 10-minute warm-up at 70% of maximum heart rate (HR_{MAX}), followed by four 4-minute intervals at 90% HR_{MAX} , interspersed with 3-minute active recovery periods at 70% HR_{MAX} , and concluded with a 5-minute cool-down. Exercise intensity was prescribed as a percentage of HR_{MAX} determined during the pre-intervention maximal exercise test. Heart rate was continuously monitored using a telemetry system (Seego, RealTrack Systems, Spain) and displayed on a large screen. Participants adjusted the cycling workload to remain within their individualized target HR zones under the direct supervision of a research team member. Training progression was implemented over the first three weeks (nine sessions), gradually increasing the number and duration of high-intensity intervals. HR_{MAX} was reassessed monthly, and workloads were adjusted accordingly to maintain the prescribed training intensity. Participants were instructed to maintain their usual dietary and physical activity habits throughout the intervention. Monthly, they completed a 3-day dietary record (CESNID v1.0, Barcelona, Spain) and wore a wrist-based activity monitor (Polar Loop Electro, Polar, Kempele, Finland) for 48 hours. Personalized feedback was provided each month to minimize fluctuations in caloric intake and non-training physical activity.

Outcomes measures

Clinical investigation. Before and after the intervention, participants reported to the laboratory in the morning following an overnight fast (8–12 h). Body weight (Hawk, Mettler; Toledo, USA), height (Stadiometer, SECA 217; Hamburg, Germany), and waist circumference were measured by the same investigator according to the protocol proposed by Alberti et al.¹⁴, using a non-elastic measuring tape. BMI was calculated, and fat mass (FM) and fat-free mass (FFM) were assessed using dual-energy X-ray absorptiometry (DXA; Hologic Discovery Wi QDR Series, Bedford, USA). Resting blood pressure was measured in triplicate using a calibrated ECG-gated automated sphygmomanometer (Tango, SunTech Medical; Morrisville, USA) after 10 minutes of supine rest. Exercise testing was performed at least 48 hours apart from fasting venous blood collection, which was used to determine serum glucose, insulin, and lipid profile (triglycerides, total cholesterol, HDL-c, and LDL-c). Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR). Sex-specific Z scores were calculated for each MetS criterion using the group SD, and the sum of the Z scores for each MetS component was divided by 6 to obtain the MetS risk score. The equations used were as follows:

Men's MetS Z Score= $[(40 - \text{HDL-cholesterol})/\text{SD}] + [(\text{triglycerides} - 150)/\text{SD}] + [(\text{glucose} - 100)/\text{SD}] + [(\text{waist circumference} - 94)/\text{SD}] + [(\text{systolic blood pressure} - 130)/\text{SD}] + [(\text{diastolic blood pressure} - 85)/\text{SD}]$

Women's MetS Z Score= $[(50 - \text{HDL-cholesterol})/\text{SD}] + [(\text{triglycerides} - 150)/\text{SD}] + [(\text{glucose} - 100)/\text{SD}] + [(\text{waist circumference} - 80)/\text{SD}] + [(\text{systolic blood pressure} - 130)/\text{SD}] + [(\text{diastolic blood pressure} - 85)/\text{SD}]$

Cardiorespiratory fitness and maximal power output. Maximal oxygen uptake (VO_{2MAX}), maximal cycling power (W_{MAX}), and maximal heart rate (HR_{MAX}) were determined during a graded exercise test (GXT) performed on an electronically braked cycle ergometer (Ergoselect 200, Ergoline; Bitz, Germany). Gas

exchange was continuously measured using indirect calorimetry (Quark RMR, Cosmed; Rome, Italy), and cardiac electrical activity was monitored via a standard 12-lead ECG (Quark T12, Cosmed; Rome, Italy). Following a 3-minute warm-up at 30 W for women and 50 W for men, the workload was increased by 15 W for women and 20 W for men every minute until volitional exhaustion. Immediately afterward, a verification test was conducted at 110% of the maximal workload achieved during the GXT to confirm attainment of $\text{VO}_{2\text{MAX}}$.

Blood pressure monitoring during exercise. During the GXT, BP was manually measured by a trained practitioner using a calibrated sphygmomanometer (Gamma G7, Heine; Gilching, Germany), following established methodological standards¹⁵. Measurements were obtained from the left arm, with an appropriately sized cuff positioned at heart level and the arm supported throughout the test to minimize motion artifacts and ensure accuracy. BP was recorded with participants seated on the cycle ergometer at the onset of the exercise protocol (15 W for women, 50 W for men at minute 3), and every 2 minutes at the end of each odd-numbered stage. Peak BP was determined immediately upon cessation of exercise at maximal exertion. Exercise was terminated either upon volitional exhaustion or if any predefined safety criteria for test termination were met, including chest pain with ischemic ECG changes, complex ectopy or high-grade atrioventricular block, symptomatic SBP drop > 20 mmHg, severe exercise hypertension (SBP > 240 mmHg or DBP > 120 mmHg), oxygen desaturation, neurological symptoms, or at the discretion of the supervising physician.

Statistical analysis. A per-protocol analysis was conducted, including only participants who completed the intervention. Sample size calculations were based on expected changes in CRF, using data from our previous study in which individuals with MetS who completed a 16-week exercise program similar to the present protocol¹⁶. In this study, participants increased $0.24 \pm 0.27 \text{ L} \cdot \text{min}^{-1}$ following HIIT, translating to an effect size of $d = 1.11$. Therefore, 23 participants per group should be sufficient to achieve a power of 0.95 at an alpha level of 0.05. Due to account for potential dropouts of exercise interventions (i.e., ~ 30% exercise intervention attrition rates) or changing medications (primary care follow-up), the sample size was increased in each group ($N = 40$). Data are reported as mean $\pm$ standard deviation, with 95% confidence intervals (CI) calculated for all outcome measures. Normality was verified using the Shapiro–Wilk test. Baseline comparisons between groups were performed using independent samples t-tests. To assess the effects of training over time and between groups, a mixed-design (split-plot) ANCOVA was used for all variables, with baseline values entered as covariates. This approach allowed evaluation of time $\times$ group interactions while accounting for repeated measures (PRE and POST) within participants. Post hoc pairwise comparisons with Bonferroni correction were conducted only when significant interactions were observed. All statistical analyses were performed using SPSS v28 (IBM, Chicago, IL, USA), with significance set at $p \leq 0.05$.

RESULTS

Baseline subjects' characteristics. Participants were Caucasians living in southern Europe. Women comprise 48% of the AHM group and 46% of the CONTROL. Data were analyzed without stratification by sex, since all female participants were postmenopausal, not receiving hormone replacement therapy, and showed no significant differences compared to male participants in the main study outcomes (time x sex interaction; MetS Z score, $p = 0.31$; SBP, $p = 0.25$; DBP, $p = 0.17$; body weight, $p = 0.31$; and $\text{VO}_{2\text{MAX}}$ ($\text{mL}\cdot\text{Kg}^{-1}\cdot\text{min}^{-1}$), $p = 0.16$). Subjects' adherence to training sessions was 91% for AHM and 90% for CONTROL ($p > 0.05$). There were no differences in calorie intake or physical activity between groups. On average, subjects ingested 2296 ± 93 at baseline and $2322 \pm 82 \text{ kcal}\cdot\text{day}^{-1}$ after the intervention (both $p > 0.05$). Macronutrient distribution remained stable across groups ($47 \pm 5\%$ carbohydrate, $33 \pm 2\%$ fat [40% saturated fat], and $20 \pm 1\%$ protein). Baseline physical activity averaged $6025 \pm 362 \text{ steps}\cdot\text{day}^{-1}$, $196 \pm 147 \text{ min}\cdot\text{day}^{-1}$ of standing, and $496 \pm 165 \text{ min}\cdot\text{day}^{-1}$ supine rest, with similar values after 16 weeks ($587 \pm 224 \text{ steps}\cdot\text{day}^{-1}$, $189 \pm 77 \text{ min}\cdot\text{day}^{-1}$ standing and $499 \pm 201 \text{ min}\cdot\text{day}^{-1}$ supine rest; all $p > 0.05$).

Body weight and composition. At baseline, participants had similar body weight, BMI, fat mass, and fat-free mass (all $p > 0.05$; Table 2). After 16 weeks of HIIT, no significant main effects of *time* or *time* $\times$ *group* interaction effects were observed for any anthropometric variable (all $p > 0.05$).

Table 2

Changes in anthropometric, cardiometabolic factors, and maximal exercise variables after 16 weeks of training in both groups.

	AHM (n = 27)		CONTROL (n = 35)		P value		
	Baseline	16 weeks	Baseline	16 weeks	Baseline	Time	Time x group
Age (yr)	55 ± 7		51 ± 9		0.028		
% Women	48%		46%				
Anthropometric							
Weight (kg)	94.1 ± 18.5	93.1 ± 18.5	89.8 ± 15.4	88.2 ± 14.8	0.338	0.443	0.330
BMI (kg·m ⁻²)	34.2 ± 4.7	33.8 ± 4.8	32.4 ± 3.9	31.8 ± 3.8	0.119	0.695	0.226
Fat mass (kg)	36.3 ± 10.8	35.6 ± 11.0	33.8 ± 11.6	32.6 ± 11.1	0.383	0.771	0.315
Fat-free mass (kg)	57.8 ± 13.8	57.4 ± 13.0	55.2 ± 14.9	54.8 ± 14.7	0.476	0.057	0.747
Metabolic Syndrome factors							
Waist circumference (cm)	109.9 ± 12.9	108.1 ± 13.1	106.4 ± 10.4	103.6 ± 9.4	0.259	0.110	0.148
Glucose (mg·dL ⁻¹)	102.1 ± 12.1	102.5 ± 10.4	105.5 ± 16.5	104.3 ± 18.0	0.366	0.002	0.899
Triglycerides (mg·dL ⁻¹)	127.1 ± 48.4	111.2 ± 41.8	149.8 ± 76.6	136.9 ± 72.4	0.165	0.027	0.350
HDL-c (mg·dL ⁻¹)	41.7 ± 8.6	43.0 ± 8.4	43.2 ± 10.9	43.7 ± 10.2	0.567	0.001	0.758
MetS Z-score	0.23 ± 0.55	0.01 ± 0.50	0.32 ± 0.61	0.02 ± 0.58	0.554	< 0.001	0.580
Cardiometabolic risk factors							
Total Cholesterol (mg·dL ⁻¹)	192.0 ± 21.3	193.3 ± 28.3	214.4 ± 38.8	215.1 ± 36.9	0.005	0.096	0.687
Data are presented as mean ± SD. Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure.							

	AHM (n = 27)		CONTROL (n = 35)		P value		
	Baseline	16 weeks	Baseline	16 weeks	Baseline	Time	Time x group
LDL-c (mg·dL ⁻¹)	124.8 ± 21.3	128.1 ± 24.4	141.3 ± 33.4	144.0 ± 30.7	0.023	0.005	0.538
Insulin (μIU·mL ⁻¹)	14.4 ± 6.8	13.0 ± 7.2	12.0 ± 6.6	10.3 ± 4.8	0.161	0.009	0.303
HOMA-IR	3.7 ± 1.8	3.3 ± 2.0	3.2 ± 2.0	2.7 ± 1.6	0.360	0.061	0.405
Maximal Exercise parameters							
Maximal Heart Rate (beats·min ⁻¹)	154 ± 15	156 ± 13	155 ± 17	160 ± 14	0.803	< 0.001	0.192
O ₂ Pulse at VO ₂ MAX (mL·beat ⁻¹)	12.9 ± 3.5	15.0 ± 4.0	13.3 ± 5.0	15.5 ± 5.2	0.697	0.003	0.750
Heart Rate Reserve (beats·min ⁻¹)	86 ± 18	91 ± 17	88 ± 20	93 ± 17	0.635	< 0.001	0.966
Maximal SBP (mmHg)	179.4 ± 22.4	175.5 ± 19.9	170.7 ± 26.4	171.8 ± 18.0	0.432	< 0.001	0.961
Maximal DBP (mmHg)	93.1 ± 13.8	87.5 ± 12.2	93.6 ± 17.0	89.6 ± 19.1	0.933	0.138	0.770
Maximal MAP (mmHg)	121.8 ± 15.9	116.9 ± 13.5	119.3 ± 18.1	117.0 ± 15.6	0.743	0.008	0.806
Data are presented as mean ± SD. Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure.							

MetS components and additional physiological parameters. Changes in MetS components after 16 weeks of training are depicted in Table 2. Before intervention, MetS components were not different among groups (all $p > 0.05$). After intervention, we observed a significant *time* effect in glucose (AHM, 0.4; 95% CI -4.8 to 4.2 mg·dL⁻¹ and CONTROL, -1.2; 95% CI -4.7 to 3.4 mg·dL⁻¹; $p = 0.002$), triglycerides (AHM, -15.9; 95% CI -35.5 to -4.0 mg·dL⁻¹ and CONTROL, -12.8; 95% CI -23.8 to 4.2 mg·dL⁻¹; $p = 0.027$), and HDL-c (AHM, 1.3; 95% CI -1.1 to 3.3 mg·dL⁻¹ and CONTROL, 0.5; 95% CI -1.3 to 2.6 mg·dL⁻¹; $p = 0.001$). Similarly, the MetS Z-score showed a significant *time* effect ($p < 0.001$), with improvements of 96% in the AHM group (- 0.22 SDs; 95% CI - 0.37 to - 0.11) and 93% in the CONTROL group (- 0.30 SDs; 95% CI - 0.41 to - 0.17). However, no significant *time* × *group* interaction effects were observed for any MetS components and MetS

Z-score (all $p > 0.05$). At baseline, total cholesterol ($p = 0.005$) and LDL-c ($p = 0.023$) were higher in the CONTROL than in the AHM group. Following the intervention, a significant *time* effect was observed for LDL-c (AHM, 3.2; 95% CI -4.8 to 7.8 mg·dL⁻¹ and CONTROL, 2.8; 95% CI -1.4 to 9.7 mg·dL⁻¹; $p = 0.005$) and insulin (AHM, -1.4; 95% CI -2.6 to 0.7 μ U·mL⁻¹ and CONTROL, -1.7; 95% CI -3.5 to -0.6 μ U·mL⁻¹; $p = 0.009$). However, no significant *time* $\times$ *group* interaction was detected for either variable (all $p > 0.05$).

Resting blood pressure. Changes in resting BP over 16 weeks of training are shown in Fig. 2. At baseline, systolic blood pressure (SBP, $p = 0.65$), diastolic blood pressure (DBP, $p = 0.77$), and mean arterial pressure (MAP, $p = 0.69$) did not differ between groups. After intervention, we observed a significant *time* effect in rest SBP (AHM, -3.2; 95% CI -7.7 to 0.6 mmHg and CONTROL, -8.0; 95% CI -11.5 to -4.2 mmHg; $p = 0.005$), DBP (AHM, -4.6; 95% CI -7.0 to -2.5 mmHg and CONTROL, -5.8; 95% CI -7.7 to -3.7 mmHg; $p = 0.005$), and MAP (AHM, -4.2; 95% CI -7.0 to -1.7 mmHg and CONTROL, -6.5; 95% CI -8.7 to -4.2 mmHg; $p = 0.005$). However, no significant *time* $\times$ *group* interaction effects were observed for any component of resting blood pressure (all $p > 0.05$).

Cardiorespiratory fitness and maximal exercise responses. CRF (i.e., VO_{2MAX}) and maximal power output (W_{MAX}) evolution after intervention are shown in Fig. 3. Before intervention, CRF (expressed as VO_{2MAX} in L·min⁻¹ [$p = 0.79$] and mL·Kg⁻¹·min⁻¹ [$p = 0.59$]) and W_{MAX} ($p = 0.41$) were similar between AHM and CONTROL groups. After 16 weeks of HIIT, we observed a significant *time* effect in CRF (AHM, 0.33; 95% CI 0.24 to 0.43 L·min⁻¹ and CONTROL, 0.42; 95% CI 0.34 to 0.50 L·min⁻¹; $p = 0.05$) and W_{MAX} (AHM, 33; 95% CI 25 to 41 W and CONTROL, 40; 95% CI 33 to 47 W; $p = 0.003$). However, no significant *time* $\times$ *group* interaction effects were observed for any component of exercise performance (all $p > 0.05$). Since body weight and fat mass decreased similarly in both groups (Table 2), changes in CRF per kilogram of body weight responded similarly to the absolute values (AHM, 3.9; 95% CI 2.8 to 4.9 mL·Kg⁻¹·min⁻¹ and CONTROL, 5.0; 95% CI 4.1 to 5.9 mL·Kg⁻¹·min⁻¹; $p = 0.003$). The maximal heart rate (HR_{MAX}), oxygen pulse (O_2 Pulse at VO_{2MAX}), and heart rate reserve (HRR) response are shown in Table 2. At baseline, there were no differences between groups on any of these variables (all $p > 0.05$). After exercise training, we observed a significant *time* effect in HR_{MAX} (AHM, 2; 95% CI -1 to 5 beats·min⁻¹ and CONTROL, 5; 95% CI 2 to 7 beats·min⁻¹; $p < 0.001$), O_2 Pulse at VO_{2MAX} (AHM, 2.1; 95% CI 1.4 to 2.7 mL·beat⁻¹ and CONTROL, 2.2; 95% CI 1.6 to 2.8 mL·beat⁻¹; $p = 0.003$) and HRR (AHM, 6; 95% CI 1 to 9 beats·min⁻¹ and CONTROL, 5; 95% CI 1 to 9 beats·min⁻¹; $p < 0.001$).

Blood pressure during graded exercise. BP response during the graded exercise test GXT is shown in Table 2 and Fig. 4. At baseline, maximal SBP, maximal DBP, and maximal MAP did not differ between groups (all $p > 0.05$). Following the intervention, a significant main effect of *time* was observed for maximal SBP (AHM, -3.9; 95% CI -12.7 to 11.1 mmHg and CONTROL, 1.1; 95% CI -11.9 to 9.6 mmHg; $p = 0.001$) and maximal MAP (AHM, -5.0; 95% CI -13.4 to 4.9 mmHg and CONTROL, -2.3; 95% CI -11.0 to 5.4 mmHg; $p = 0.008$). However, no significant *time* $\times$ *group* interaction was detected for either variable (both $p > 0.05$; Table 2). Blood pressure responses at each stage of the graded exercise test—normalized to the

percentage of maximal heart rate achieved ($\%HR_{MAX}$)—showed a significant main effect of *time* only for DBP ($p = 0.047$; Fig. 4B) with no *time* $\times$ *group* interaction observed for any variable (all $p > 0.05$).

DISCUSSION

In this 16-week supervised HIIT intervention, chronic treatment with ACEi or ARBs did not attenuate exercise-induced physiological adaptations in middle-aged adults with MetS. Both pharmacologically treated and untreated participants exhibited clinically meaningful improvements in resting and exercise blood pressure, cardiorespiratory fitness (CRF, as assessed by VO_{2MAX}), and metabolic health (assessed by MetS Z-score). Importantly, no significant *time* $\times$ *group* interactions were detected for any cardiometabolic, hemodynamic, or performance-related outcomes, suggesting that chronic renin–angiotensin system inhibition does not impair the beneficial effects of HIIT. Additionally, body composition, dietary intake, and habitual physical activity remained stable, supporting the interpretation that observed improvements were primarily exercise-induced.

Blood pressure reduction and cardiometabolic adaptations. The decrease in resting blood pressure observed in our participants (~ 3 – 8 mmHg in SBP and ~ 5 – 6 mmHg in DBP) is consistent with meta-analyses showing average decreases of ~ 3 – 6 mmHg and ~ 2 – 3 mmHg, respectively, after aerobic training, including HIIT ⁸. Prior evidence also indicates that structured exercise can elicit SBP reductions comparable to first-line antihypertensive therapy ¹¹. Within this context, our data showed that chronic RAAS inhibition neither attenuated nor enhanced HIIT-induced adaptations, as medicated and non-medicated participants demonstrated comparable metabolic, hemodynamic, and fitness responses. These findings are consistent with placebo-controlled evidence showing that AHM and HIIT exert independent and additive effects on ambulatory BP in hypertensive individuals with MetS ¹⁰. Although RAAS blockade altered biochemical indices (e.g., increased renin activity and a lower aldosterone-to-renin ratio), exercise-induced BP reductions appeared to occur through mechanisms independent of RAAS suppression. In accordance with these findings, our previous work showed that only hypertensive individuals—regardless of treatment status or antihypertensive class—exhibited training-induced BP reductions, and that the magnitude of this response scaled with baseline BP, consistent with Wilder’s principle ¹⁷.

Acute and chronic interactions between exercise and RAAS Inhibition. Following these observations, acute studies have shown that combining a single session of aerobic exercise with AHM produces greater immediate BP reductions than either intervention alone ¹⁸, particularly at higher intensities ¹⁹. However, whether such acute synergistic effects persist with long-term training remains unclear. Chronic aerobic or interval training has been shown to reduce arterial stiffness, improve endothelial function ²⁰, and decrease systemic vascular resistance ²¹ in individuals with MetS. However, evidence regarding the preservation of these adaptations during chronic ACEi or ARB therapy remains limited, with available data largely derived from animal models suggesting complementary effects of ARBs and exercise on blood pressure and cardiac function ²². Our findings demonstrate that 16 weeks of HIIT elicited favorable hemodynamic and vascular adaptations in medicated participants, with no evidence that RAAS blockade interfered with these responses. Collectively, these findings support the compatibility of angiotensin antagonist medication with

exercise training and reinforce the combined use of pharmacologic and lifestyle interventions in the management of hypertension and MetS.

Cardiorespiratory fitness and clinical implications. Evidence on whether RAAS-targeting medications influence exercise-induced improvements in CRF has been controversial. Some studies in older adults have reported that ACEi therapy alone enhances exercise capacity^{23,24} and may augment functional adaptations in frail populations²⁵. However, other trials in functionally impaired older adults^{26,27} and healthy individuals¹³ observed no additive effect of ACEi on training-induced gains. The present findings align with this latter evidence, demonstrating that chronic ACEi or ARBs therapy does not attenuate CRF improvements following HIIT. Absolute $\text{VO}_{2\text{MAX}}$ increased by approximately 22% in the AHM group and 18% in the control group, equivalent to gains of ~ 1.4 and ~ 1.1 metabolic equivalents (METs), respectively. Exercise capacity is a strong predictor of cardiovascular and all-cause mortality in patients with hypertension¹². Our improvements correspond to a $\sim 13\%$ reduction in all-cause mortality and a $\sim 15\%$ reduction in cardiovascular events²⁸. Epidemiological data from an extensive Swedish registry indicate that individuals who increase CRF by $> 3\%$ per year have an 11% lower risk of incident hypertension. In contrast, individuals who experience CRF declines have a 25% increased risk, independent of lifestyle factors²⁹. Collectively, these results suggest that HIIT-induced improvements in CRF may contribute to both short-term BP control and long-term decreases in cardiovascular risk, and that these benefits are preserved despite chronic RAAS inhibition.

Blood pressure responses during exercise. During dynamic exercise, SBP rises in proportion to intensity due to increased cardiac output driven by sympathetic activation, whereas DBP typically remains stable or slightly decreases owing to peripheral vasodilation. Exaggerated SBP responses reflect impaired vascular regulation and are associated with arterial stiffness, endothelial dysfunction, and increased long-term cardiovascular risk³⁰. Chant et al.³¹ showed that individuals with treated and apparently controlled hypertension exhibit elevated SBP responses during both submaximal and maximal exercise, comparable to those observed in untreated or uncontrolled hypertension. This phenomenon has been attributed, at least in part, to heightened metaboreflex sensitivity that appears relatively resistant to conventional antihypertensive pharmacotherapy. In contrast, in the present study, baseline SBP responses across exercise intensities did not differ between groups, suggesting that chronic angiotensin receptor blockade did not materially alter the acute exercise pressor response. Differences in baseline hypertension severity and treatment burden may explain the discrepancies between our findings and those of Chant et al. Notably, their participants' cohort entered the study with resting SBP values near the hypertensive threshold (~ 138 mmHg). It was predominantly managed with multidrug regimens, a clinical phenotype more likely to exhibit persistently exaggerated pressor responses during physical stress.

After 16 weeks of HIIT, both groups exhibited a significant *time* effect in maximal MAP (Table 2) and submaximal DBP (Fig. 4B), accompanied by improvements in workload capacity, CRF, heart rate reserve, and maximal oxygen pulse (Fig. 3, Table 2). Consistent with previous findings, oxygen pulse kinetics during exercise are closely associated with both systolic and diastolic left ventricular performance in older adults with mild hypertension³², supporting its use as an indirect marker of improved central hemodynamic

responses to exercise. Importantly, indexing SBP to external workload has been shown to predict all-cause mortality more accurately than peak SBP, underscoring the clinical relevance of improved hemodynamic efficiency during exercise³³. These results align with prior studies reporting modest reductions in exercise BP following training³⁴, and with a pooled analysis of 10 RCTs showing a ~ 7 mmHg decrease in exercise SBP after aerobic training despite heterogeneity in age, BP status, and intervention protocols³⁵. Collectively, the data suggest that HIIT improves vascular dynamics and exercise tolerance, moderating MAP and DBP responses through enhanced vascular compliance, improved endothelial function, and attenuated sympathetic activation, even in the context of chronic inhibition of the RAAS

Strengths and Limitations. The primary strength of this study is its prospective, supervised intervention design, which enabled a direct comparison of exercise-induced adaptations between two clinically relevant populations: adults with MetS under chronic ACEi or ARBs therapy and those not receiving pharmacological treatment. This pragmatic approach enhances clinical applicability and provides insights into real-world interactions between pharmacologic RAAS inhibition and exercise-induced cardiovascular adaptations. However, several limitations should be acknowledged. First, although baseline adjustment was performed, the absence of randomization warrants caution when inferring causality. Second, pharmacologic heterogeneity—specifically the use of multiple ACEi and ARBs agents at varying doses—may have influenced vascular and hemodynamic outcomes. Future randomized controlled trials with standardized pharmacotherapy protocols are needed to delineate the specific contributions of individual RAAS inhibitors to exercise-induced adaptations.

Conclusions

In summary, chronic ACEi or ARBs therapy did not attenuate the cardiometabolic, hemodynamic, or functional adaptations elicited by 16 weeks of supervised HIIT in adults with MetS. Medicated and non-medicated participants exhibited comparable improvements in resting and exercise blood pressure, CRF, and metabolic health, with no evidence of impaired responsiveness associated with chronic RAAS inhibition. These findings support the physiological compatibility of RAAS blockade with structured exercise training and reinforce the role of HIIT as an effective therapeutic strategy in the management of MetS among individuals receiving long-term antihypertensive treatment.

Declarations

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

ILS and FMP conceived and designed the study. ILS, AMC, LGG, RMR and FMP conducted the investigation and data collection. ILS., AMC., DMG, and FMP performed data curation and formal statistical analysis.

ILS, AMC and FMP. drafted the original manuscript. AMC, LGG, DMG, and RMR critically reviewed and revised the manuscript for important intellectual content. RMR and FMP supervised the project. RMR acquired funding. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Virgen de la Salud Hospital of Toledo (reference #170). All participants provided written informed consent. The work is a substudy of a registered clinical trial (ClinicalTrials.gov: NCT03019796).

References

1. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *The Lancet* 2020; 395(10226): 795–808.
2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nature Reviews Nephrology* 2020; 16(4): 223–237.
3. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *Journal of hypertension* 2023; 41(12): 1874–2071.
4. Jayawardana S, Campbell A, Aitken M, Andersson CE, Mehra MR, Mossialos E. Global consumption patterns of combination hypertension medication: An analysis of pharmaceutical sales data from 2010–2021. *PLOS global public health* 2024; 4(9): e0003698.
5. Caulfield L, Heslop P, Walesby KE, Sumukadas D, Sayer AA, Witham MD. Effect of Angiotensin System Inhibitors on Physical Performance in Older People – A Systematic Review and Meta-Analysis. *Journal of the American Medical Directors Association* 2021; 22(6): 1215–1221.e2.
6. Wei J, Galaviz KI, Kowalski AJ, Magee MJ, Haw JS, Narayan KMV et al. Comparison of Cardiovascular Events Among Users of Different Classes of Antihypertension Medications: A Systematic Review and Network Meta-analysis. *JAMA Network Open* 2020; 3(2): e1921618-e1921618.

7. Cornelissen VA, Fagard RH. Effects of Endurance Training on Blood Pressure, Blood Pressure–Regulating Mechanisms, and Cardiovascular Risk Factors. *Hypertension* 2005; 46(4): 667–675.
8. Edwards JJ, Deenmamode AHP, Griffiths M, Arnold O, Cooper NJ, Wiles JD et al. Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomised controlled trials. *British journal of sports medicine* 2023; 57(20): 1317–1326.
9. Baffour-Awuah B, Man M, Goessler KF, Cornelissen VA, Dieberg G, Smart NA et al. Effect of exercise training on the renin-angiotensin-aldosterone system: a meta-analysis. *Journal of human hypertension* 2024; 38(2): 89–101.
10. Ramirez-Jimenez M, Morales-Palomo F, Moreno-Cabañas A, Alvarez-Jimenez L, Ortega JF, Mora-Rodriguez R. Effects of antihypertensive medication and high-intensity interval training in hypertensive metabolic syndrome individuals. *Scandinavian journal of medicine & science in sports* 2021; 31(7): 1411–1419.
11. Naci H, Salcher-Konrad M, Dias S, Blum MR, Sahoo SA, Nunan D et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *British journal of sports medicine* 2019; 53(14): 859–869.
12. Kokkinos P. Cardiorespiratory Fitness, Exercise, and Blood Pressure. *Hypertension* 2014; 64(6): 1160–1164.
13. Sjúrdarson T, Bejder J, Breenfeldt Andersen A, Bonne T, Kyhl K, Róin T et al. Effect of angiotensin-converting enzyme inhibition on cardiovascular adaptation to exercise training. *Physiological reports* 2022; 10(13): e15382.
14. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120(16): 1640–5.
15. Naylor M, Gajjar P, Murthy VL, Miller PE, Velagaleti RS, Larson MG et al. Blood Pressure Responses During Exercise: Physiological Correlates and Clinical Implications. *Arteriosclerosis, thrombosis, and vascular biology* 2023; 43(1): 163–173.
16. Morales-Palomo F, Ramirez-Jimenez M, Ortega JF, Mora-Rodriguez R. Effectiveness of Aerobic Exercise Programs for Health Promotion in Metabolic Syndrome. *Medicine and science in sports and exercise* 2019; 51(9): 1876–1883.
17. Mora-Rodriguez R, Ortega JF, Morales-Palomo F, Ramirez-Jimenez M, Moreno-Cabañas A, Alvarez-Jimenez L. Endurance Exercise Training reduces Blood Pressure according to the Wilder's Principle. *International journal of sports medicine* 2022; 43(4): 336–343.
18. Ramirez-Jimenez M, Morales-Palomo F, Ortega JF, Mora-Rodriguez R. Post-exercise Hypotension Produced by Supramaximal Interval Exercise is Potentiated by Angiotensin Receptor Blockers. *International journal of sports medicine* 2019; 40(12): 756–761.

19. Morales-Palomo F, Ramirez-Jimenez M, Ortega JF, Pallarés JG, Mora-Rodriguez R. Acute Hypotension after High-Intensity Interval Exercise in Metabolic Syndrome Patients. *International journal of sports medicine* 2017; 38(7): 560–567.
20. Mora-Rodriguez R, Ramirez-Jimenez M, Fernandez-Elias VE, Guio de Prada MV, Morales-Palomo F, Pallares JG et al. Effects of aerobic interval training on arterial stiffness and microvascular function in patients with metabolic syndrome. *Journal of clinical hypertension (Greenwich, Conn.)* 2018; 20(1): 11–18.
21. Mora-Rodriguez R, Fernandez-Elias VE, Morales-Palomo F, Pallares JG, Ramirez-Jimenez M, Ortega JF. Aerobic interval training reduces vascular resistances during submaximal exercise in obese metabolic syndrome individuals. *Eur J Appl Physiol* 2017; 117(10): 2065–2073.
22. Aguilar BA, Vieira S, Veiga AC, da Silva JVMB, Paixao TV, Rodrigues KP et al. Physical exercise is essential for increasing ventricular contractility in hypertensive rats treated with losartan. *Hypertension Research* 2024; 47(5): 1350–1361.
23. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. *Heart (British Cardiac Society)* 2002; 88(4): 373–7.
24. Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne* 2007; 177(8): 867–74.
25. Buford TW, Manini TM, Hsu FC, Cesari M, Anton SD, Nayfield S et al. Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise. *Journal of the American Geriatrics Society* 2012; 60(7): 1244–52.
26. Sumukadas D, Band M, Miller S, Cvorov V, Witham M, Struthers A et al. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2014; 69(6): 736–43.
27. Baptista LC, Machado-Rodrigues AM, Veríssimo MT, Martins RA. Exercise training improves functional status in hypertensive older adults under angiotensin converting enzymes inhibitors medication. *Experimental gerontology* 2018; 109: 82–89.
28. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama* 2009; 301(19): 2024–35.
29. Holmlund T, Ekblom B, Björjesson M, Andersson G, Wallin P, Ekblom-Bak E. Association between change in cardiorespiratory fitness and incident hypertension in Swedish adults. *European journal of preventive cardiology* 2021; 28(13): 1515–1522.
30. Carlén A, Lindow T, Cauwenberghs N, Elmberg V, Brudin L, Ekström M et al. Exercise systolic blood pressure response during cycle ergometry is associated with future hypertension in normotensive individuals. *European journal of preventive cardiology* 2024; 31(9): 1072–1079.
31. Chant B, Bakali M, Hinton T, Burchell AE, Nightingale AK, Paton JFR et al. Antihypertensive Treatment Fails to Control Blood Pressure During Exercise. *Hypertension* 2018; 72(1): 102–109.

32. Lim JG, McAveney TJ, Fleg JL, Shapiro EP, Turner KL, Bacher AC et al. Oxygen pulse during exercise is related to resting systolic and diastolic left ventricular function in older persons with mild hypertension. *American heart journal* 2005; 150(5): 941–6.
33. Hedman K, Cauwenberghs N, Christle JW, Kuznetsova T, Haddad F, Myers J. Workload-indexed blood pressure response is superior to peak systolic blood pressure in predicting all-cause mortality. *European journal of preventive cardiology* 2020; 27(9): 978–987.
34. Barone BB, Wang NY, Bacher AC, Stewart KJ. Decreased exercise blood pressure in older adults after exercise training: contributions of increased fitness and decreased fatness. *British journal of sports medicine* 2009; 43(1): 52–6.
35. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. *Medicine and science in sports and exercise* 2004; 36(3): 533–53.

Figures

Figure 1

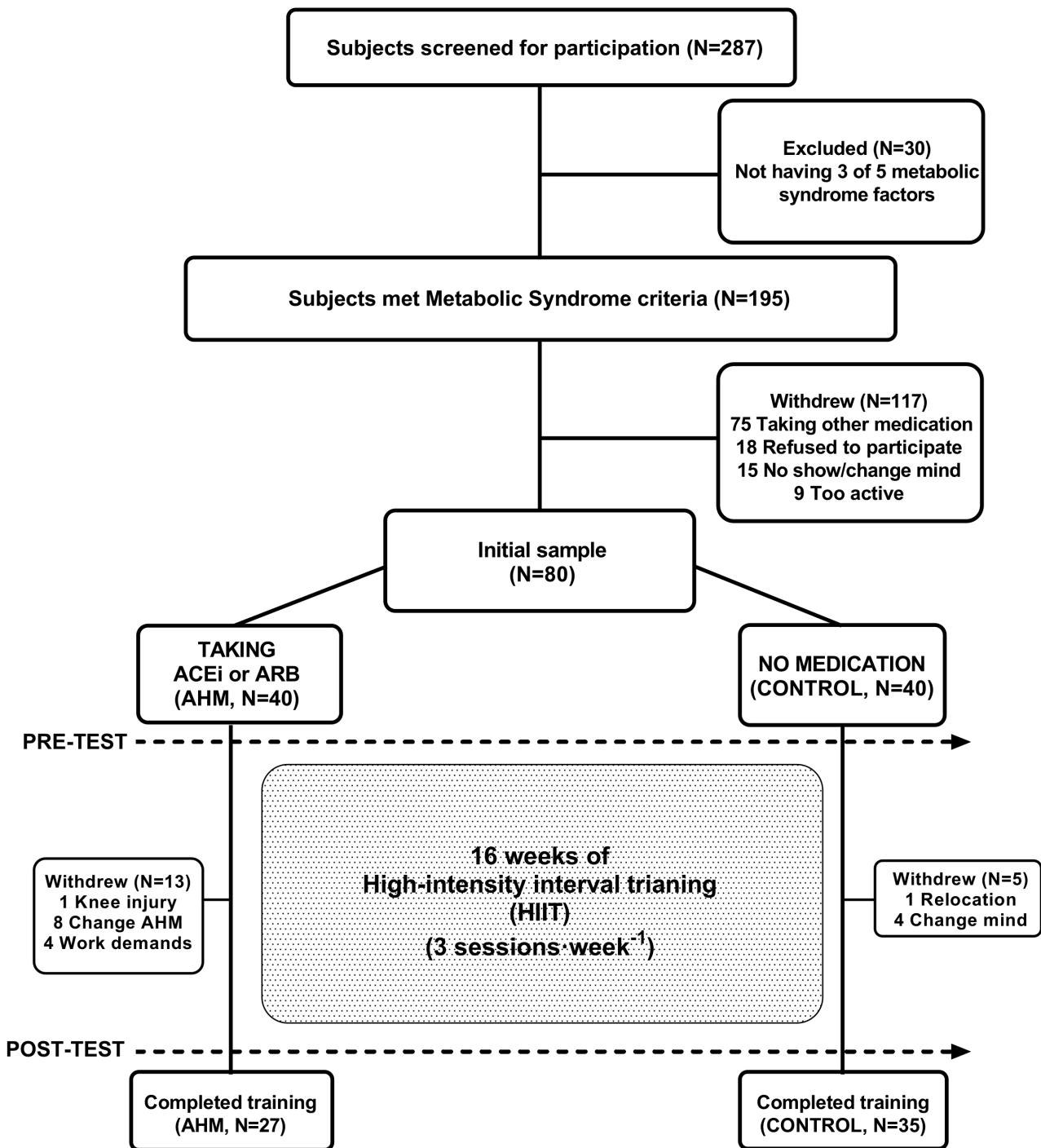


Figure 1

Flow diagram of participant recruitment, group allocation based on medication status, intervention, and follow-up.

Figure 2

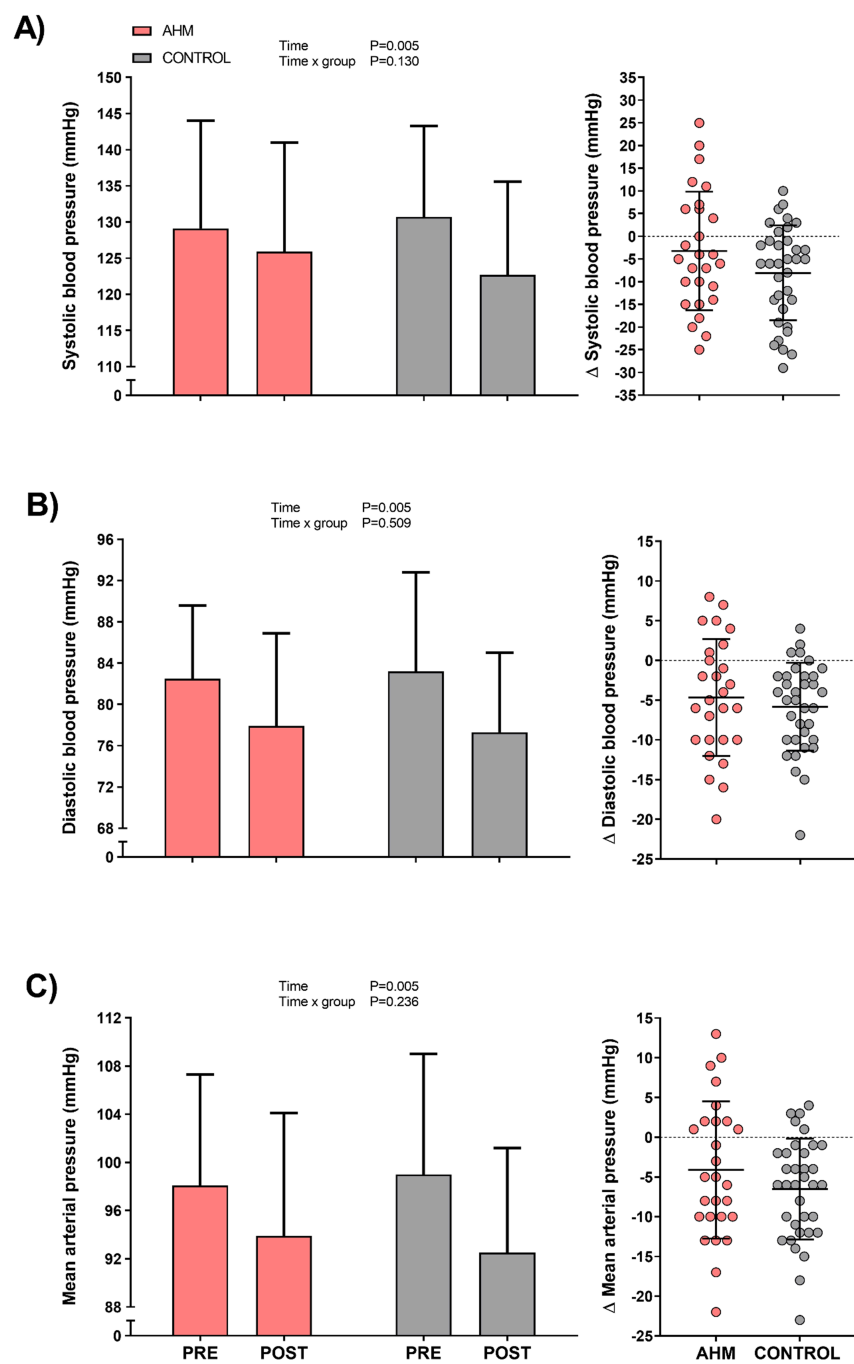


Figure 2

Changes in resting systolic blood pressure (A), diastolic blood pressure (B), and mean arterial pressure (C) after 16 weeks of high-intensity interval training in the AHM and CONTROL groups. Values are presented as bars and dot plots with mean $\pm$ SD.

Figure 3

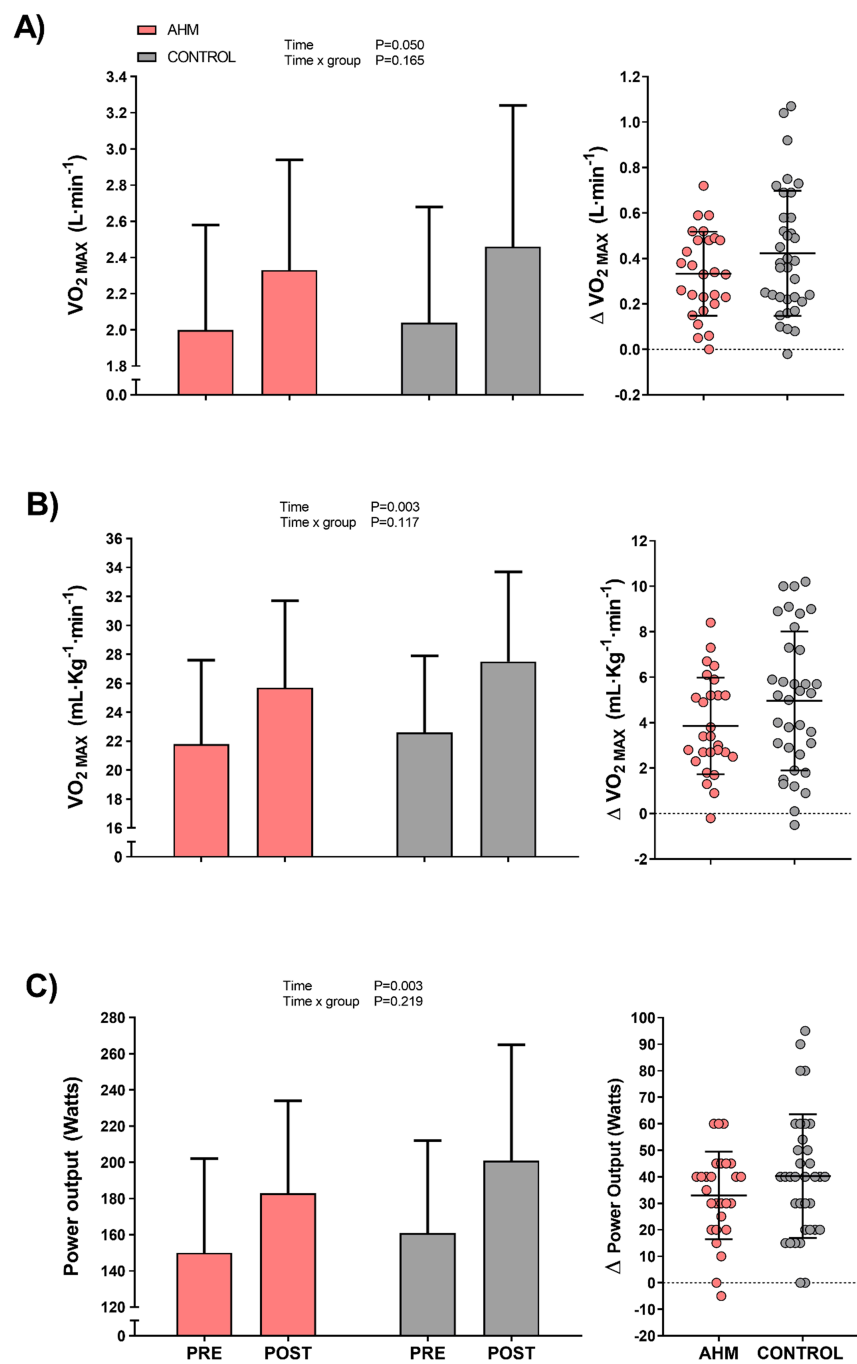


Figure 3

Changes in absolute $VO_{2\text{MAX}}$ (A), relative $VO_{2\text{MAX}}$ (B), and maximal power output (C) after 16 weeks of high-intensity interval training in the AHM and CONTROL groups. Values are presented as bars and dot plots with mean $\pm$ SD.

Figure 4

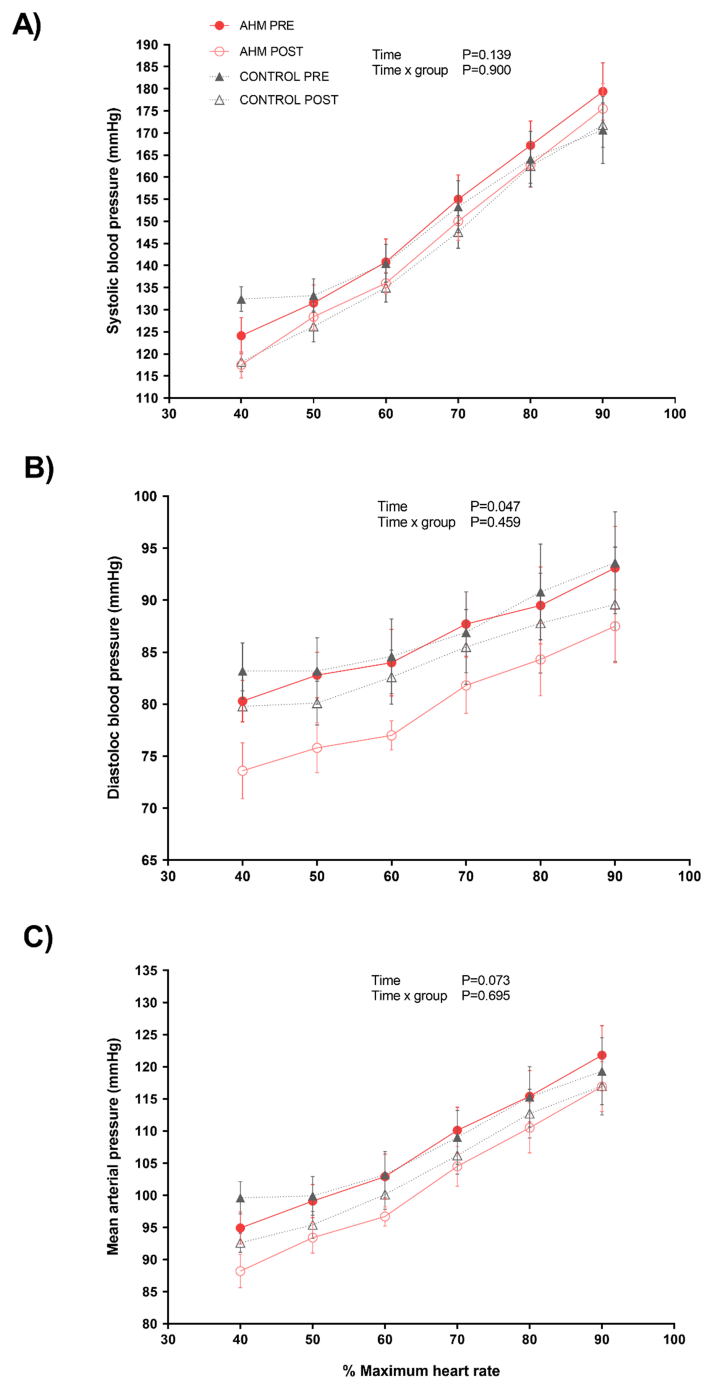


Figure 4

Systolic blood pressure (A), diastolic blood pressure (B), and mean arterial pressure (C) responses during graded exercise before and after 16 weeks of high-intensity interval training in the AHM and CONTROL groups. Blood pressure values are normalized to the percentage of HR_{MAX} to allow direct comparisons between groups and over time and are presented as mean ± SD with individual data points.