Effect of Yearly Exercise on Medication Expense and Benefit–Cost Ratio in Individuals with Metabolic Syndrome: A Randomized Clinical Trial

FELIX MORALES-PALOMO, ALFONSO MORENO-CABAÑAS, LAURA ALVAREZ-JIMENEZ, JUAN F. ORTEGA, and RICARDO MORA-RODRIGUEZ

Exercise Physiology Lab at Toledo, University of Castilla-La Mancha, Toledo, SPAIN

ABSTRACT

MORALES-PALOMO, F., A. MORENO-CABAÑAS, L. ALVAREZ-JIMENEZ, J. F. ORTEGA, and R. MORA-RODRIGUEZ. Effect of Yearly Exercise on Medication Expense and Benefit–Cost Ratio in Individuals with Metabolic Syndrome: A Randomized Clinical Trial. *Med. Sci. Sports Exerc.*, Vol. 55, No. 2, pp. 158–166, 2023. **Introduction:** Lifestyle modification through incorporation of exercise training could improve metabolic syndrome (MetS) clinical components (hypertension, dyslipidemia, hyperglycemia, and visceral abdominal obesity). We aimed to assess if long-term exercise training could restrain the increased pharmacological cost of the clinical management of the MetS. **Methods:** Medicine cost during a 5-yr-long randomized controlled exercise intervention trial was analyzed. After a per-protocol analysis, a group of 64 individuals 53 ± 2 yr old, with overweight (body mass index, 33.4 ± 0.9 $kg \cdot m^{-2}$) and MetS (3.6 ± 0.2 factors) were randomized to a training (4 $months \cdot yr^{-1}$ for 5 yr; EXERCISE, $n = 25$) or to a control group (CONTROL, $n = 26$). Subjects were studied on three occasions during the 5-yr follow-up. Participants continued their routine medication managed by their general practitioner. The main outcome is the 5-yr evolution of medication cost to treat MetS (hyperglycemia, hypertension, and hyperlipidemia). A secondary outcome is the benefit–cost ratio of the exercise intervention. **Results:** In CONTROL, medicine cost increased 160% from baseline ($P < 0.001$), whereas in EXERCISE, it remained unchanged (33%; $P = 0.25$). After the 5-yr follow-up, medicine use was 60% and medicine cost 74% higher in CONTROL than EXERCISE ($P < 0.05$ in both cases). However, MetS z score was similarly reduced over time in both groups ($P = 0.244$ for group–time interaction). The number of prescribed medications increased after 5 yr in CONTROL (89%; $P < 0.001$), whereas it remained stable with yearly training (17%; $P = 0.72$ in EXERCISE). Ten-year atherosclerotic cardiovascular disease risk estimation increased only in CONTROL (15%; $P = 0.05$ for group–time interaction). The benefit in medicine savings (€153 per year and patient) triplicated the estimated cost (€50.8 per year and patient) of the exercise intervention. **Conclusions:** A 5-yr-long supervised exercise training program in middle-age individuals with MetS prevents the need for increasing medicine use. The savings in pharmacological therapy outweighs the estimated costs of implementing the exercise program. **Key Words:** LONG-TERM EXERCISE, METABOLIC SYNDROME, MEDICATION USE, LIFESTYLE MODIFICATION, HEALTH CARE COST, EXERCISE IS MEDICINE

The metabolic syndrome (MetS) is an insidious and progressive disorder in response to an adverse lifestyle, and its prevalence has reached almost 34% of adults in the United States (1). MetS treatment generally requires polypharmacy, but even after using several medicines, individual risk factors are not always well controlled (2). In turn, polypharmacy leads to drug–drug interactions and inadequate treatment adherence, resulting in poor management of the disease (3). The first-line defense against MetS and other cardiometabolic diseases is lifestyle therapy, which most often will coexist with the pharmacological treatment (4). Lifestyle modification should be introduced early and aggressively and maintained to improve clinical management of MetS (5).

The high prevalence, morbidity, and mortality associated with the MetS have important social and may also have economic consequences (6). The increasing prevalence of the MetS could raise the medical costs associated with increasing prevalence of diseases like diabetes and cardiovascular disease (CVD) (7). Hence, subjects with MetS may have a higher utilization of inpatient, primary care, and pharmacy services than persons without MetS factors, even after 2 yr (8). Although the association between the prevalence of MetS risk factors and adverse clinical outcomes is well established, the health cost–benefit effects of different clinical approaches (nonpharmacological vs pharmacological) to treat MetS are unclear.

Recently we reported that a 4-month training program repeated in five consecutive years prevented a twofold increase

Address for correspondence: Ricardo Mora-Rodriguez, Ph.D., Exercise Physiology Lab at Toledo, University of Castilla-La Mancha, 45071 Toledo, Spain; E-mail: ricardo.mora@uclm.es.
Submitted for publication June 2022.
Accepted for publication September 2022.

0195-9131/23/5502-0158/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000003053

in medication for MetS management while also preventing an 8% decline in cardiorespiratory fitness (as assessed by $\dot{V}O_{2max}$ [9]). A unique feature of the study was that all medications used were carefully recorded throughout the intervention and that all exercise sessions were supervised (i.e., through 5 yr). Increases in medicine use raise health expenses and could become a burden for public health systems (10). As the main novelty, in this secondary analysis, we present the 5-yr analysis of the cost–benefit of pharmacological therapy in MetS individuals who combined or not their pharmacological treatment with exercise training.

MATERIALS AND METHODS

Participants. Fifty-one middle-age (mean age, 58 ± 8 yr), overweight and obese, sedentary subjects (mean body mass index (BMI), 33.4 ± 0.9 $kg \cdot m^{-2}$; <150 $min \cdot wk^{-1}$ of moderate-intensity activity (11)) with MetS completed the study. MetS was defined according to the updated International Diabetes Federation 2009 criteria (12). Exclusion criteria included untreated cardiovascular or renal disease, or any condition associated with exercise intolerance. All subjects provided written, witnessed, informed consent of the protocol approved by the local hospital's ethics committee in accordance with the World Medical Association Declaration of Helsinki.

Experimental design and intervention. We followed a randomized controlled trial design (9). Participants were recruited, clinically screened, and tested in compliance with CONSORT (i.e., Consolidated Standards of Reporting Trials statement [13]; Fig. 1). Participants were stratified in blocks by age, number of MetS factors, and BMI and were randomized to the exercise training (EXERCISE) or standard care (CONTROL) groups. Subjects were studied on three occasions on a 5-yr span always in early November to avoid seasonal effects (14). All participants received attention from the Spanish health care system that included medical counseling and lifestyle advice at least every 6 months. The CONTROL group (n = 26) did not participate in exercise training, whereas the EXERCISE group (n = 25) underwent supervised high-intensity interval cycling (HIIT [15]) with a frequency of three times per week for 4 months per year (end of November to early April). Each session was supervised by a member of the research team for compliance with the training scheme. At testing times, subjects filled out a 3-d nutritional diary analyzed for caloric intake and macronutrient composition (CESNID v1.0; Barcelona, Spain) and wore a wristband activity monitor (Polar Loop Electro, Kempele, Finland) for 48 h to monitor steps per day, standing time, and supine resting time (i.e., physical activity (PA)).

Assessments. We tested subjects in early November, 8 months after the last training bout in the EXERCISE group, to assess the chronic rather than the acute effects of training. Patients arrived at the laboratory in the morning after an overnight fast. Nude body weight (Hawk; Metler, Toledo, OH), height (Stadiometer; Secca 217, Hamburg, Germany), and waist circumference were measured using a nonelastic measuring tape. Fat mass and fat-free mass were determined by bioelectrical impedance analysis (Tanita BC-418; Tanita Corp, Tokyo, Japan). After 10 min of supine rest, blood pressure (BP) was measured in triplicate using a calibrated ECG-gated electrosphygmomanometer (Tango; Suntech Medical, Morrisville, NC).

Then, a 7-mL blood sample was collected to determine serum glucose, insulin, and lipids concentration (i.e., triglycerides, total cholesterol, HDL cholesterol (HDL-c), and LDL cholesterol concentration calculated by Friedewald et al. [16]). Insulin sensitivity was calculated using the homeostasis model assessment (17). We calculated a MetS z score to assess the continuous rather than dichotomous (have/not have MetS) evolution of each MetS component into a compound score. Z score was calculated as the difference between the subject's and threshold value divided by the group standard deviations for each MetS criterion (15). Ten-year cardiovascular risk percentage was determined using the atherosclerotic cardiovascular disease (ASCVD) algorithm (18), which includes race, sex, age, TC, HDL-c, systolic BP, treatment for hypertension, diabetes status, and smoking status as predicting factors.

Medication use and cost. The 51 patients were followed by 38 different general practitioners. Practitioners followed the Spanish Society of Family and Community Medicine guidelines for the management of MetS (19). Guidelines indicate treatment with lifestyle advice, blood analysis every 6 months, and pharmacological prescription adjusted to blood chemistry, BP values, and body weight evolution. Physicians were blinded to group allocation. Participants brought all prescription medications to the laboratory at baseline and at 2- and 5-yr visits to ensure recording accuracy. Only medicines to control hyperglycemia, hypertension, and hyperlipidemia (MetS factors) were computed. We used the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) system (20) to monitor the evolution in the number and dose of medications as follows:

$$\begin{aligned}\text{Medicine use score} = {} & [\text{medicine 1 (subject used dose/DDD index)}] \\ & + [\text{medicine 2 (subject used dose/DDD index)}] + \ldots \\ & + [\text{medicine } n \text{ (subject used dose/ATC/DDD index)}]\end{aligned}$$

We used the DDD (21) as the international standard in drug utilization research as recommended by the World Health Organization since 1996. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Only one DDD is assigned per ATC code. DDDs provide a standard dose of drug use, independent of manufacturer presentation, enabling the researcher to follow up medication evolution in patients taking different brands of the same drug.

Medication cost calculation for subject's medicines was based on the Spanish Ministry of Health official web page (www.sanidad.gob.es/profesionales/nomenclator.do). We multiplied the cost of one pill by the number of pills per day by 365 d to calculate the yearly cost for each medication. Costs

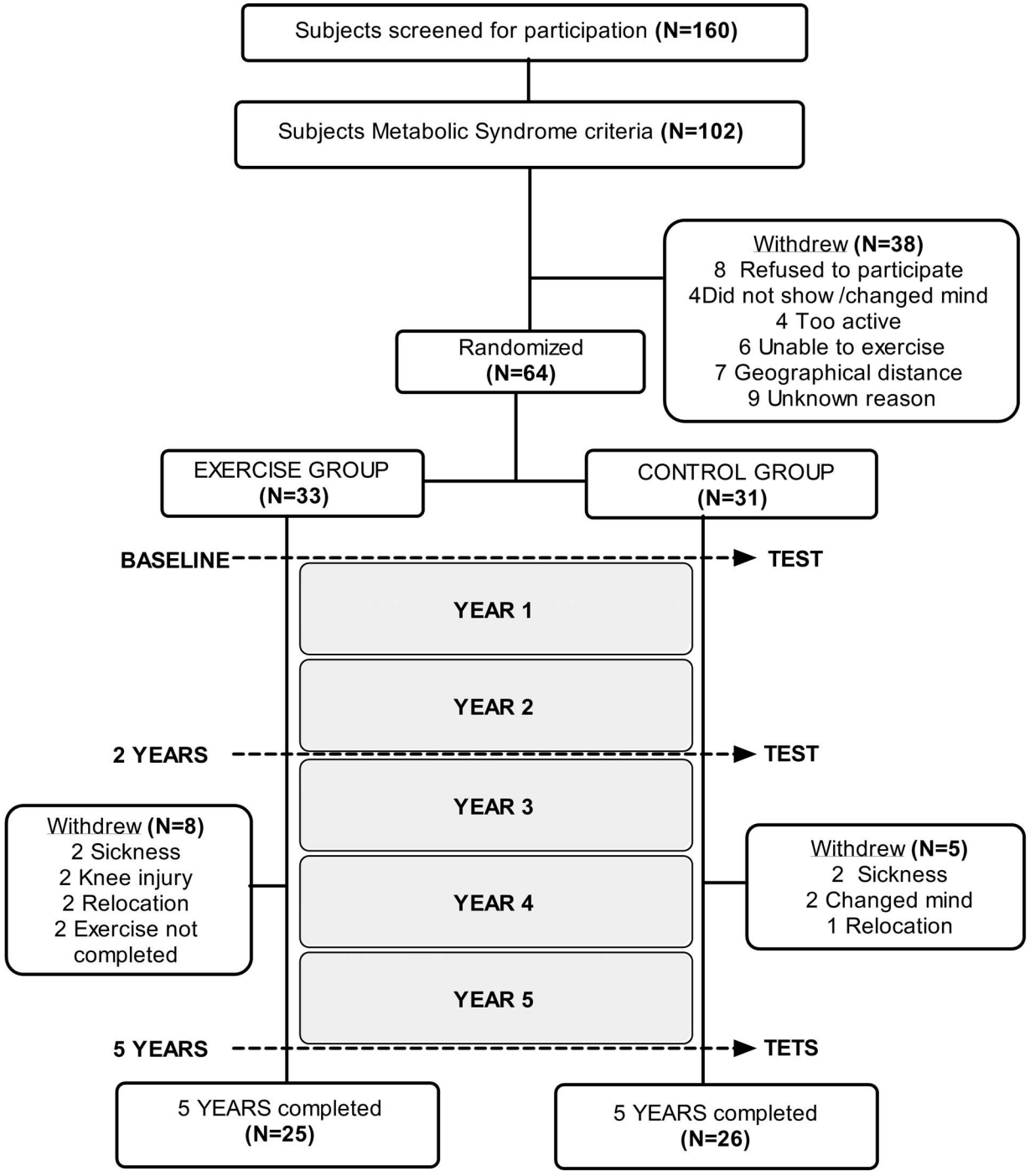

FIGURE 1—CONSORT schematic representation of the study procedures.

include public payer and patient payment (drug retail price = reimbursement + patient's co-payment) and are reported in euros (EUR).

The calculation of the costs of the supervised exercise program included the following: *a*) the cost of the sport specialist personnel, *b*) the cost of renting the sports facility, and *c*) the cost of accident insurance for each patient. The yearly cost of the whole program and the cost per participant were calculated in euros for the city of Toledo (Spain).

Statistical analysis. We used per protocol analysis, and only patients who completed the treatment protocol were included in the statistical analysis. Data are presented as mean ± SEM.

TABLE 1. Five-year evolution of anthropometric MetS factors and other clinical variables by group.

	CONTROL (n = 26)			EXERCISE (n = 25)			P	
	Baseline	2 yr	5 yr	Baseline	2 yr	5 yr	Time	Time–Group
BMI (kg·m^{-2})	34.0 ± 0.9	34.2 ± 1.0	33.6 ± 1.1	32.7 ± 1.0	31.9 ± 0.9	31.7 ± 0.9	0.139	0.094
Weight (kg)	91.9 ± 3.8	92.7 ± 4.2	90.9 ± 4.5	94.3 ± 3.1	91.7 ± 2.7	91.6 ± 2.6	0.156	0.074
Fat mass (kg)	34.8 ± 1.8	34.4 ± 2.0	33.9 ± 2.2	31.3 ± 1.7	29.1 ± 1.5	28.8 ± 1.6	0.097	0.331
Fat-free mass (kg)	57.1 ± 2.5	57.6 ± 2.5	57.0 ± 2.7	62.3 ± 2.1	61.7 ± 1.9	62.3 ± 1.9	0.989	0.314
Waist circumference (cm)	109.5 ± 2.4	111.6 ± 2.8	112.1.5 ± 2.9	107.7 ± 2.4	106.5 ± 2.1	107.2 ± 1.9	0.536	0.089
Glucose (mg·dL^{-1})	112.7 ± 4.3	120.3 ± 7.3	109.7 ± 4.7	114.4 ± 5.1	113.6 ± 6.2	112.6 ± 5.8	0.162	0.235
Triglycerides (mg·dL^{-1})	132.6 ± 17.1	139.2 ± 16.3	124.1 ± 13.9	124.7 ± 9.0	126.3 ± 8.0	116.9 ± 7.7	0.240	0.880
HDL-c (mg·dL^{-1})	43.2 ± 3.5	45.2 ± 2.7	44.0 ± 2.9	43.2 ± 2.2	47.1 ± 2.2	48.9 ± 2.7	**0.022**	0.121
Mean arterial pressure (mm Hg)	100.5 ± 2.6	97.9 ± 1.8	92.8 ± 1.7	98.9 ± 2.3	93.0 ± 1.7	91.7 ± 1.8	**<0.001**	0.190
MetS z score	0.43 ± 0.10	0.18 ± 0.11	0.00 ± 0.13	0.24 ± 0.11	0.01 ± 0.13	–0.04 ± 0.13	**<0.001**	0.451
10-yr ASCVD risk (%)	15.5 ± 1.7	17.0 ± 1.9	17.9 ± 1.9	16.5 ± 1.7	14.4 ± 1.6	16.4 ± 1.4	0.120	**0.049**

Data are presented as mean ± SEM for 51 MetS patients divided into the CONTROL (n = 26) and EXERCISE (n = 25) groups.

Smirnov–Kolmogorov test revealed that data were normally distributed. Preintervention differences between groups were studied using Student t-test for independent samples. Mixed-design ANOVA was used to analyze differences across time (repeated measures) and between experimental groups (CONTROL vs EXERCISE) in all reported variables. When the time–group interaction was significant, vertical multiple comparisons among pairwise groups were performed using Bonferroni *post hoc* testing. The 95% confidence intervals (CI) were also calculated. The difference in proportion within-and-between groups in medication use (per type of drug) at 2- and 5-yr follow-up compared with baseline was tested using a Cochrane Q test and χ^2 test, respectively. Changes within-and-between groups in yearly medication cost from baseline to 2- and 5-yr follow-up were assessed using the Friedman test and Mann–Whitney U test, respectively. Statistical analyses were performed using SPSS (IBM Corporation, Armonk, NY), version 28, and the statistical significance level was set at $\alpha < 0.05$ (two-tailed).

RESULTS

Baseline characteristics, PA, and diet. As designed, no differences existed between CONTROL and EXERCISE at preintervention baseline in age (54 ± 2 vs 52 ± 2 yr), number of MetS factors (3.5 ± 0.2 vs 3.7 ± 0.2), or BMI (34.0 ± 0.9 vs 32.7 ± 1.0 kg·m^{-2}). Participants were all Caucasians, with 71% men and 29% women (all of them postmenopausal). There were no differences between groups in caloric intake or PA at any time point ($P > 0.05$).

MetS and other health parameters. The effects of the exercise intervention on the different MetS components and health-related parameters are displayed in Table 1. MetS z score and mean arterial pressure responded with reductions over time (both $P < 0.001$). A significant time effect ($P = 0.022$) was observed also for HDL. A significant group–time interaction effects was found ($P = 0.050$), with 10-yr ASCVD risk increasing from baseline to 5-yr follow-up only in the control group (15%; 95% CI, 0.003–0.049).

Medication use and cost. The evolution in medicine use score (DDD index) and the number of prescribed medications in each group during 5-yr are depicted in Table 2. A significant time effect was observed for BP- and glucose-lowering medications in the number of prescribed medications ($P = 0.001$ and $P = 0.003$, respectively). A time effect was also observed for BP-lowering medication in the medicine use score ($P = 0.006$). A significant group–time interaction effect was found in the total medicine use score ($P = 0.005$) and the total number of prescribed medications per patient ($P = 0.017$). The medicine

TABLE 2. Five-year evolution of medication use by group.

	CONTROL (n = 26)			EXERCISE (n = 25)			P	
	Baseline	2 yr	5 yr	Baseline	2 yr	5 yr	Time	Time–Group
BP-lowering								
Number of prescribed medications	0.7 ± 0.2	0.9 ± 0.2	1.4 ± 0.3	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.2	**0.001**	0.095
Medicine use score (DDD index)	0.8 ± 0.3	1.4 ± 0.4	1.7 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	1.4 ± 0.3	**0.006**	0.186
Cholesterol-lowering								
Number of prescribed medications	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.172	0.382
Medicine use score (DDD index)	0.7 ± 0.3	1.0 ± 0.4	1.0 ± 0.4	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.061	0.571
Glucose-lowering								
Number of prescribed medications	0.3 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.2	**0.003**	0.235
Medicine use score (DDD index)	0.3 ± 0.2	1.4 ± 0.4	1.7 ± 0.3	1.2 ± 0.2	1.3 ± 0.3	1.4 ± 0.3	0.069	0.192
Triglyceride-lowering								
Number of prescribed medications	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.583	0.105
Medicine use score (DDD index)	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.1 ± 0.1	0.399	0.140
Total medications								
Number of prescribed medications	1.4 ± 0.3	1.8 ± 0.3[a]	2.7 ± 0.4[a,b]	1.6 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	**<0.001**	**0.017**
Medicine use score (DDD index)	2.0 ± 0.6	3.2 ± 0.8[a]	3.9 ± 0.7[a,b]	2.4 ± 0.4	2.7 ± 0.4	2.7 ± 0.4	**<0.001**	**0.005**

Data are presented as mean ± SEM for 51 MetS patients divided into the CONTROL (n = 26) and EXERCISE (n = 25) groups.
Significant P values for time or group–time interaction effects are in bold.
[a]Significant change from baseline within each group.
[b]Significant change from 2 yr within each group.

use score increased above baseline after 2 and 5 yr in the CONTROL (1.15 [56% increase; 95% CI, 0.15–2.15] and 1.89 [93% increase; 95% CI, 1.03–2.75], respectively; both $P < 0.02$) and from years 2 to 5 (0.75 [23% increase; 95% CI, 0.01–1.48]; $P = 0.046$). Similarly, number of prescribed medications per patient increased above baseline after 2 and 5 yr in the CONTROL (0.42 [30% increase; 95% CI, 0.10–0.74] and 1.27 [89% increase; 95% CI, 0.69–1.84], respectively; both $P < 0.006$), and from years 2 to 5 (0.85 [46% increase; 95% CI, 0.36–1.32]; $P < 0.001$).

Table 3 shows the evolution of each type of medicine (percent of subjects taking that drug) and its yearly cost. The number of patients in the CONTROL group under BP-lowering treatment and sum of total medication increased from baseline after 5 yr ($P = 0.014$ and $P = 0.025$, respectively). From baseline to 2-yr follow-up, the annual medication cost in the CONTROL group increased for glucose-lowering (159%; $P < 0.001$) and total medication (73%; $P = 0.005$). This difference was observed also after 5 yr of follow-up for BP- (76%; $P = 0.01$), cholesterol- (118%; $P = 0.02$), glucose-lowering (333%; $P = 0.05$), and total medication (160%; $P < 0.001$). From years 2 to 5, the increase was significant for BP-lowering (43%; $P = 0.002$) and total medication (51%; $P = 0.005$). In EXERCISE, the annual medication cost increased for BP lowering (27%; $P = 0.025$) from baseline to 5 yr.

At baseline, annual medication cost per patient was similar between the CONTROL and EXERCISE groups (i.e., €139 vs €151; $P = 0.32$). However, after 5 yr, annual medication cost was 74% higher in CONTROL than in EXERCISE (€361 vs €208; $P = 0.043$; Fig. 2).

Yearly cost of the training program was calculated for a group of 25 individuals and per participant (Table 4). The exercise program consisted of 48 exercise sessions per year, each one of 1-h duration. The salary of the sports specialist amounted to €547.2 per year. The sports facility renting was calculated based on the 2021 published prices of the city council of Toledo (Spain). The use of the facilities amounted to €422.4 per year. Each trainee paid a compulsory fee of €12 for accident insurance per year. Yearly costs of the exercise program were €1270.6. As a result, the average cost per patient was €50.8 per year.

DISCUSSION

This study was specifically designed to examine the efficacy of long-term yearly exercise training on the clinical management of MetS. The main finding was that the CONTROL group needed a higher medication cost than the EXERCISE group to manage their MetS. This happened because the CONTROL group undertook a substantial increase in total medication use, assessed by medication use score based on DDD

TABLE 3. Five-year evolution of medicine cost per drug type.

	CONTROL ($n = 26$)			EXERCISE ($n = 25$)		
	Baseline	2 yr	5 yr	Baseline	2 yr	5 yr
BP-lowering						
ACE inhibitors[a,b]	3 (12)	4 (15)	5 (19)	4 (16)	4 (16)	4 (16)
ARB[a,b]	4 (15)	4 (15)	6 (23)	9 (36)	11 (44)	11 (44)
Calcium-channel blocker[a,b]	2 (8)	0 (0)	3 (12)	2 (8)	2 (8)	4 (16)
Thiazide diuretics[a,b]	5 (19)	10 (38)	15 (58)	4 (16)	4 (16)	5 (20)
β-Blockers[a,b]	4 (15)	4 (15)	6 (23)	0 (0)	0 (0)	0 (0)
Subjects under pharmacological treatment[a,b]	11 (42)	13 (50)	17 (65)[e]	15 (60)	16 (64)	16 (64)
Yearly cost (€)[c,d]	53 (0)	65 (10)	93 (33)[e, f]	72 (43)	86 (63)	91 (54)[e]
Cholesterol-lowering						
Statins[a,b]	10 (38)	10 (38)	13 (50)	8 (31)	8 (31)	8 (31)
Ezetimibe[a,b]	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)	1 (4)
Subjects under pharmacological treatment[a,b]	10 (38)	10 (38)	13 (50)	8 (32)	8 (32)	9 (36)
Yearly cost (€)[c,d]	39 (0)	58 (0)	84 (6)[e]	21 (0)	45 (0)	54 (0)
Glucose-lowering						
Biguanides[a,b]	4 (15)	7 (27)	7 (27)	6 (23)	7 (27)	9 (35)
DDP-4[a,b]	3 (12)	4 (15)	4 (15)	3 (12)	3 (12)	1 (4)
Sulphonylureas[a,b]	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
SGLT-2[a,b]	0 (0)	1 (4)	3 (12)	0 (0)	0 (0)	1 (4)
Meglitinides[a,b]	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
GLP-1[a,b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Subjects under pharmacological treatment[a,b]	4 (15)	7 (27)	7 (27)	6 (24)	6 (24)	9 (36)
Yearly cost (€)[c,d]	40 (0)	102 (0)[e]	171 (0)[e]	34 (0)	33 (0)	55 (0)
Triglyceride-lowering						
Fibrates[a,b]	1 (4)	2 (8)	3 (12)	5 (19)	5 (19)	2 (8)
Subjects under pharmacological treatment[a,b]	1 (4)	2 (8)	3 (12)	4 (16)	4 (16)	2 (8)
Yearly cost (€)[c,d]	8 (0)	13 (0)	13 (0)	23 (0)	23 (0)	7 (0)
Total medications						
Subjects under pharmacological treatment[a,b]	17 (65)	19 (73)	22 (85)[e]	18 (72)	19 (76)	20 (80)
Yearly cost (€)[c,d]	139 (36)	240 (82)[e]	361 (114)[e,f]	151 (108)	187 (144)	208 (145)[g]

Data are presented as number of subjects taking that drug (%) and yearly cost data (median) for 51 MetS patients divided into the CONTROL ($n = 26$) and EXERCISE ($n = 25$) groups.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DDP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose co-transporter-2.
[a]Between-group difference using x^2 test.
[b]Within-group difference using Cochran Q test.
[c]Between-group difference using Mann–Whitney U test.
[d]Within-group difference using Friedman test.
[e]Significant change from baseline within each group.
[f]Significant change from 24 months within each group.
[g]Significant difference between CONTROL and EXERCISE groups at that time point (all $P < 0.05$).

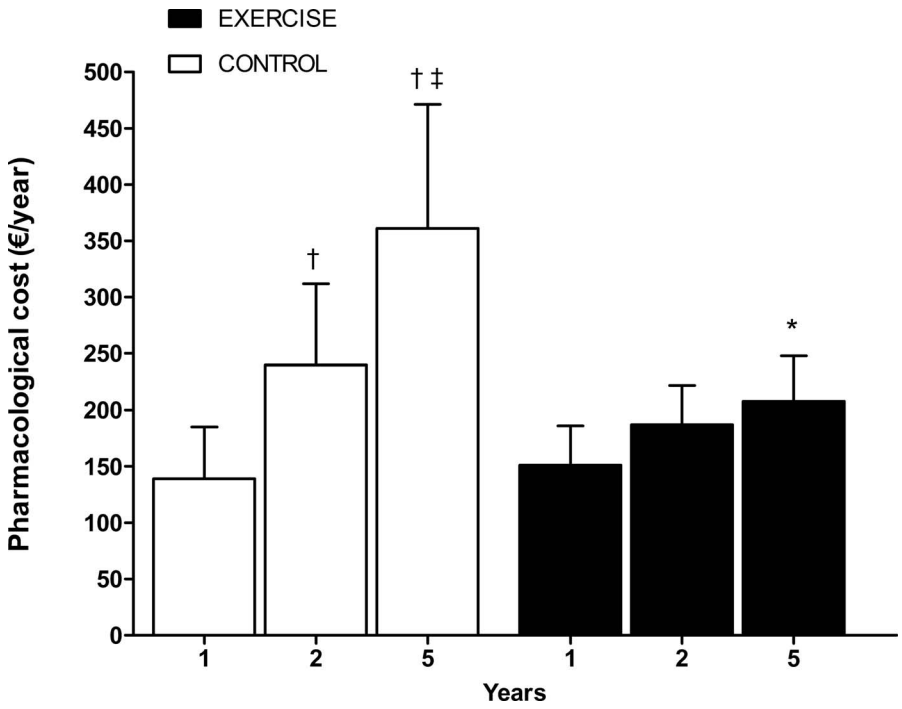

FIGURE 2—Evolution of yearly pharmacological cost during the 5-yr follow-up. Data are presented as mean ± SEM for 51 MetS patients divided into CONTROL and EXERCISE groups. †Significant change from baseline within each group. ‡Significant change from 2 yr within each group. *Significant difference between groups at that time point (all $P < 0.05$).

index, whereas the EXERCISE group avoided any significant increases in total medicine cost. After 5 yr of follow-up, individuals in the CONTROL group necessitated progressive increases in medicine use to manage their MetS condition (Table 2). Specifically, the cost of their BP and glucose-lowering medications increased over the 5-yr testing period.

We found that at baseline, participants were taking an average of 1.5 medications, with an estimated cost of €145 per year for management of the hyperglycemia, hypertension, and hyperlipidemia of their MetS. After 5 yr of supervised exercise training program, participants in the EXERCISE group had significant improvements in MetS parameters (assessed by MetS *z* score; Table 1), while at the same time maintaining medication use and cost. The CONTROL group experienced a similar improvement in MetS *z* score, but with increased medication use and pharmacological cost. The total cost of diabetes, BP, and lipid prescription medications for CONTROL participants at 5 yr was €361 per year compared with €208 per year for EXERCISE participants. At 5 yr, CONTROL group participants increased the number of medications to manage their diabetes, hypertension, and hyperlipidemia by 89% (i.e., 1.4–2.7; Table 2) compared with only 17% in EXERCISE participants.

Strong evidence for the economic burden of MetS comes from large representative data sets such as the National Medical Expenditure Survey (22) and Medical Expenditure Panel Survey (23). Individuals diagnosed with MetS have a yearly extra $2,000 in healthcare costs (8). Average annual total costs among subjects with MetS were 60% ($2150) and 20% ($7863) higher after 2 (8) and 10 (24) yr, respectively. In addition, total costs increased by an average of 24% for each additional MetS component (8,25). Medications to treat the complications of MetS are estimated at 30% of the total medical expenses to treat the MetS and account for $4 of every $10 spent on prescription drugs for adults (7). Information on how to reduce health care costs in this population is important. However, there are a limited number of studies that analyze the cost-effectiveness of exercise programs and its effects on the use of drugs to manage MetS.

Before the intervention, there was no difference in the annual cost of medications between groups. However, after 5 yr of treatment, the CONTROL group augmented medication use and the associated cost increased by 160% (i.e., €139–€361;

TABLE 4. Yearly training program cost and benefit–cost ratio (n = 25).

Parameter	Unit Cost	Details
Sports specialist salary	€11.4 per hour	University graduate in sports sciences × 48 sessions of 1 h
Sports facility renting	€8.8 per hour	Equipped training room in the city of Toledo (Spain) × 48 sessions of 1 h
Insurance	€12 per trainee	25 participants completed the training program
Cost per participant	€50.8	
Benefit in medicine expenses[a]	€153	
Benefit–cost ratio	€3	

[a]Difference in cost of medication at 5 yr between CONTROL and EXERCISE groups as shown at the bottom of Table 3.

Fig. 2). This resulted in €153 larger medicine expenses per subject and year in the CONTROL than in the EXERCISE group. To the best of our knowledge, these are the first data assessing MetS polypharmacy (routinely taking two or more medicines daily [26]) cost evolution. Most of the studies reporting medication use reduction with lifestyle intervention relate to patients with type 2 diabetes mellitus (27,28). In the Look AHEAD study, there was a reduction in the cost of total medication when comparing lifestyle intervention with a standard care group. The significant reduction was 17% after 1 yr ($360 per year [29]) and 7% after 10 yr ($281 per year [27]). Lastly, a reduction of 8% in total medication cost (€113 per year (30)) was reported in a study confining subjects into a controlled environment while applying a combination of a hypocaloric diet and large training volume (15–20 $h \cdot wk^{-1}$).

Expenses on retail pharmaceuticals (i.e., excluding those used during hospital treatment) represented the third largest component of health spending in inpatient and outpatient care. The Organization for Economic Cooperation and Development countries (OECD [31]) reported that per-capita retail pharmaceutical expenditure in 2019 averaged $571 (adjusted for differences in purchasing power). Spending in the United States was more than double the OECD average, whereas most OECD countries fell within a relatively narrow 15% spending range from the average. Taking as a reference the annual expenditure on retail pharmaceuticals per capita in Spain ($505) and the expenditure per CONTROL participants at 5 yr (€361 ($404 in the year 2019)), only the cost of the drugs to manage the MetS components would account for 80% of the total expenditure. Considering the growing prevalence of MetS (32) and its associated polypharmacy (4), the inclusion of yearly exercise programs for MetS individuals could improve clinical management while reducing the financial burden on the health care system.

Exercise therapy is a cost-effective intervention to both prevent and mitigate the impact of the MetS, but it remains underutilized (33). To our knowledge, there are no intervention studies analyzing the impact of long-term exercise on the cost of medications to manage MetS. In contrast, there is plenty of epidemiological cross-sectional data examining the association between physical inactivity and cardiometabolic risk that suggest an increased risk of developing diabetes mellitus and CVD (34,35). Country-specific estimate of the total annual health care expenditure attributable to physical inactivity ranges from 1.2% to 2.5% (36). Recently, two reports have described the relationship between poor levels of PA and health costs. Using questionnaires, both studies observed an association between higher PA levels and lower spending on health care (37), with greater savings in the group of patients with higher CVD risk (38). Insufficient PA poses a huge economic burden on economies and health systems (39). Other study suggests that meeting PA guidelines is associated with a 20% reduction in health care expenditures and resource use among patients with CVD (38).

Data on the benefit–cost of treating a population with high CVD risk (i.e., MetS individuals) with exercise training are scarce. A benefit–cost analysis is usually defined as the ratio between the associated savings divided by the cost of the intervention (36). We computed the yearly cost of the training program including all the factors that contributed to the costs (personnel, facility use, and insurance; Table 4), which is likely similar to many cities in the south of Europe. We divided the yearly medicine saving with exercise training by the costs of providing the training. Because yearly saving per patient in medicine expenses amounted to €153 (benefit) and the cost of the exercise program amounted to €50.8 (cost), the benefit–cost ratio was roughly 3. Thus, for each euro spent on a training program with the duration and characteristic here described, there is a €3 benefit in lowering medicine expense.

The MetS is associated with a twofold increase in the risk of CVD and a 1.5-fold increase in the risk of all-cause mortality (40). Pharmacological treatment of hyperglycemia, hypertension, and hyperlipidemia has been shown to reduce CVD risk in people with MetS, and this triad is now the cornerstone of optimal-care goals in the chronic disease management of MetS (41). Clinical trials and clinical experience show that polypharmacy is required to meet current optimal-care goals (4). Unfortunately, polypharmacy comes at a price of increased cost, side effects, risk of adverse drug interactions, decreased compliance, and decreased quality of life (42). After 5 yr, CONTROL participants in our study were taking, on average, almost three medications daily for the management of MetS (89% increase for $361 per year). Their EXERCISE counterparts were taking slightly less than two medications daily (17% increase for $155 per year). Consistent with our previous 3-yr follow-up study (43), we observed that 5 yr of repeated exercise exposure prevented the increase in the Framingham-predicted 10-yr ASCVD risk index (18), which, however, rose in the CONTROL patients despite the increase in the number of medications.

Several limitations of this study should be mentioned. First, the analysis only includes spending on drugs for the management of MetS (hyperglycemia, hypertension, and hyperlipidemia) and does not include costs of other health goods and services like inpatient and outpatient services and long-term care services (31). Second, our study only included one type of exercise program (i.e., high-intensity interval aerobic exercise), whereas some evidence suggests that including strength training improves the management of MetS, particularly insulin sensitivity (44) and muscle adaptations (45). In contrast, a major strength and novelty of the study is that we performed a 5-yr follow-up supervised exercise training after a compensated randomization of MetS individuals, and that allow us to directly assess the effect of lifestyle therapy (i.e., exercise training) on pharmacy expenses in comparison to the control group.

CONCLUSIONS

In conclusion, 4 months of high-intensity aerobic exercise in MetS individuals (i.e., EXERCISE group) prevented the 2.5-fold increase in the cost of their pharmacological treatment that was observed in the nonexercising group (i.e., CONTROL group). The estimated cost of the training program was only

one-third of the saving obtained in medicine treatment reduction. Furthermore, exercise training prevented an increase in the rate of atherosclerotic cardiovascular risk in the next 10 yr. The health and economic impact (benefit–cost) of incorporating exercise training lifestyle to individuals with the MetS (20%–40% of the adult population in many countries) is positive and significant within 5 yr of implementation.

The authors thank the volunteers for their dedication to the training. This work has not been previously presented. This study was partially funded by a grant from the Spanish Ministry of Science and Innovation (PID2020-116159RB-IOOMCIN/AEI/10.13039/501100011033). The authors have no conflicts of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

ClinicalTrials.gov identifier: NCT03019796.

REFERENCES

1. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA*. 2015; 313(19):1973–4.
2. Lillich FF, Imig JD, Proschak E. Multi-target approaches in metabolic syndrome. *Front Pharmacol*. 2021;11:554961.
3. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028–35.
4. Grundy SM. Drug therapy of the metabolic syndrome: minimizing the emerging crisis in polypharmacy. *Nat Rev Drug Discov*. 2006; 5(4):295–309.
5. Bassi N, Karagodin I, Wang S, et al. Lifestyle modification for metabolic syndrome: a systematic review. *Am J Med*. 2014;127(12):1242.e1–10.
6. Brixner D, Said Q, Kirkness C, Oberg B, Ben-Joseph R, Oderda G. Assessment of cardiometabolic risk factors in a national primary care electronic health record database. *Value Health*. 2007;10(S1):S29–36.
7. Marangos PJ, Okamoto LJ, Caro JJ. Economic burden of the components of the metabolic syndrome. In: Preedy VR, editor. *Handbook of Disease Burdens and Quality of Life Measures*. New York (NY): Springer; 2010. pp. 1135–49.
8. Boudreau DM, Malone DC, Raebel MA, et al. Health care utilization and costs by metabolic syndrome risk factors. *Metab Syndr Relat Disord*. 2009;7(4):305–14.
9. Morales-Palomo F, Moreno-Cabañas A, Ramirez-Jimenez M, et al. Exercise reduces medication for metabolic syndrome management: a 5-year follow-up study. *Med Sci Sports Exerc*. 2021;53(7):1319–25.
10. Institute of Medicine Committee on Assuring the Health of the Public in the 21st Century. *The Future of the Public's Health in the 21st Century*. Washington (DC): National Academies Press (US); 2002.
11. WHO Guidelines Approved by the Guidelines Review Committee. In: *Global Recommendations on Physical Activity for Health*. Geneva (Switzerland): World Health Organization; 2010.
12. Alberti KG, Eckel RH, Grundy SM, 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.
13. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA*. 1996;276(8):637–9.
14. Kamezaki F, Sonoda S, Nakata S, et al. Association of seasonal variation in the prevalence of metabolic syndrome with insulin resistance. *Hypertens Res*. 2013;36(5):398–402.
15. Morales-Palomo F, Ramirez-Jimenez M, Ortega JF, Mora-Rodriguez R. Effectiveness of aerobic exercise programs for health promotion in metabolic syndrome. *Med Sci Sports Exerc*. 2019;51(9):1876–83.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–9.
18. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743–53.
19. Vilaseca Canals J, Espinàs Boquet J. *Guía terapéutica en Atención Primaria; basada en la selección razonada de medicamentos (Therapeutic Guide in Primary Care; Based on the Reasoned Selection of Drugs)*. 6th ed. Barcelona (Spain): semFYC ediciones; 2016, 584 p.
20. WHO Collaborating Center for Drug Statistics Methodology. ATC/DDD Index. 2017. Available from: https://www.whocc.no/atc_ddd_index/.
21. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2022*. Oslo (Norway): Norwegian Inst Publ Hlth; 2021.
22. Thorpe KE, Howard DH. The rise in spending among Medicare beneficiaries: the role of chronic disease prevalence and changes in treatment intensity. *Health Aff (Millwood)*. 2006;25(5):w378–88.
23. Xu KT, Moloney M, Phillips S. Economics of suboptimal drug use: cost-savings of using JNC-recommended medications for management of uncomplicated essential hypertension. *Am J Manag Care*. 2003;9(8):529–36.
24. Curtis LH, Hammill BG, Bethel MA, Anstrom KJ, Gottdiener JS, Schulman KA. Costs of the metabolic syndrome in elderly individuals: findings from the Cardiovascular Health Study. *Diabetes Care*. 2007;30(10):2553–8.
25. Nichols GA, Moler EJ. Metabolic syndrome components are associated with future medical costs independent of cardiovascular hospitalization and incident diabetes. *Metab Syndr Relat Disord*. 2011; 9(2):127–33.
26. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017; 17(1):230.
27. Espeland MA, Glick HA, Bertoni A, et al. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the action for health in diabetes. *Diabetes Care*. 2014;37(9):2548–56.
28. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318(7):637–46.
29. Redmon JB, Bertoni AG, Connelly S, et al. Effect of the Look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care*. 2010;33(6):1153–8.
30. Lanhers C, Walther G, Chapier R, et al. Long-term cost reduction of routine medications following a residential programme combining physical activity and nutrition in the treatment of type 2 diabetes: a prospective cohort study. *BMJ Open*. 2017;7(4):e013763.
31. OECD. *Health at a Glance, OECD Indicators. Pharmaceutical Sector: Pharmaceutical Expenditure*. Paris (France): Organization for Economic Cooperation and Development; 2021.
32. Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. *JAMA*. 2020;323(24):2526–8.
33. Myers J, Kokkinos P, Nyelin E. Physical activity, cardiorespiratory fitness, and the metabolic syndrome. *Nutrients*. 2019;11(7):1652.

34. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation*. 2010;122(7):743–52.
35. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia*. 2012;55(11): 2895–905.
36. Katzmarzyk PT. Cost-effectiveness of Exercise is Medicine. *Curr Sports Med Rep*. 2011;10(4):217–23.
37. Coughlan D, Saint-Maurice PF, Carlson SA, Fulton J, Matthews CE. Leisure time physical activity throughout adulthood is associated with lower medicare costs: evidence from the linked NIH-AARP diet and health study cohort. *BMJ Open Sport Exerc Med*. 2021;7(1): e001038.
38. Valero-Elizondo J, Salami JA, Osondu CU, et al. Economic impact of moderate-vigorous physical activity among those with and without established cardiovascular disease: 2012 Medical Expenditure Panel Survey. *J Am Heart Assoc*. 2016;5(9):e003614.
39. Pratt M, Norris J, Lobelo F, Roux L, Wang G. The cost of physical inactivity: moving into the 21st century. *Br J Sports Med*. 2014;48(3):171–3.
40. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56(14):1113–32.
41. Grundy SM, Hansen B, Smith SC, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome. *Circulation*. 2004;109(4):551–6.
42. Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol*. 2014;64(20):2071–82.
43. Morales-Palomo F, Ramirez-Jimenez M, Ortega JF, Lopez-Galindo PL, Fernandez-Martin J, Mora-Rodriguez R. Effects of repeated yearly exposure to exercise-training on blood pressure and metabolic syndrome evolution. *J Hypertens*. 2017;35(10):1992–9.
44. Moreno-Cabañas A, Ortega JF, Morales-Palomo F, Ramirez-Jimenez M, Alvarez-Jimenez L, Mora-Rodriguez R. Substitution of parts of aerobic training by resistance training lowers fasting hyperglycemia in individuals with metabolic syndrome. *Appl Physiol Nutr Metab*. 2021;46(1):69–76.
45. Moreno-Cabañas A, Ortega JF, Morales-Palomo F, Ramirez-Jimenez M, Alvarez-Jimenez L, Mora-Rodriguez R. Concurrent endurance and resistance training enhances muscular adaptations in individuals with metabolic syndrome. *Scand J Med Sci Sports*. 2021;31(7):1440–9.