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Article

Relationship between Cardiometabolic Factors and the Response of Blood Pressure to A One-year Primary Care Lifestyle Intervention in Metabolic Syndrome Patients

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Abstract: Introduction: Systemic hypertension has been recognized as a modifiable traditional cardiovascular risk factor and influenced by many factors such as eating habits, physical activity, diabetes and obesity. **Objective:** The objective of this study was to identify factors that predict changes in blood pressure induced by a one-year lifestyle intervention in primary care settings involving a collaboration between family physicians, dietitians, and exercise specialists. **Design:** Cohort study and lifestyle intervention. **Participants:** Patients with metabolic syndrome diagnosis were recruited by family physicians participating in primary care lifestyle intervention among several family care clinics across Canada. **Interventions:** Participants for whom all cardiometabolic data at the beginning (T0) and the end (T12) of the intervention were available were included in the present analysis (n=101). Patients visited the dietitian and the exercise specialist weekly for the first three months and monthly for the last nine months. Diet quality, exercise capacity, anthropometric indicators, and cardiometabolic variables were evaluated at T0 and at T12. **Main outcomes:** The intervention induced a significant decrease in waist circumference (WC), systolic (SBP) and diastolic (DBP) blood pressure, and plasma triglycerides and an increase in cardiorespiratory fitness (estimated VO_2max). **Results:** Body weight ($p<0.001$), body mass index (BMI) ($p<0.001$), and plasma glucose ($p=0.006$) reduction and VO_2max increase ($p=0.048$) were all related to changes in SBP. WC was the only variable for which changes were significantly correlated with those in both SBP ($p<0.0001$) and DBP ($p=0.0004$). Variations in DBP were not associated with changes in other cardiometabolic variables to a statistically significant extent. Twelve participants were identified as adverse responders (AR) in both SBP and DBP and displayed less favorable changes in WC. **Conclusion:** The beneficial effects of the primary care lifestyle intervention on blood pressure were significantly associated with cardiometabolic variables, especially WC. These findings suggest that a structured lifestyle intervention in primary care can help improve cardiometabolic risk factors in patients with metabolic syndrome.

Keywords: blood pressure; cardiorespiratory fitness; waist circumference; lifestyle intervention; primary care; adverse responders; metabolic syndrome

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1. Introduction

Systemic hypertension has been recognized as a modifiable traditional cardiovascular risk factor affecting almost 25% of the Canadian adult population[1]. High blood pressure (BP) is influenced by many factors such as eating behaviors, physical activity, diabetes, and obesity[1], especially visceral adipose tissue (VAT)[2-4], and cardiorespiratory fitness (CRF) levels[4-6]. Results from our laboratory previously demonstrated that individuals characterized with low VAT systematically displayed favorable values of systolic (SBP) and diastolic blood pressure (DBP), independent of their fitness level[7], and presented a reduced cardiometabolic risk[8]. VAT can be directly measured using axial tomography scans, although waist circumference (WC) was shown to be a valid clinical marker of VAT that is easy to use in a clinical setting[9].

The current literature suggests that lifestyle interventions may reduce BP[10], body weight, and diabetes incidence[9,11-14]. Nakao et al.[15] assessed the impact of a three-year lifestyle intervention including a minimal exercise prescription in patients with a metabolic syndrome (MetS) diagnosis. They showed significant reductions in WC, body mass index (BMI), SBP, DBP, and plasma triglyceride (TG) levels and an increase in HDL-cholesterol compared to control participants[15]. Gomez-Huelgas et al.[16] evaluated the effect of a three-year lifestyle intervention conducted by primary care providers in a randomized controlled trial among MetS patients and showed significant beneficial changes in WC, SBP, DBP, and HDL-cholesterol in the experimental group compared to control participants. To the best of our knowledge, few studies have investigated the relationship between BP and the response to lifestyle interventions and its association with other cardiometabolic factors in primary care settings following a lifestyle intervention in patients with MetS. Thus, the objective of the present study was to identify cardiometabolic factors that predict changes in BP induced by a one-year lifestyle intervention designed to reverse MetS. We hypothesized that an increase in maximal oxygen uptake (VO_2max) and a decrease in WC would predict the changes of SBP and DBP in a pre-post structured intervention study such as the Canadian Health Advanced by Nutrition and Graded Exercise (CHANGE) program.

2. Methods

2.1. Study population

The characteristics of participants in the CHANGE program have been previously reported[17]. The CHANGE program (website: https://www.metabolicsyndromecanada.ca/change-program) is a registered clinical trial (clinicaltrials.gov, ID: NCT01616563). Briefly, individuals having received a diagnosis of MetS by their family physician were approached for consent and participation in this prospective study[17,18]. Initially, 305 patients were recruited in the CHANGE program through their family physicians. In the present study, 101 patients were analyzed according to the criterion of having all cardiometabolic data available at both T0 and T12. As further described, the study sample was also subdivided into adverse responders (AR) (n =10) and other participants (n =91). Ethics approvals were obtained from Health Research Ethics Board-Biomedical (University of Alberta), Comité d'éthique de la recherche des Centres de santé et de services sociaux de la Vieille-Capitale, and the Institutional Review Board Services, A Chesapeake IRB Company (Aurora, Ont.)[17].

2.2. Experimental design

Participants were followed over a one-year lifestyle intervention involving a collaboration between family physicians, registered dietitians, and exercise specialists (Figure 1)[17]. Participants were given individualized diet and physical activity plans that were supervised by the dietitian and the exercise specialist[17,18] on a weekly basis for the first three months and monthly for the last nine months of the intervention[18]. The family physician monitored the participant throughout the program and evaluated MetS variables at baseline (T0) and 12 months (T12)[17]. Diet quality, assessed by a Canadian version of the

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Healthy Eating Index (HEI-C) score, and exercise capacity were also measured at T0 and T12[18,19].

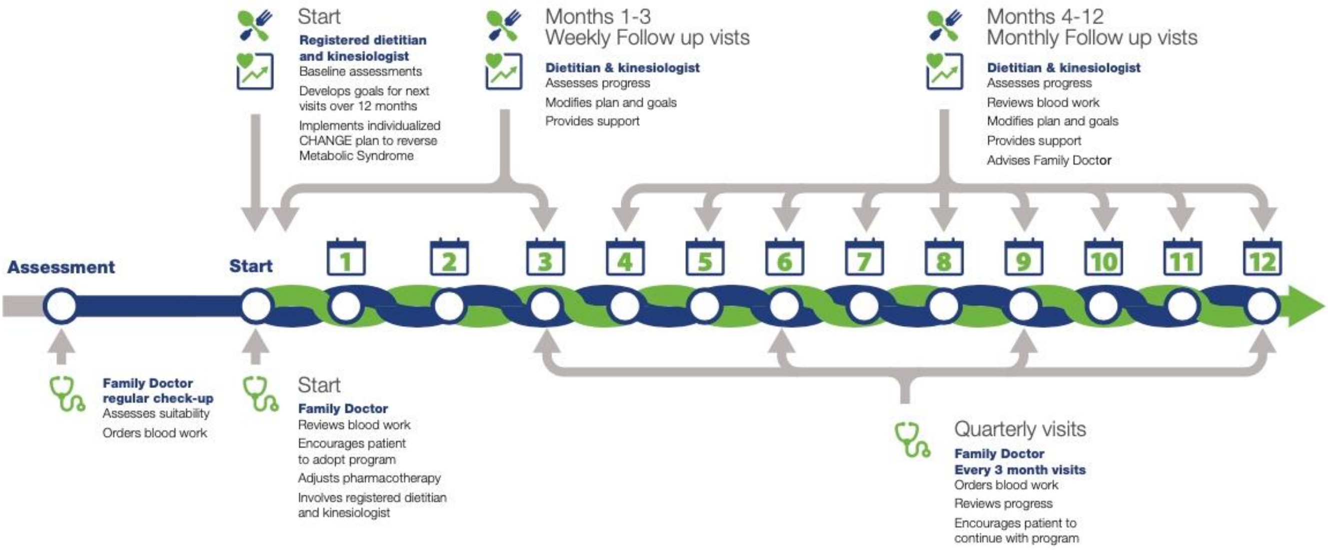

Figure 1. The CHANGE program protocol.

2.3. Measurements

2.3.1. Metabolic measurements

BP measurement and blood sample collection were performed according to usual standardized procedures. Hemodynamic measures (resting BP and heart rate) were taken (Welch Allyn spot vital LXi, Hill-Rom Holdings Inc, Chicago, IL). Blood samples were taken to measure blood lipid and glycemic profiles.

2.3.2. Anthropometric measurements

Body weight was measured with a beam balance (Health o meter Professional scale, Biofix). Height was measured without wearing shoes while heels, buttocks and upper part of the back were in contact with a wall-mounted stadiometer. These measurements were used to calculate BMI. WC was measured according to standardized procedures at the midpoint between the last rib and the superior iliac crest.

2.3.3. Maximal oxygen uptake assessment

The procedure of the Ebbeling single-stage walking test was used in the context of the CHANGE program, as previously reported[20]. Briefly, the test begins with a 4-min walking warm-up to achieve an estimated heart rate (HR) between 50% and 70% of the maximal HR estimated with the Karvonen equation[21]. Afterwards, the exercise specialist maintains the initially determined speed while increasing the treadmill grade to 5% for an additional 4-min period[21]. A steady-state HR (± 5 bpm) needs to be achieved between the third and the fourth minute of the second period to complete the test, otherwise the test needs to be extended for an additional minute[21]. The VO_2max is estimated using a validated formula that considers age, sex, treadmill speed, and steady-state HR[21].

2.4. Statistical analyses

A paired t-test was used to compare results obtained at T0 and T12 in all participants. Multiple regression analyses were performed to quantify the associations between changes in SBP and DBP and those of other measured variables using a multivariate regression model implemented in the REG procedure of SAS (SAS University Edition version 9.04.01M6P11072018). A Student's t-test was used to compare baseline values and changes observed in AR for both SBP and DBP to those who favorably responded to the intervention. All values are expressed as mean ± SD and differences were considered significant at p<0.05.

3. Results

The cardiometabolic variables of the 101 participants at T0 and T12 of the lifestyle intervention are presented in Table 1. A significant decrease in WC, blood TG levels, and both SBP and DBP was observed at T12. The intervention led to a significant increase in VO_2max. This table also shows that favorable changes in body weight, BMI, as well as fasting plasma glucose and HDL-cholesterol, were achieved at the end of the study, although they did not reach statistical significance.

Table 1. Anthropometric and metabolic characteristics of participants (n=101).

Variable	Baseline (T0)	12 months (T12)	% change	p value
Age	60.1 ± 9.3			
Height (m)	1.68 ± 0.1			
Body weight (kg)	88.0 ± 13.8	85.4 ± 13.7	-3.0	NS
Body mass index (kg/m²)	31.2 ± 3.4	30.3 ± 3.5	-2.9	0.0687
Waist circumference (cm)	105.9 ± 9.8	101.6 ± 10.5	-4.1	0.0040
Systolic blood pressure (mm Hg)	133.7 ± 13.0	129.1 ± 12.7	-3.4	0.0099
Diastolic blood pressure (mm Hg)	80.0 ± 13.0	76.8 ± 8.1	-4.0	0.0056
Total cholesterol (mmol/L)	4.83 ± 1.40	4.62 ± 1.28	-4.3	NS
HDL-cholesterol (mmol/L)	1.20 ± 0.27	1.24 ± 0.28	3.3	NS
LDL-cholesterol (mmol/L)	2.69 ± 1.13	2.58 ± 1.06	-4.1	NS
Plasma triglycerides (mmol/L)	2.07 ± 1.00	1.82 ± 0.71	-12.1	0.0380
Plasma glucose (mmol/L)	6.32 ± 1.26	6.25 ± 1.19	-1.1	NS
VO_2max (mLO_2/kg/min)	33.1 ± 6.4	35.7 ± 6.44	7.9	0.0033

The multivariate regression analyses considering the differences in cardiometabolic variables and the changes in SBP and DBP between T0 and T12 are presented in Table 2. Body weight (p<0.0001), BMI (p<0.0001), and fasting plasma glucose (p=0.0061) reductions, as well as the VO_2max increase (p=0.0475), were related with the change in SBP (Table 2). Variations in DBP were associated with changes in body weight, BMI, and TG levels although not to a statistically significant extent (Table 2). WC was the only variable for which changes were significantly correlated with those in both SBP (p<0.0001) and DBP (p=0.0004) (Table 2).

Table 2. Multivariate regression of the changes in cardiometabolic variables and changes in systolic and diastolic blood pressures (n=101).

Variable	Systolic blood pressure	Diastolic blood pressure
Body weight	<0.0001	0.0760
Body mass index	<0.0001	0.0775
Waist circumference	<0.0001	0.0004
Total cholesterol	NS	NS
HDL-cholesterol	NS	NS
LDL-cholesterol	NS	NS
Plasma triglycerides	NS	0.0984
Plasma glucose	0.0061	NS
VO_2max	0.0475	NS

There were 33 participants (32.7%) who increased their SBP in response to the CHANGE program whereas an increase in DBP was observed in 30 subjects (29.7%). Furthermore, an increase in both SBP and DBP was observed following the intervention in 12 participants (11.9%) who were considered as AR in the present study. Table 3 shows the comparison between the cardiometabolic profile and the variations over time between AR and the other participants. At T0, SBP was significantly lower in AR and the same trend was found for DBP. As expected, the mean changes for both groups were significantly different for SBP (p<0.0001) and DBP (p<0.0001). The changes in WC between T0 and T12 were significantly lower in AR (-0.4 ± 3.5 cm) than in other participants (-4.7 ± 4.9 cm) (p=0.0038).

Table 3. Comparison of the cardiometabolic profile and variations over time between adverse responders (n=12) in blood pressure and other participants (n=89).

Variable	Baseline (T0)			End of intervention (T12)			Variations between T0 and T12		
	AR (n = 12)	OP (n = 89)	*p* value	AR (n = 12)	OP (n = 89)	*p* value	AR (n = 12)	OP (n = 89)	*p* value
Body weight (kg)	93.4 ± 16.7	87.4 ± 13.4	NS	92.2 ± 15.6	84.5 ± 13.3	0.0668	-1.1 ± 3.1	-2.9 ± 4.3	NS
Body mass index (kg/m²)	32.6 ± 4.4	31.1 ± 3.3	NS	32.2 ± 4.1	30.0 ± 3.4	0.0468	-0.4 ± 1.1	-1.0 ± 1.5	NS
Waist circumference (cm)	107.0 ± 11.0	105.7 ± 9.7	NS	106.7 ± 11.6	100.9 ± 10.2	0.0758	-0.4 ± 3.5	-4.7 ± 4.9	0.0038
Systolic blood pressure (mm Hg)	125,9 ± 14,4	135,0 ± 12.5	0.0222	133.0 ± 14.9	128.7 ± 12.3	NS	7.1 ± 3.9	-6.3 ± 9.7	<.0001
Diastolic blood pressure (mm Hg)	75.9 ± 9.99	80.6 ± 8.7	0.0860	81.2 ± 8.5	76.2 ± 7.9	0.0467	5.3 ± 5.2	-4.4 ± 6.3	<.0001
Total cholesterol (mmol/L)	4.55 ± 1.50	4.88 ± 1.38	NS	4.04 ± 1.6	4.71 ± 1.2	0.0891	-0.51 ± 0.89	-0.17 ± 0.63	NS
LDL-cholesterol (mmol/L)	2.26 ± 1.23	2.76 ± 1.11	NS	2.17 ± 1.19	2.65 ± 1.02	NS	-0.09 ± 0.55	-0.11 ± 0.56	NS
HDL-cholesterol (mmol/L)	1.21 ± 0.25	1.20 ± 0.28	NS	1.20 ± 0.24	1.24 ± 0.29	NS	-0.01 ± 0.13	0.04 ± 0.18	NS
Plasma triglycerides (mmol/L)	2.36 ± 1.46	2.10 ± 1.00	NS	1.92 ± 0.73	1.87 ± 0.89	NS	-0.45 ± 1.00	-0.22 ± 0.69	NS
Plasma glucose (mmol/L)	6.34 ± 1.30	6.27 ± 1.39	NS	6.28 ± 1.14	6.19 ± 1.32	NS	-0.06 ± 0.47	-0.08 ± 0.96	NS
VO_2max (mLO_2/kg/min)	33.7 ± 4.5	33.1 ± 6.6	NS	36.8 ± 64.4	35.7 ± 6.7	NS	3.2 ± 2.6	2.6 ± 2.5	NS

Values are mean ± SD. Abbreviations: AR = adverse responders, OP = other participants.

Figure 2 presents mean values of SBP (figure 2A) and DBP (figure 2B) in participants classified into five groups according to WC changes. Participants who displayed less favorable changes in WC were also those who exhibited lower benefits in the response of SBP and DBP. Figure 3 shows an equivalent classification for changes in VO_2max. Participants who achieved the greatest improvement in VO_2max were also those who exhibited the most pronounced decrease in SBP. This association was not observed for DBP.

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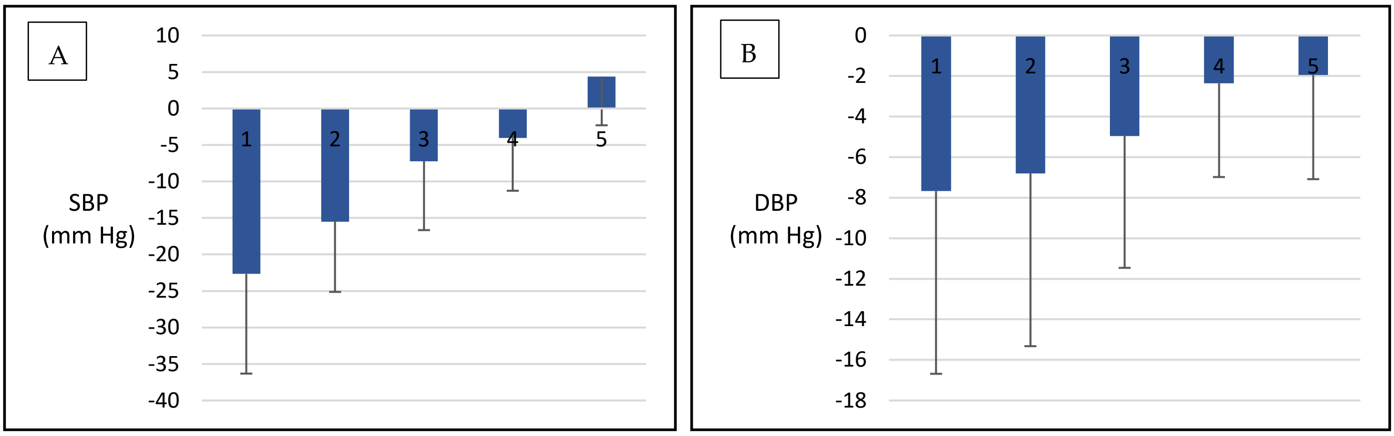

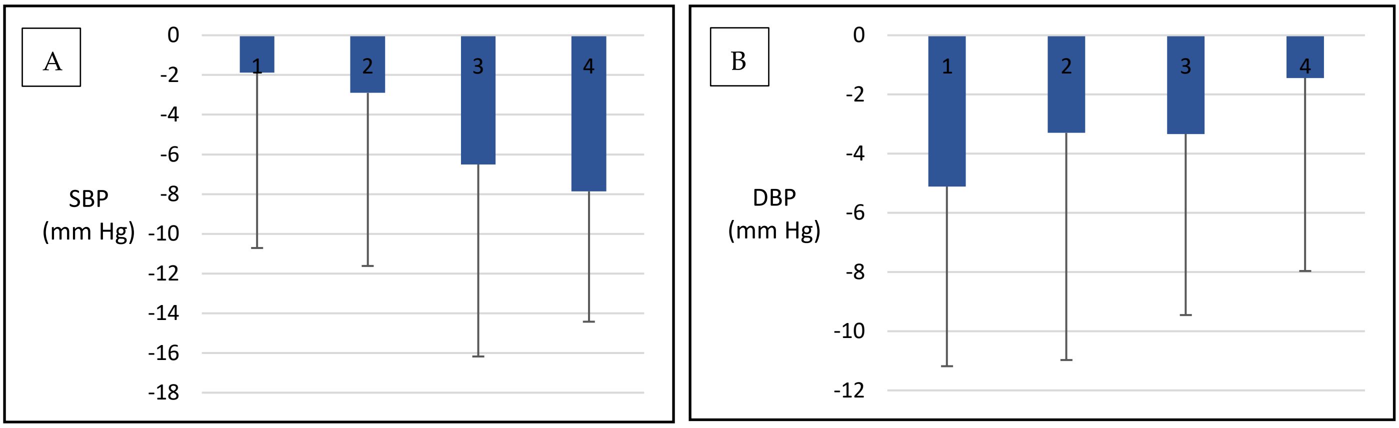

4. Discussion

Results of the present lifestyle intervention study show that changes in WC were positively associated with those observed in both SBP and DBP. Changes in body weight, BMI, plasma glucose, and VO_2max were also positively associated with changes in SBP. In addition, a positive association was observed between body weight, BMI, and TG with changes in DBP, but not to a statistically significant extent. Moreover, the results showed that ~12% of the participants included in the present study were AR to the CHANGE intervention for both SBP and DBP. The AR in BP were also low or non-responders for changes in WC to the intervention. These results suggest that the beneficial effects of a one-year lifestyle intervention on BP are associated with cardiometabolic and anthropometric variables changes, especially those in WC.

The beneficial impact of a lifestyle intervention on the cardiometabolic profile has been documented[22-24], although only few studies have investigated this effect in primary care settings[11-14,25]. Höchsmann et al.[26] report that "there is a gap between obesity management and what is currently implemented in primary care". This statement is also valid in the context of the management of systemic hypertension. The *International Society of Hypertension* and *Hypertension Canada* both recently revised their guidelines regarding systemic hypertension and mentioned that healthy lifestyle behaviors can prevent hypertension onset, reduce BP, and is considered as the first antihypertensive treatment[27,28]. Thus, implement structured lifestyle interventions in primary care settings by health professionals could be a good way to reach to the patients and prevent or treat systemic hypertension. Furthermore, supervised interventions such as the CHANGE program seem to induce beneficial lifestyle changes[17,29-31] that persists post-intervention.[32]

WC reflects abdominal fat deposition and was shown to be a valid indicator of the accumulation of intra-abdominal adipose tissue which is composed of intra and retroperitoneal fat[33]. Some evidence show that intraperitoneal fat better predicts insulin resistance and metabolic syndrome [34] and that patients displaying visceral fat, especially high intra-abdominal fat deposition, present higher risk of systemic hypertension[35,36] and deteriorated cardiometabolic profiles [37,38]. These results are in accordance with those reported in the present study and with some pathophysiological mechanisms that may explain the observed changes in BP and their relationship with those in WC such as a sympathetic nervous system overactivation, a stimulation of the renin-angiotensin-aldosterone system, an alteration in adipose-derived cytokines such as leptin, insulin resistance as well as structural and functional renal changes[39,40]. In this regard, given the significant association between visceral obesity and the atheroinflammatory process, it is likely that targeting a reduction in WC with lifestyle interventions may provide improvements of the cardiometabolic profile such as favorable changes in BP and considerable reductions of cardiovascular disease risk.

Individuals displaying an adverse response in BP to the intervention were identified in the present study. Bouchard et al.[41] were probably the first investigators to report adverse response in common cardiometabolic variables following a well-controlled exercise program. They observed that one out of eight participants enrolled in the study presented an adverse response in SBP. Alvarez et al.[42] demonstrated that there were AR for WC, SBP, and DBP in 28 adult women participating in a 20-week exercise program. As indicated above, we also observed AR in BP to the program who had the particularity to display significantly lower values at baseline. Conversely, they tended to present greater BP values than other participants at the end of the study. Up to now, this unfavorable effect cannot be explained although it is worthy to emphasize that these AR for BP tended to display less favorable changes in WC. More specifically related to the CHANGE program, the results from the investigations of Lowry et al.[43] and Lowry et al.[44] showed that individuals displaying certain genotypes or bioclinical measurements may benefit more from a lifestyle intervention than others and that, therefore, specific interventions should be considered for those predicted to be AR. Globally, our study further indicates that there exists a cluster of cardiorespiratory and metabolic variables predicting the outcome of a lifestyle intervention in MetS patient and that AR would benefit from healthcare professionals support to improve their cardiometabolic profiles.

A strength of this study is the demonstration of the feasibility in primary care settings of an individualized diet and fitness plan among MetS patients with the collaboration of family physicians, dieticians, and exercise specialists. Another strength of this study was to permit the examination of the profile of adverse BP responders supervised in a controlled clinical trial. The study also has some limitations. Indeed, the absence of a control group not exposed to the lifestyle intervention limits to a certain extent the evaluation of the outcome of the CHANGE program, The use of WC as a marker of VAT[7,8] may also be perceived as a limitation, although it has been shown to provide valid estimates of abdominal adiposity[9].

In summary, the beneficial effects of a structured lifestyle intervention (CHANGE program) on BP variations were significantly associated with changes in cardiometabolic variables, especially WC for both SBP and DBP in MetS patients in primary care setting. Changes in CRF was also associated with those in SBP. Since the variations of WC seem to reflect the changes in SBP and DBP, we believe that health professionals in primary care facilities should measure WC to stratify the patient's systemic hypertension risk. Additionally, our study documents for the first time the profile of AR in BP to a structured lifestyle intervention in MetS patients. Further structured lifestyle studies are needed to characterize mechanisms that underlie variations in the response of BP and other cardiometabolic indicators to this type of intervention in the context of primary care settings.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations (alphabetic order):

AR: adverse responders

BMI: body mass index

BP: blood pressure

CHANGE program: Canadian Health Advanced by Nutrition and Graded Exercise

CRF: cardiorespiratory fitness

CSEP: Canadian Society for Exercise Physiology

DBP: diastolic blood pressure

HR: heart rate

HEI-C: Healthy Eating Index-C

MetS: metabolic syndrome

SBP: systolic blood pressure

TG: plasma triglycerides

T0: baseline

T12: after 12 months

VAT: visceral adipose tissue

VO2max: maximal oxygen uptake

WC: waist circumference

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