Exercise Training with Weight Loss and either a High- or Low-Glycemic Index Diet Reduces Metabolic Syndrome Severity in Older Adults

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Key Words

Aging • Obesity • Lifestyle modification • Diabetes •
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Abstract

Background: The efficacy of combining carbohydrate quality with exercise on metabolic syndrome risk is unclear. Thus, we determined the effects of exercise training with a low (LoGlx)- or high (HiGlx)-glycemic index diet on the severity of the metabolic syndrome (Z-score). **Methods:** Twenty-one adults (66.2 ± 1.1 years; BMI = 35.3 ± 0.9 kg/m²) with the metabolic syndrome were randomized to 12 weeks of exercise (60 min/day for 5 days/week at about 85% HR_{max}) and provided a LoGlx (n = 11) or HiGlx (n = 10) diet. Z-scores were determined from: blood pressure, triglycerides (TGs), high-density lipoproteins (HDLs), fasting plasma glucose (FPG), and waist circumference (WC) before and after the intervention. Body composition, aerobic fitness, insulin resistance, and nonesterified fatty acid (NEFA) suppression were also assessed. **Results:** LoGlx and HiGlx diets decreased body mass and insulin resistance and increased aerobic fitness comparably (p < 0.05). LoGlx and HiGlx diets decreased the Z-score

similarly as each intervention decreased blood pressure, TGs, FPG and WC (p < 0.05). The HiGlx diet tended to suppress NEFA during insulin stimulation compared with the LoGlx diet (p = 0.06). **Conclusions:** Our findings highlight that exercise with weight loss reduces the severity of the metabolic syndrome whether individuals were randomized to a HiGlx or a LoGlx diet.

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Introduction

Approximately 35 million adults in the USA over the age of 60 years suffer from metabolic syndrome [1]. Components of metabolic syndrome (i.e. central obesity, hypertension, dyslipidemia and hyperglycemia) increase the risk for type 2 diabetes and cardiovascular disease. Given that nearly 20% of the USA population is expected to be over the age of 65 years by 2030, the number of individuals with the metabolic syndrome will rise. Thus, there is a need to identify optimal treatments to prevent the metabolic syndrome, and reduce the associated health and economic burden.

Table 1. LoGIx and HiGIx diets while exercise training in patients with the metabolic syndrome

	HiGIx diet	LoGIx diet
Glycemic index, AU	80.3 ± 0.6*	40.3 ± 0.2
Glycemic load, AU	241.7 ± 16.9*	105.0 ± 4.8
Energy intake, kcal/day	2,082.0 ± 131.7	1,827.7 ± 81.7
Carbohydrate, g/day	301.0 ± 20.2	256.7 ± 11.8
Fiber, g/day	30.5 ± 2.1	29.5 ± 1.3
Fat, g/day	88.6 ± 5.6	78.9 ± 3.5
Protein, g/day	66.3 ± 3.9	58.2 ± 2.3

* p < 0.05.

The USA Diabetes Prevention Program demonstrated that lifestyle modification consisting of increased physical activity and a low-fat diet reduced the prevalence of metabolic syndrome compared to metformin treatment or placebo [2]. Exercise training reduces cardiometabolic risk factors, including blood pressure, lipids and insulin resistance, in older adults with the metabolic syndrome [3, 4]. Despite reports that greater weight loss reverses the constellation of metabolic syndrome risk factors [5], exercise training with hypocaloric diets has not translated into greater reductions in cardiometabolic risk compared with exercise training alone [6, 7]. This suggests that exercise may be sufficient to correct many of the underlying metabolic syndrome risk factors. However, it may be possible to enhance the effect of exercise on cardiometabolic health by adjusting the glycemic content of the diet.

Although lifestyle interventions often recommend carbohydrate-based diets, few studies have determined the role of carbohydrate type in combination with exercise on metabolic syndrome severity. High-glycemic index (HiGIx) carbohydrates increase plasma glucose concentrations, blood lipids, ectopic lipid storage and the demand for insulin [8] whereas low-glycemic index (LoGIx) diets improve glycemic control and lower triglycerides (TGs), blood pressure, and hyperinsulinemia [9, 10]. We have shown that a LoGIx diet combined with exercise training raised insulin sensitivity [11] and lowered glucose concentrations, inflammation, and systolic blood pressure to a greater extent than a HiGIx diet in older adults [12, 13]. To date, however, no study has determined the efficacy of a LoGIx diet combined with exercise on the severity of the metabolic syndrome (i.e. Z-score) as opposed to the metabolic syndrome being present or absent. Considering the metabolic syndrome in this way has clinical

relevance as it allows a change in cardiometabolic health to be measured across a continuum. Therefore, the purpose of this study was to determine the effect of exercise training combined with a LoGIx diet, compared with a HiGIx diet, on the severity of the metabolic syndrome and insulin resistance in older adults. We hypothesized that a LoGIx diet combined with exercise training would reduce the severity of the metabolic syndrome and insulin resistance more than a HiGIx diet.

Methods

Subjects

Twenty-one older (66.2 ± 1.1 years) obese ($BMI = 35.5 \pm 0.9$ kg/m²) adults (table 2) who met the National Cholesterol Education Program Adult Treatment Panel (ATP) III criteria for the metabolic syndrome were used in this analysis from our past work [13–15]. Subjects were nonsmoking, weight stable (<2 kg in previous 6 months), sedentary (less than <30 min/day <3 days/week), and free of chronic disease (i.e. hematological, renal, hepatic and cardiovascular) or medications known to affect the primary outcomes. Participants were randomly assigned to exercise training combined with a LoGIx diet (n = 11) or a HiGIx diet (n = 10). Postmenopausal women were not on hormone replacement therapy and all subjects provided signed informed consent approved by our Institutional Review Board.

Aerobic Fitness

Maximum oxygen consumption (VO₂max) was determined using a continuous incremental treadmill exercise test (Jaeger Oxycon Pro; Viasys, Yorba Linda, Calif., USA). VO₂max was determined as previously described [12]. Maximal heart rate (HR_{max}) obtained during this test was used during exercise training.

Body Composition

Height was measured without shoes using a wall-mounted stadiometer and weight was recorded on a digital scale in a hospital gown. Dual-X-ray absorptiometry (DEXA; Lunar Prodigy, Madison, Wisc., USA) was used to quantify total fat mass and fat-free mass.

Inpatient Control Period

Pre- and posttreatment assessments of cardiometabolic risk factors and insulin resistance were conducted during a 3-day inpatient stay in the Clinical Research Unit. Subjects were provided weight maintenance meals (resting metabolic rate × 1.2 activity factor; 55% carbohydrate, 30% fat, 15% protein). Following the intervention, cardiometabolic risk factors and insulin resistance measurements were made approximately 16–18 h after the last exercise bout. Subjects maintained their respective dietary intervention after testing.

Exercise Training and Nutritional Intervention

All participants underwent a 12-week supervised exercise training program consisting of treadmill walking and cycle ergometer exercise at approximately 85% of HR_{max}. All meals and

Table 2. Effects of HiGIx and LoGIx diets on body composition, blood pressure, lipids, insulin resistance and aerobic fitness in patients with the metabolic syndrome

	HiGIx diet		LoGIx diet		ANOVA (p value)	
	before	after	before	after	test	group × test
Patients (M:F)	10 (7:3)	–	11 (4:7)	–	–	–
Age, years	65.6 ± 1.3	–	67.2 ± 1.6	–	–	–
Weight, kg	107.9 ± 4.3	96.9 ± 3.8	93.6 ± 4.0	86.8 ± 3.5	≤0.001	≤0.09
BMI, kg/m ²	36.7 ± 0.9	33.1 ± 1.2	33.8 ± 1.3	31.4 ± 1.3	≤0.001	≤0.10
Fat mass, kg	45.1 ± 2.1	36.2 ± 3.2	41.6 ± 2.1	35.9 ± 2.2	≤0.001	≤0.07
Fat-free mass, kg	62.4 ± 4.0	60.7 ± 3.7	52.1 ± 3.3	50.9 ± 2.8	≤0.01	≤0.67
HbA1c, %	5.6 ± 0.2	5.4 ± 0.1	5.8 ± 0.2	5.7 ± 0.2	≤0.02	≤0.97
2-Hour glucose, mg/dl	137.4 ± 11.6	131.5 ± 16.8	152.5 ± 8.7	142.9 ± 9.8	≤0.18	≤0.39
Fasting plasma insulin, μU/ml	21.9 ± 5.8	11.9 ± 1.4	31.2 ± 8.5	15.2 ± 2.0	≤0.01	≤0.53
2-Hour plasma insulin, μU/ml	111.6 ± 27.7	88.1 ± 24.2	164.4 ± 34.8	94.0 ± 31.9	≤0.02	≤0.22
HOMA-IR	4.3 ± 0.6	2.7 ± 0.3	5.2 ± 0.7	3.2 ± 0.5	≤0.003	≤0.80
Total cholesterol, mg/dl	205.6 ± 9.5	183.5 ± 9.7	200.8 ± 12.0	180.6 ± 10.3	≤0.002	≤0.87
LDL, mg/dl	136.2 ± 6.8	123.0 ± 7.5	120.3 ± 9.3	112.1 ± 9.9	≤0.05	≤0.63
VO ₂ max, ml/kg/min	22.2 ± 1.5	28.3 ± 2.7	19.6 ± 0.9	25.2 ± 1.9	≤0.0001	≤0.87

Data are means ± SEM. There were no statistical differences at baseline between groups for any outcome.

fluids were provided to the participants throughout the intervention. A registered dietitian (H.B.) created the diets to be isocaloric to the individual requirements at baseline (i.e. resting metabolic rate measurement × 1.2 activity factor). As a result, weight loss during the interventions was primarily due to exercise energy expenditure, not caloric restriction. The macronutrient composition, including fiber, was matched between groups. However, the LoGIx subjects received a diet corresponding to a glycemic index of 40 arbitrary units (AUs), while the HiGIx subjects were provided an 80-AU glycemic index diet (table 1). Recipes were identical between diets, with only substitutions made between the types of carbohydrate. Dietary compliance was determined by daily food container weight backs, and diet analysis was performed with the Nutritionist Pro software (Axxya Systems, Stafford, Tex., USA).

Cardiometabolic Risk Factors

After an overnight fast, blood pressure was measured in the seated position after 10 min of rest and was based on the average of 3 measurements. Mean arterial pressure (MAP) was calculated as: $MAP = 2/3 (DBP) + 1/3 (SBP)$. Waist circumference (WC) was measured up to 3 times using a plastic tape measure approximately 2 cm above the umbilicus. Measurements within 0.5 cm were used for analysis. It is possible that we overestimated our WC results by measuring at the umbilicus compared to the NCEP bony landmark recommendation [15]. However, our WC data parallel the change in visceral adiposity as measured by CT scans in our previous work [13–15]. Fasting plasma glucose (FPG), TGs, and high-density lipoprotein (HDL) measurements were obtained from blood sampling. Sex-specific Z-scores were calculated to indicate changes in metabolic syndrome severity before and after the intervention [16]. The equations used were: $Z\text{-score}_{men} = [(40 - HDL)/10.3] + [(TG - 150/66.5)] + [(FPG - 100)/13.4] + [(WC -$

$102)/8.5] + [(MAP - 100)/10.0]$, and $Z\text{-score}_{women} = [(50 - HDL)/12.4] + [(TAG - 150/66.5)] + [(FPG - 100)/13.4] + [(WC - 88)/11.7] + [(MAP - 100)/10.03]$. ATP III scores were also calculated for each subject based on the sum of risk factors meeting metabolic syndrome criteria.

Insulin Resistance

After an overnight fast, a 2-hour euglycemic-hyperinsulinemic clamp was performed as previously described [14]. In summary, a constant infusion (40 mU/m²·min^{−1}) of insulin was administered via an indwelling catheter placed in an antecubital vein. Glucose (20%) was infused at a variable rate to maintain plasma glucose at 90 mg/dl. Arterialized plasma samples were collected from a retrograde hand vein warmed to 60°C. Blood samples were collected every 5 min for the analysis of glucose and every 15 min for analysis of insulin. Nonesterified fatty acid (NEFA) plasma samples were collected at baseline and 120 min. Insulin-stimulated NEFA suppression was calculated as: $[1 - (NEFA_{clamp}/NEFA_{base}) \times 100]$. Respiratory gases (VO₂ and VCO₂) were analyzed via indirect calorimetry for 20 min in the fasted and insulin-stimulated state (last 20 min of clamp) while the subject rested in the supine position. The last 10 min were averaged for determination of substrate oxidation [17, 18]. Nonoxidative glucose disposal was calculated as: glucose disposal rate – total carbohydrate oxidation rate. Homeostatic model assessment (HOMA-IR), a surrogate for hepatic insulin resistance, was calculated as fasting glucose (mg/dl) × fasting insulin (μU/ml)/405.

Glucose Tolerance

After an overnight fast, blood samples were collected from an antecubital vein and a 75-gram glucose load was administered orally. Blood samples were then obtained at 120 min.

Fig. 1. a Effects of HiGlx and LoGlx diets on metabolic syndrome Z-score outcomes. Data are means $\pm$ SEMs. **b** Effects of HiGlx and LoGlx diets on metabolic syndrome criteria. Data are means $\pm$ SEM. ^a LoGlx diet compared with HiGlx diet (group $\times$ test interaction; $p < 0.05$). ^b Test effect ($p < 0.05$).

Biochemical Analysis

Plasma glucose was determined using a glucose oxidase assay (YSI 2300 STAT Plus, Yellow Springs, Ohio, USA). Plasma insulin was measured by radioimmunoassay (Millipore, Billerica, Mass., USA). TGs and cholesterol were analyzed using enzymatic methods with an automated platform (Roche Modular Diagnostics, Indianapolis, Ind., USA). Plasma NEFA was measured by enzymatic colorimetry (Wako Chemicals, Richmond, Va., USA).

Statistical Analysis

Data are expressed as means $\pm$ standard error of the mean (SEM). Group means were compared using the R statistical software package (Version 2.4.0, The R Foundation, Vienna, Austria, 2006). Diet and baseline variables were assessed by unpaired *t* tests. Baseline variables were not different between groups. Outcomes were assessed using a two-way (group $\times$ test) repeated-measures ANOVA. Unpaired *t* tests were used to determine statistical differences between group mean differences (i.e. change from pre to post) when there was a significant group $\times$ test interaction. Pearson's correlation was used to examine associations between outcomes. Significance was accepted as $\alpha \leq 0.05$.

Results

Exercise and Diet Compliance

Exercise adherence and dietary data were previously reported [13, 14]. However, dietary intake data are reported here for clarity (i.e. about 55% carbohydrate, 28% fat and 16% protein; table 1). By design, glycemic index and load were statistically different between groups ($p < 0.05$; table 1).

Metabolic Syndrome Severity

There was no statistical differences at baseline between HiGlx and LoGlx for SBP (135.2 ± 6.0 vs. 132.9 ± 3.6 mm Hg; $p = 0.75$), DBP (80.6 ± 3.4 vs. 80.5 ± 3.2 mm Hg; $p = 0.99$), TGs (139.1 ± 21.1 vs. 180.9 ± 23.6 mg/dl; $p = 0.20$), HDL (42.4 ± 3.7 vs. 46.8 ± 3.9 mg/dl; $p = 0.42$) and WC (121.9 ± 2.3 vs. 115.0 ± 3.9 cm; $p = 0.16$). HiGlx and LoGlx reduced body mass, WC, and fat mass by approximately 8% each ($p < 0.05$; fig. 1a, b, table 2). Both groups lowered the metabolic syndrome Z-score ($p = 0.001$; fig. 1a) and ATP III score (HiGlx = pre: 3.6 ± 0.2 vs. post: 2.4 ± 0.5 ; LoGlx = pre: 3.6 ± 0.2 vs. post: 2.2 ± 0.3 ; $p = 0.001$). There were no group differences between the reduction in Z-score ($p \leq 0.85$), ATP III score ($p \leq 0.85$) or presence of the metabolic syndrome (HiGlx = 5 out of 10 vs. LoGlx = 6 out of 11). Consistent with these data, SBP and DBP and TGs were lowered by HiGlx and LoGlx diets (fig. 1a, b; $p < 0.05$). Neither group had effects on HDL.

Glycemic Control

Baseline fasting glucose concentrations were not different between HiGlx and LoGlx (103.8 ± 3.5 vs. 112.3 ± 5.2 mg/dl; $p = 0.19$). Fasting glucose concentrations were reduced comparably between HiGlx and LoGlx (fig. 1a, b; $p < 0.05$), and both groups lowered HbA1c ($p < 0.05$; table 2).

Table 3. Effects of HiGIx and LoGIx diets on insulin sensitivity, carbohydrate and fat metabolism in patients with the metabolic syndrome

	HiGIx diet		LoGIx diet		ANOVA (p value)	
	before	after	before	after	test	group × test
Fasted						
NEFA, mmol	0.56 ± 0.04	0.57 ± 0.03	0.60 ± 0.04	0.55 ± 0.04	≤0.19	≤0.21
Carbohydrate utilization, %	35.7 ± 2.7	27.9 ± 2.9	26.3 ± 4.5	31.1 ± 4.8	≤0.68	≤0.10
Lipid utilization, %	65.3 ± 2.8	72.1 ± 2.9	73.7 ± 4.5	68.9 ± 4.8	≤0.68	≤0.10
Clamp						
GDRI, mg/kg-FFM/min/μU/ml	0.04 ± 0.01	0.08 ± 0.01	0.04 ± 0.01	0.06 ± 0.01	≤0.001	≤0.95
Insulin, μU/ml	96.6 ± 5.2	92.7 ± 5.2	101.1 ± 8.1	101.6 ± 7.2	≤0.66	≤0.58
NOGD, mg/kg-FFM/min	1.4 ± 0.6	3.7 ± 0.7	1.0 ± 0.5	2.1 ± 0.4	≤0.003	≤0.13
CHO utilization, %	55.8 ± 2.1	63.0 ± 4.0	52.9 ± 3.4	56.3 ± 2.3	≤0.03	≤0.98
Lipid utilization, %	44.2 ± 6.8	36.9 ± 4.0	47.0 ± 3.4	43.7 ± 2.3	≤0.03	≤0.98
NEFA, mmol	0.15 ± 0.3	0.11 ± 0.3	0.13 ± 0.3	0.15 ± 0.3	≤0.73	≤0.12
NEFA suppression, %	74.1 ± 4.8	80.7 ± 4.9	76.8 ± 6.4	71.9 ± 5.9	≤0.85	≤0.06

Data are means ± SEM. There were no statistical differences at baseline between groups for any outcome. GDRI = Glucose disposal rate divided by insulin; NOGD = nonoxidative glucose disposal.

Insulin Resistance and NEFA Suppression

HiGIx and LoGIx diets reduced insulin resistance measured by clamp and HOMA-IR to a similar extent ($p < 0.05$; tables 2, 3). Decreased insulin resistance was a result of both increased nonoxidative glucose disposal ($p < 0.05$) and carbohydrate oxidation ($p < 0.03$; table 3). The HiGIx diet showed a strong trend to increase insulin-stimulated NEFA suppression, compared with the LoGIx diet ($p = 0.06$) and both groups decreased lipid oxidation during insulin stimulation ($p < 0.03$; table 3).

Correlations

Reductions in fasting insulin concentrations ($r = -0.38$; $p = 0.09$), total cholesterol ($r = 0.49$; $p < 0.05$) and total fat mass ($r = 0.46$; $p < 0.04$) were correlated with lower severity of the metabolic syndrome (i.e. Z-score). Insulin resistance calculated by HOMA-IR ($r = 0.48$; $p < 0.05$), but not the clamp ($r = -0.29$; $p = 0.20$), was correlated with lower metabolic syndrome severity. Finally, the change in NEFA_{suppression} correlated with the change in fat mass ($r = -0.45$; $p < 0.05$).

Discussion

The novel finding from this study is that 12 weeks of exercise can successfully reduce metabolic syndrome severity and that a LoGIx diet has little added benefit on

reducing cardiometabolic risk factors when compared to a HiGIx diet matched on fiber content in older men and women. Lifestyle modification consisting of a low-fat diet and increased physical activity reduces the prevalence of the metabolic syndrome by approximately 45% in glucose-intolerant adults and postmenopausal women [2, 6]. This is consistent with previous work from our laboratory demonstrating significant improvements in aerobic fitness and reductions in cardiometabolic risk factors after high-intensity exercise and diet-induced weight loss in older men and women with the metabolic syndrome [7]. Aerobic fitness is related to reductions in many of the underlying metabolic syndrome risk factors (e.g. insulin resistance, inflammation and blood pressure) [19, 20]. In the current study, both exercise groups increased VO₂max by approximately 27%; however, only reductions in body fat correlated with decreased severity of the metabolic syndrome. Decreased body fat was correlated with increased insulin-stimulated NEFA suppression. Reduced availability of NEFA may have contributed to less inflammation and improved cardiometabolic health [21, 22]. Thus, these observations suggest that increasing physical activity leads to fat loss, which decreases the cardiometabolic risk in adults with the metabolic syndrome.

Aerobic exercise, and to some extent resistance exercise, decreases TG and increases HDL concentrations [23], reduces WC [24, 25], and lowers blood pressure [26]. Although exercise may not improve the outcomes of all

ATP III criteria, the collective change in these outcomes (i.e. Z-score) has clinical utility. We found that exercise training combined with a HiGIx or LoGIx diet decreased the severity of the metabolic syndrome. Moreover, 5 out of 10 in the HiGIx group and 6 out of 10 in the LoGIx group no longer had the metabolic syndrome after the intervention. These findings are not entirely surprising given that HiGIx and LoGIx diets improved insulin sensitivity, aerobic fitness and adiposity comparably [27]. Our data are consistent with previous work showing that aerobic exercise training, with or without resistance exercise, reduces metabolic syndrome severity in middle-aged men and women regardless of exercise intensity, duration, or caloric deficit [16, 28, 29]. We acknowledge the small sample size may have limited our ability to detect statistical differences in the severity of the metabolic syndrome. Thus, future studies with larger sample sizes are warranted to examine whether exercise training without weight loss, or at lower exercise intensities, while consuming either a LoGIx or a HiGIx diet yields similar results on the severity of the metabolic syndrome [30, 31].

Glucose abnormalities are found in approximately 40% of adults with the metabolic syndrome [32]. Although exercise decreases or maintains glucose concentrations [7, 29, 33], Cheong et al. [34] reported that a lifestyle intervention consisting of increased steps and consumption of low-glycemic foods, compared with walking only, induced similar reductions in HbA1c in adults with type 2 diabetes. Similarly, we show that 12 weeks of supervised exercise training, independent of strict dietary control, was effective at lowering HbA1c levels in adults with metabolic syndrome. LoGIx and HiGIx diets likely improved glycemic control because of reduced insulin resistance [14]. Interestingly, similar reductions in HbA1c occurred despite increased NEFA suppression in 80% of the individuals after the HiGIx compared with only 20% in the LoGIx intervention. Although kinetic tracer studies would have more accurately assessed lipid flux in this study, we previously demonstrated that exercise training with approximately 8% weight loss reduced NEFA concentrations by decreasing palmitate turnover rates and increasing lipid utilization in obese older adults [35]. In the current study, individuals lost approximately 8% body weight, and we found a significant correlation between fat mass loss and NEFA suppression. Together, these observations suggest that fat mass loss, not increased fat utilization, leads to decreased NEFA mobilization [21, 22]. However, we cannot rule out the possibility that exercise training while consuming a HiGIx carbohydrate diet increased extramucellar lipid storage

[36]. Regardless of the exact mechanism, changes in NEFA concentrations after the HiGIx intervention did not translate into enhanced glycemic control. Thus, the clinical relevance of altered lipid availability after the HiGIx intervention remains unclear. Longer-duration clinical trials comparing HiGIx and LoGIx diets are needed to confirm our observation, as differences in glycemic control may become evident after 12 months [10].

In conclusion, these findings indicate that exercise training with approximately 8% weight loss reduces the severity of the metabolic syndrome whether individuals followed a LoGIx or a HiGIx diet. However, similar fiber intakes in the two diets may reduce the 'real-world' relevance of these findings because fiber intake was approximately 15 g/day more than what the typical American is currently consuming. Thus, it remains possible that a LoGIx and high-fiber diet combined with exercise may have greater efficacy in lowering metabolic syndrome severity compared with a HiGIx and low-fiber diet. More studies are needed to fully understand the utility of exercise training combined with the intake of different types of carbohydrates in reducing the risk of cardiovascular and type 2 diabetes in adults with metabolic syndrome.

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Disclosure Statement

The authors report no conflict of interest.

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