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the "Plants for Joints" randomized controlled trial

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A multidisciplinary lifestyle program for metabolic syndrome-associated osteoarthritis: the "Plants for Joints" randomized controlled trial

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SUMMARY

Objective: To determine the effectiveness of the "Plants for Joints" multidisciplinary lifestyle program in patients with metabolic syndrome-associated osteoarthritis (MSOA).
Design: Patients with hip or knee MSOA were randomized to the intervention or control group. The intervention group followed a 16-week program in addition to usual care based on a whole food plant-based diet, physical activity, and stress management. The control group received usual care. The patient-reported Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) total score (range 0–96) was the primary outcome. Secondary outcomes included other patient-reported, anthropometric, and metabolic measures. An intention-to-treat analysis with a linear-mixed model adjusted for baseline values was used to analyze between-group differences.
Results: Of the 66 people randomized, 64 completed the study. Participants (84% female) had a mean (SD) age of 63 (6) years and body mass index of 33 (5) kg/m^2. After 16 weeks, the intervention group (n = 32) had a mean 11-point larger improvement in WOMAC-score (95% CI 6–16; p = 0.0001) compared to the control group. The intervention group also lost more weight (−5 kg), fat mass (−4 kg), and waist circumference (−6 cm) compared to the control group. Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue, pain interference, C-reactive protein, hemoglobin A1c, fasting glucose, and low-density lipoproteins improved in the intervention versus the control group, while other PROMIS measures, blood pressure, high-density lipoproteins, and triglycerides did not differ significantly between the groups.
Conclusion: The "Plants for Joints" lifestyle program reduced stiffness, relieved pain, and improved physical function in people with hip or knee MSOA compared to usual care.

Introduction

Osteoarthritis (OA) is a chronic condition that affects 7% of the global population and it is responsible for 2.2% of the global years of healthy life lost due to disability.[1,2] OA mostly affects the hands, hips

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and knees. Prevalence is expected to rise by 10–50% within the coming two decades in Western countries.[3–5]

Having OA is associated with a 2-fold higher risk of metabolic syndrome and obesity.[6,7] Mechanical load by body weight cannot fully explain this association as obesity is also related to a 30% increased risk of OA in the hand.[7]

Metabolic syndrome-associated osteoarthritis (MSOA) is a distinct phenotype of OA, based on studies showing associations between OA and the components of metabolic syndrome.[8] The impact of metabolic syndrome and increased fat mass, driven by unhealthy lifestyle factors, also explains the frequent occurrence of comorbidities in patients with OA such as diabetes type 2 and cardiovascular disease, through the shared mechanism of systemic chronic inflammation.[3,6,8–11]

OA treatment options are limited to analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), exercise therapy, and joint replacement surgery. For metabolic syndrome, lifestyle modification focused on diet and exercise is the first-line clinical therapy.[12] Although the guideline for the treatment of hip and knee OA recommends exercise, weight loss, and mental health interventions, development and research on the effectiveness of multidisciplinary OA management programs is needed.[13,14]

A low-calorie diet in combination with exercise was found to be more effective to reduce pain and improve function in overweight and obese people with OA than either diet or exercise alone.[15,16] Also, higher baseline “mindfulness” scores in patients with knee OA were associated with a better response to exercise than in patients with lower baseline mindfulness.[17]

Although research is limited, it suggests that low-inflammatory diets, such as the Mediterranean diet, are associated with weight loss and lower inflammation in OA, when compared to a usual diet.[18] Healthy plant-based diets are classified as low-inflammatory because of their similarity with the Mediterranean diet, high levels of fiber and low levels of saturated fat.[19] A small study on the effect of a plant-based diet in people with OA showed promising results.[20] A plant-based diet is also associated with a lower risk for metabolic syndrome and a multidisciplinary program including a whole food plant-based diet, increased physical activity, stress reduction, and social support produced favorable effects that have lasted for up to 5 years in patients with coronary artery disease or prostate cancer.[21–23] However, a plant-based diet was not yet tested in combination with physical activity and stress management in patients with MSOA. Therefore, we designed a randomized controlled trial (RCT) comparing a multidisciplinary lifestyle program with usual care, aiming to reduce stiffness, relieve pain, and improve physical function in patients with hip or knee MSOA.

Methods

The “Plants for Joints” project consisted of three trials to investigate the effect of a multidisciplinary lifestyle program in people with (1) rheumatoid arthritis, (2) a high risk of rheumatoid arthritis or (3) MSOA. The intervention was executed in mixed groups. The present article covers the MSOA trial. A detailed protocol was published previously.[24]

Design

A 16-week open-label RCT with parallel design was conducted between May 2019 and December 2021 at the Reade outpatient clinic for rehabilitation and rheumatology in Amsterdam, the Netherlands. Eleven patient partners gave feedback during a focus group meeting on the first draft of the intervention, which led to the inclusion of a module on sleep. They also selected the most relevant domains of the Dutch-Flemish Patient-Reported Outcomes Measurement Information System (PROMIS).[25]

Study visits took place at baseline, 8, and 16 weeks. The Medical Ethical Committee of the Amsterdam University Medical Centers approved the study protocol (EudraCT number NL66649.048.18). The protocol was prospectively registered (Netherlands Trial Register number NL7801, which was transferred to the International Clinical Trials Registry Platform of the WHO: https://trialsearch.who.int/) and published.[24] Participants gave written informed consent. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[26]

Recruitment, selection, and randomization

Participants aged ≥18 years were included if they had metabolic syndrome according to the National Cholesterol Education Program criteria and hip or knee OA according to the American College of Rheumatology (ACR) clinical criteria.[27–29] Radiographs of hip and knee were made according to the Buckland–Wright protocol[30] by health professionals unaware of group allocation, unless already available from within the previous 2 years, and the Kellgren–Lawrence score[31] was independently determined by a rheumatologist (DvS) and a radiologist, both blinded for randomization. The mean score was taken unless the scores differed more than 2 points, in which case the score was determined by consensus. People with a low body weight (body mass index (BMI) < 18.5 kg/m^2), already following a plant-based diet, unwilling to quit smoking for at least the duration of the study and pregnant women were excluded. Randomization was concealed using the digital CASTOR electronic data capture system that allocated participants to the intervention or control group in a 1:1 ratio, with block randomization in block sizes of 2 and 4.

Intervention

At the start, participants randomized to the intervention group received individual intakes with a registered dietitian and a physical therapist. During the program, groups of 6–12 people gathered 10 times for 2–3-hour meetings in which time dedicated to diet, physical activity, and stress management was divided equally. In the intervention group, 12 participants had all meetings live, 11 participants received the intervention in hybrid form of 2–4 live sessions, and the rest online and 9 participants had all meetings online due to COVID-19 restrictions. Peer education and peer support were actively promoted. The intervention group received theoretical and practical education about a whole food plant-based diet (including a cooking class), physical activity and exercise, and stress management based on previous protocols and guidelines.[22,32–35] This included a plant-based version of a diet in line with the 2015 Guidelines on Healthy Nutrition from the Health Council of the Netherlands, personal goals for physical activity in accordance with the 2017 Dutch physical activity guidelines (150 min/week moderately intense physical activity and 2 days/week muscle and bone-strengthening activities), psychoeducation on the effects of psychological stress on health and stress management and coaching on sleep. Education was provided by registered dietitians, physiotherapists, personal trainers, and therapists with expertize in sleep and stress reduction.

The intervention group was facilitated with general information and videos, exercises for at home, fully elaborated weekly menus and daily supplementation with methylcobalamin (1500 mcg) and cholecalciferol (50 mcg).[36] The intervention group received the lifestyle program in addition to usual care according to the Dutch OA management guideline consisting of analgesics, NSAIDs, exercise therapy and recommendations on physical activity and a healthy

body weight.[37] The control group received usual care only and was advised not to change their lifestyle habits.

Medication in both groups was kept stable whenever possible.

Primary and secondary outcomes

The primary endpoint was the mean change in the patient-reported Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) total score (range 0–96, from best to worst) over time measured using digital questionnaires administered through the CASTOR electronic data capture system, with subscores of the WOMAC (pain, range 0–20; stiffness, range 0–8; physical function, range 0–68) as secondary outcomes.[38] The validated (PROMIS) was used to measure depression, fatigue, pain interference, and physical function, as domains of health-related quality of life.[25] WOMAC physical function measures *difficulty* when performing tasks, while PROMIS physical function—included by request of patient partners—measures *ability* to perform tasks.

Additional secondary outcomes included: body weight (measured on a Seca mechanical floor scale, rounded to the nearest 0.5 kg), fat mass (measured by dual-energy X-ray absorptiometry [DEXA]), waist circumference (midpoint between lowest rib and iliac crest), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting glucose, hemoglobin A1c (HbA1c), low-density lipoproteins (LDL), high-density lipoproteins (HDL) triglycerides, and blood pressure. Blood samples were drawn in a fasting state and processed in the hospital's routine analysis laboratory and blood pressure was measured in a supine position using a validated automated sphygmomanometer. Body weight, waist circumference, and blood pressure were measured by a researcher aware of the allocation.

Dietary intake was measured using the "MijnEetmeter," a validated digital food diary that can be used online or as an app containing over 90,000 foods from Dutch food databases.[39] Mean intakes of all macro nutrients and energy per day, based on 4–7 full day diaries, were calculated.

Furthermore, adverse events and changes in pain medication and medication for metabolic syndrome associated factors were recorded.

Adherence

To measure adherence, an adapted version of the *Lifestyle index adherence score* as developed by Ornish et al.[23] was used, in which adherence is defined by the attendance of meetings, stress-reducing activities, physical activity, and diet. In the original version, the diet score was defined by total fat and cholesterol intake. Since the diet intervention was not based on a low-fat diet, these vectors were changed into fiber and saturated fatty acids as indicators for a whole food plant-based diet. Full adherence (100% score) was defined as attendance of all meetings, performing stress-reducing activities 6 days per week for 10 minutes per day, physical activity 5 days per week for 30 minutes per day, and mean intake of at least 14 g of fiber per 1000 kilocalories (kcal) and less than 10% saturated fatty acids of total kcal per day. Stress-reducing and physical activities were self-reported and based on a digital questionnaire referring to activities in the past week. In case of missing data for one of the components (e.g. diet), we based the adherence score on the remaining components. A detailed description of the score was published previously.[24]

Sample size calculation

To determine the sample size, two previous interventions that combined diet and exercise were used. Both studies showed outcomes at 6 months with between-group mean differences of the WOMAC pain of –2.4[41] and –0.72[40]. Both studies reported a standard error of the mean (0.50 and 0.45, respectively) as measure for variability, which was erroneously interpreted in our protocol as standard deviation. Based on these data, we assumed an effect size of 0.7, whereas this should have been 0.51 with a standard deviation of 4.66. Our sample size calculation, using an α of 0.05 and power $(1 - \beta)$ of 0.80, resulted in 68 (rounded to 80 to account for possible dropouts estimated at 20%), but should have been 124 (rounded to 150 to account for possible dropouts).

Statistical analysis

Outcomes were measured at baseline, 8, and 16 weeks. After closure of the trial, data were cleaned and verified by two researchers. Baseline values of dropouts and participants included in the full analysis were compared for WOMAC, age, and BMI, using the Mann–Whitney test for independent samples.

Intention-to-treat analyses with a linear mixed model, adjusted for the baseline value of the particular primary or secondary outcome, were performed to calculate the mean difference and 95% confidence intervals between the groups in change in continuous outcomes over time.

An additional analysis was conducted in which the model was adjusted for potential confounders including sex, age, and BMI. Also, a mediation analysis was added to determine whether weight loss mediated the effect of the intervention on the WOMAC total score.

Based on the *Lifestyle index adherence score*,[23] adherence in the intervention group at 16 weeks was ranked and differences in WOMAC outcomes between quartiles of adherence were analyzed over time with a linear mixed model analysis, adjusted for baseline values of the particular outcome.

All analyses were performed with R version 4.0.5 (2021-03-31) and p-values < 0.05 were considered statistically significant.

Results

Participant characteristics

Participants were referred by healthcare professionals (37%) or enrolled via a webpage (63%). Of the 92 people assessed for eligibility, 66 were randomized (Figure 1). One participant in the intervention group dropped out due to health problems (not related to the intervention) and intolerance for the diet. One participant in the control group dropped out due to health problems and low e-health competencies. Both dropouts occurred shortly after randomization (without WOMAC measurement for control group dropout) and were lost to follow-up. Data from the two dropouts were excluded from analyses. All data from all remaining 64 people were used in the analyses (Figure 1).

The two dropouts were similar to the other participants regarding WOMAC, age, and BMI at baseline.

Study participants had a mean age of 63 years, were mostly female (84%), and had a mean BMI of 33 kg/m^2. All participants fulfilled the clinical criteria for OA and most of them ($n = 28$ (88%) in intervention group; $n = 29$ (91%) in control group) also fulfilled the ACR radiological criteria for hip or knee OA. Thirty-five participants (55%) used analgesics, mostly paracetamol. Thirty-nine participants (61%) used antihypertensives, 10 (16%) diabetes medication, and 23 (36%) lipid-lowering medication (Table 1).

A detailed overview of changes in medication use is available in Supplementary Table 1.

Randomization resulted in similar groups regarding age, sex, weight, and fat mass, Kellgren–Lawrence grades and WOMAC (sub) scores. The distribution of individuals with OA of the hip, knee, or both differed between the two groups, with more people in the

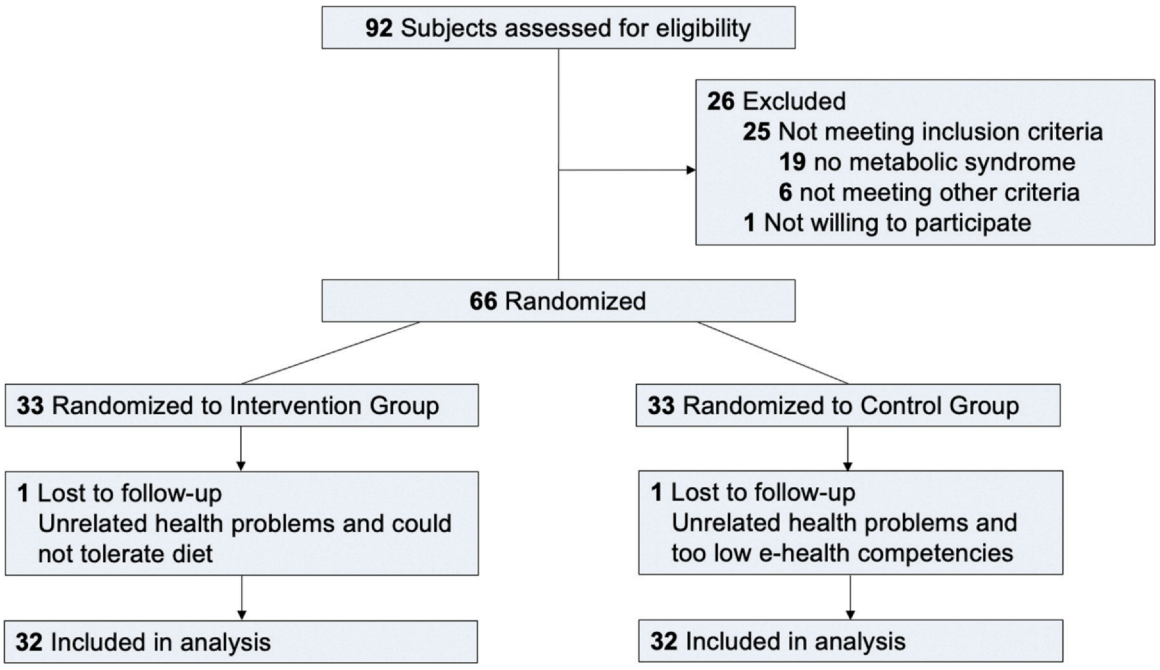

Fig. 1 Osteoarthritis and Cartilage

CONSORT flow diagram in the "Plants for Joints" Osteoarthritis Trial.

control group with OA of the knee, while the intervention group consisted of more people with OA of the hip or OA of both the hip and knee.

During the intervention, participants in the intervention group had a mean (SD) of 1.2 (1.7) visits to the general practitioner, 4.9 (7.8) visits to the physiotherapist, and 0.8 (2.7) visits to the medical specialist. In comparison, the control group had a mean (SD) of 3.1 (2.8) visits to the general practitioner, 1.5 (3.0) visits to the physiotherapist, and 1.2 (2.1) visits to the medical specialist.

Pain, stiffness, and function

The intervention group had greater mean improvements in WOMAC total (11.7; 95% confidence interval (CI) 7.2–16.3; $p < 0.0001$), WOMAC pain (1.89; 95% CI: 0.77–3.01; $p < 0.01$), WOMAC stiffness (1.30; 95% CI: 0.75–1.85; $p = 0.0001$), and WOMAC physical function (8.6; 95% CI: 5.2–11.9; $p < 0.0001$) than the control group over time (from baseline to 16 weeks) (Table 2 and Figure 2). Mediation analysis showed that weight loss did not mediate the effect of the intervention on the WOMAC total.

Secondary outcomes

PROMIS fatigue and pain interference decreased over time in favor of the intervention group, whereas both depression and physical function showed a trend toward improvement but did not reach statistical significance when compared with the control group.

Reduction of body weight and fat mass were significantly larger in the intervention versus the control group with between-group differences of 5.3 and 3.9 kg, respectively, as well as a larger decrease in the intervention group for fat percentage (–2.1%), BMI (–1.8 kg/m^2), and waist circumference (–6 cm) (Table 2).

Inflammation in the intervention group decreased, although this was only significant for CRP and not for ESR when compared to the control group. The metabolic parameters fasting blood glucose, HbA1c, and LDL decreased in the intervention group, whereas blood pressure, HDL, and triglycerides did not change over time when comparing the intervention with the control group.

Prevalence of metabolic syndrome decreased with 10 in both groups in 16 weeks, leaving 22 people who met the criteria for metabolic syndrome in both the intervention and the control group.

Program adherence

Mean WOMAC total score improved in all adherence quartiles ($n = 8$ for each quartile) based on the *Lifestyle Index Adherence Score* within the intervention group. When compared to the lowest level of adherence (level 1, $n = 2$ missing data for diet), participants with the highest levels of adherence (3 [$n = 4$ missing data for diet] and 4 [$n = 1$ missing data for diet]) had larger average improvements of the WOMAC (3.3 more ($p = 0.59$) and 2.4 more ($p = 0.67$) respectively), while those in level 2 improved less (3.5 less ($p = 0.54$)). See also Supplementary Figure 1.

Energy intake/day at the end of the intervention was lower than at the beginning (mean difference (SD) –136 (270) kcal) within the intervention group, whereas within the control group energy intake/day increased with a mean 69 (260) kcal in 16 weeks. Protein intake within the intervention group decreased from 0.8 (0.2) to 0.7 (0.2) g/kg at the end of the trial, while it remained at 0.7 (0.4) g/kg body weight in the control group. At baseline, the intake of saturated

	Intervention group	Control group
Characteristic	(*n* = 32)	(*n* = 32)
Age, mean (SD), years	63.3 (6.8)	63.4 (6.1)
Female sex, number (%)	28 (85%)	26 (79%)
Body mass index, mean (SD), kg/m^2	33.2 (5.2)	33.4 (5.7)
Body weight, mean (SD), kg	94.6 (17.5)	95.3 (14.4)
Fat mass, mean (SD), kg	41.9 (11.0)	41.9 (10.4)
Location OA		
Hip OA, number (%)	7 (22%)	5 (16%)
Knee OA, number (%)	9 (28%)	16 (50%)
Hip and knee OA, number (%)	16 (50%)	11 (34%)
Kellgren–Lawrence grade hip, number (%)		
Grade hip 0	1 (3%)	0 (0%)
Grade hip 1	5 (16%)	8 (25%)
Grade hip 2	18 (56%)	19 (59%)
Grade hip 3	4 (13%)	4 (13%)
Grade hip 4	4 (13%)	1 (3%)
Kellgren–Lawrence grade knee, number (%)		
Grade knee 0	1 (3%)	1 (3%)
Grade knee 1	7 (22%)	8 (25%)
Grade knee 2	11 (34%)	6 (19%)
Grade knee 3	6 (19%)	11 (34%)
Grade knee 4	7 (22%)	6 (19%)
WOMAC total score (range, 0–96), mean (SD)	38.5 (13.4)	40.4 (19.6)
WOMAC pain (range, 0–20), mean (SD)	7.50 (2.92)	7.41 (3.71)
WOMAC stiffness (range, 0–8), mean (SD)	4.13 (1.93)	4.28 (1.80)
WOMAC physical function (range, 0–68), mean (SD)	26.8 (10.6)	28.7 (14.9)
Comorbidities		
Hypertension, number (%)	25 (78%)	29 (91%)
(Pre)diabetes type 2, number (%)	5 (16%)	7 (22%)
Hyperlipidaemia, number (%)	23 (72%)	22 (69%)
Sleep apnea, number (%)	3 (9%)	3 (9%)
Thyroid disorders, number (%)	4 (13%)	3 (9%)
Psychiatric disorders, number (%)	7 (22%)	3 (9%)
Medication		
Paracetamol, number (%)	11 (34%)	8 (25%)
Non-steroidal anti-inflammatory drugs, number (%)	3 (9%)	5 (16%)
Opioids, number (%)	4 (13%)	1 (3%)
Antihypertensives, number (%)	20 (63%)	19 (59%)
Antidiabetics, number (%)	4 (13%)	6 (19%)
Lipid lowering treatment, number (%)	12 (38%)	11 (34%)

SD = standard deviation, body mass index = body weight in kilograms divided by the square of the height in meters. All WOMAC scores: lower scores are favorable.

Table 1 Osteoarthritis and Cartilage

Baseline characteristics "Plants for Joints" OA trial

fat was 13 (3) percent of total energy intake in both groups, higher than the daily recommendation of under 10% of total energy intake. Fiber intake at baseline was at the recommended level of 14 (4) g/1000 kcal. The intervention group reached the healthy intake range of saturated fat (8 (2) percent of total energy intake) and fiber (22 (5) g/1000 kcal) at 16 weeks, while the control group improved to a lesser extent at 16 weeks (saturated fat: 12 (4) percent of total energy intake; fiber 16 (6) g/1000 kcal) (Table 3).

The average self-reported physical activity level was above the recommended 150 minutes per week at baseline in both groups and remained at the baseline level (± 200 min per week) in both groups (Table 3). Self-reported average time spent on stress-reducing activities increased within both groups from a mean (SD) 30 (30) minutes per week in the intervention group and 31 (28) minutes in the control group to 40 (33) and 39 (29) minutes per week at 16 weeks, respectively (Table 3).

Medication changes

Three people in the intervention group decreased the use of pain medication, while in the control group the use of analgesics remained unchanged (Supplementary Table 1).

In the intervention group, 3 participants stopped using an antihypertensive drug and 2 stopped using lipid lowering drugs. In the control group, 2 participants stopped the use of an antihypertensive. Medication for metabolic syndrome associated factors did not increase in the intervention group, while in the control group 1 started antidiabetic treatment and 1 started a lipid lowering drug.

Adverse events

A total of 3 adverse events were recorded in the intervention group and 7 in the control group, all not related to the study. One participant in the control group had a car accident on her way to a visit for measurements in the clinic, followed by surgery and rehabilitation. No other serious adverse events occurred.

Discussion

The multidisciplinary "Plants for Joints" lifestyle program, consisting of a whole food plant-based diet, physical activity, and stress management relieved pain, reduced stiffness, and improved physical function in patients with hip or knee MSOA compared to usual care. In addition, there was improvement in body composition as well as in several patient-reported, inflammatory, and metabolic outcomes in comparison to the control group.

The 35% reduction in WOMAC pain and 38% improvement in WOMAC physical function in patients with moderate-severe OA are in line with earlier results by Messier et al. (improvement WOMAC pain 31%, physical function 33%) and exceed the minimal clinically important improvement of 20%.[15,42] In the Messier trial, meal replacements were used to accomplish a very low energy intake whereas the "Plants for Joints" program focused on sustainable lifestyle changes: meeting dietary and physical activity guidelines, daily mindfulness and sleep hygiene. This resulted in a diet high in fiber and low in saturated fat that meets recommendations for essential nutrients. Also, the achieved lower weight, fat mass, and waist circumference are in line with the results of a recent study in overweight, young adults showing that a low-fat plant-based diet decreased body weight and fat mass more than a low carbohydrate-ketogenic diet.[43] The minor decrease in energy intake within the intervention group could not fully explain the decrease in fat mass. Higher intakes of dietary fiber, however, are associated with a lower body weight and lower fat mass regardless of energy intake, but the reasons thereof are not yet completely understood.[44]

The PROMIS improvements, such as in physical function, may appear to be less substantial than those measured by WOMAC. However, this can be explained by the fact that the WOMAC and PROMIS measure on a different scale (or metric). Consequently, small changes in PROMIS scores are already clinically relevant. For physical function, minimal important changes are estimated to be between 1.9 and 5.1 while we found a change of 2.5 within the intervention group.[45]

Characteristic	Plants for Joints group ($n = 32$)			Control group ($n = 32$)			Difference in change between groups	
	Mean (SD)			Mean (SD)				
	Baseline	8 weeks	16 weeks	Baseline	8 weeks	16 weeks	(95% CI)	p-value
WOMAC	$n = 32$	$n = 30$	$n = 32$	$n = 32$	$n = 32$	$n = 31$		
Pain (range, 0–20)	7.50 (2.93)	5.20 (3.28)	4.88 (3.92)	7.41 (3.71)	6.75 (3.65)	7.19 (3.24)	−1.89 (−3.42 to −0.36)	< 0.01
Stiffness (range, 0–8)	4.13 (1.93)	2.73 (1.78)	2.50 (1.87)	4.28 (1.80)	4.19 (1.60)	3.90 (1.68)	−1.30 (−1.89 to −0.71)	0.0001
Physical function (range, 0–68)	26.8 (10.6)	18.5 (10.8)	16.5 (13.2)	28.7 (14.9)	28.9 (15.3)	26.5 (15.1)	−8.6 (−12.0 to −5.2)	< 0.0001
Total (range, 0–96)	38.5 (13.4)	26.5 (14.8)	23.8 (18.2)	40.4 (19.6)	39.8 (19.0)	37.6 (19.3)	−11.7 (−16.4 to −7.1)	< 0.0001
PROMIS	$n = 30$	$n = 29$	$n = 29$	$n = 29$	$n = 26$	$n = 28$		
Depression	51.4 (7.2)	48.4 (11.2)	49.9 (6.3)	52.5 (6.9)	52.2 (7.7)	51.4 (7.0)	−1.6 (−4.6–1.5)	0.31
Fatigue	55.4 (7.4)	52.6 (7.6)	53.2 (8.2)	53.6 (8.9)	55.1 (7.2)	54.2 (8.4)	−3.5 (−5.5 to −1.3)	< 0.01
Pain interference	60.2 (4.7)	57.9 (6.2)	57.0 (7.2)	59.2 (6.8)	58.2 (6.1)	59.8 (5.6)	−2.5 (−5.0 to −0.2)	0.05
Physical function	40.8 (5.0)	42.8 (6.5)	43.3 (7.2)	41.6 (5.7)	43.0 (5.4)	41.9 (5.2)	1.3 (−0.5–3.4)	0.19
Inflammation								
	$n = 29$	$n = 31$	$n = 31$	$n = 30$	$n = 21$	$n = 32$		
ESR mm/h	13.6 (7.8)	12.8 (8.4)	13.7 (9.3)	11.1 (8.9)	9.1 (7.2)	13.9 (15.2)	−2.6 (−7.7–2.5)	0.32
	$n = 32$	$n = 31$	$n = 32$	$n = 32$	$n = 22$	$n = 32$		
CRP, mg/l	3.4 (4.0)	2.7 (3.1)	2.5 (2.8)	2.8 (3.2)	2.7 (2.7)	3.4 (3.6)	−1.04 (−1.84 to −0.24)	0.01
Anthropometric								
	$n = 32$	$n = 31$	$n = 32$	$n = 32$	$n = 22$	$n = 31$		
Weight, kg	94.6 (17.5)	91.6 (16.2)	88.2 (16.0)	95.3 (14.4)	97.0 (12.5)	95.2 (14.3)	−5.2 (−6.9 to −3.6)	< 0.0001
Body mass index, kg/m^2	33.2 (5.2)	32.1 (4.7)	31.2 (4.8)	33.4 (5.7)	33.2 (3.8)	33.3 (5.4)	−1.8 (−2.3 to −1.2)	< 0.0001
	$n = 31$		$n = 30$	$n = 32$		$n = 31$		
Fat mass, kg (DEXA)	41.9 (11.0)	–	38.0 (10.1)	41.9 (10.4)	–	41.8 (10.8)	−3.9 (−5.3 to −2.5)	< 0.0001
Fat percentage, %kg (DEXA)	44.5 (5.5)	–	42.7 (5.6)	43.4 (6.8)	–	43.2 (6.9)	−2.1 (−3.0 to −1.1)	< 0.0001
	$n = 32$	$n = 31$	$n = 30$	$n = 30$	$n = 21$	$n = 31$		
Waist circumference, cm	109 (14)	104 (13)	101 (11)	112 (13)	109 (8)	111 (12)	−6 (−9 to −4)	< 0.0001
Waist circumference (females), cm ($n = 54$)	108 (14)	103 (13)	100 (10)	111 (14)	108 (8)	110 (13)	−6 (−9 to −4)	< 0.0001
Waist circumference (males), cm ($n = 10$)	117 (8)	113 (10)	110 (12)	116 (9)	116 (4)	115 (10)	−5 (−9 to −2)	0.02
Metabolic								
	$n = 32$	$n = 32$	$n = 32$	$n = 29$	$n = 20$	$n = 31$		
Fasting blood glucose, mmol/l	6.1 (1.1)	5.8 (1.0)	5.6 (1.0)	6.3 (1.8)	6.1 (1.1)	6.5 (1.9)	−0.4 (−0.6 to −0.1)	< 0.01
	$n = 32$	$n = 32$	$n = 32$	$n = 32$	$n = 22$	$n = 32$		
HbA1c, mmol/mol	41 (7)	40 (6)	39 (5)	44 (10)	41 (8)	44 (10)	−2.2 (−3.2 to −1.1)	0.0001
	$n = 32$	$n = 31$	$n = 31$	$n = 32$	$n = 22$	$n = 31$		
Systolic blood pressure, mmHg	146 (19)	140 (15)	144 (19)	149 (20)	142 (20)	145 (17)	−1 (−7–6)	0.8
Diastolic blood pressure, mmHg	92 (11)	87 (8)	88 (8)	94 (9)	90 (12)	90 (11)	−2 (−6–2)	0.35
	$n = 32$	$n = 32$	$n = 32$	$n = 32$	$n = 22$	$n = 32$		
LDL, mmol/l	3.66 (1.5)	3.03 (1.2)	3.19 (1.3)	3.74 (1.3)	3.70 (1.1)	3.53 (1.0)	−0.3 (−0.6 to −0.1)	< 0.01
HDL, mmol/l	1.51 (0.33)	1.38 (0.34)	1.43 (0.30)	1.49 (0.48)	1.45 (0.43)	1.37 (0.50)	0.0 (−0.1–0.1)	0.92
Triglycerides, mmol/l	1.65 (0.78)	1.55 (0.61)	1.71 (0.88)	1.69 (0.97)	1.80 (0.92)	1.86 (0.93)	−0.2 (−0.4–0)	0.06

All values for the total group ($n = 64$), WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, PROMIS = Patient-reported Measurement Information System, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, DEXA = Dual-energy X-ray absorptiometry, SD = standard deviation. Higher WOMAC scores are worse. The p-values are based on a linear mixed model with random effect for subjects for between group analyses, adjusted for baseline values. Additional adjustment for covariates (sex, age, and BMI) did not change outcomes.

Table 2

Osteoarthritis and Cartilage

Primary and secondary outcomes of the "Plants for Joints" OA trial

This trial also showed a significant reduction of CRP, which is in line with other studies on plant-centered diets. Reductions in CRP and fat mass are associated with a lower risk of metabolic syndrome and other lifestyle-related diseases.[9,46,47] Like this trial, other interventions based on plant-based diets also showed improvements in metabolic markers such as fasting glucose, HbA1c, and LDL,[22,43,48,49] which is relevant for people with OA, who have an increased risk of lifestyle-related diseases compared with the general population.[8,50]

Strengths of this study include the high acceptability of the intervention resulting in a low dropout rate. The study responds to the long-standing need for evidence regarding a multidisciplinary lifestyle program for OA and provides evidence of the health benefits of plant-based diets, which strengthens the proposition of a plant-based diet as part of a more sustainable lifestyle.[51,52]

On the other hand, because the study combined multiple lifestyle factors, the individual contribution of these factors to the results cannot be determined. However, as described by Furman et al., chronic system inflammation is driven by multiple factors including diet, physical activity, and stress.[9] This might explain a decrease in inflammation and an overall improvement of health that is not mediated by weight loss.

Another limitation is that the intervention group received extra attention whereas there was no attention control. Therefore, the

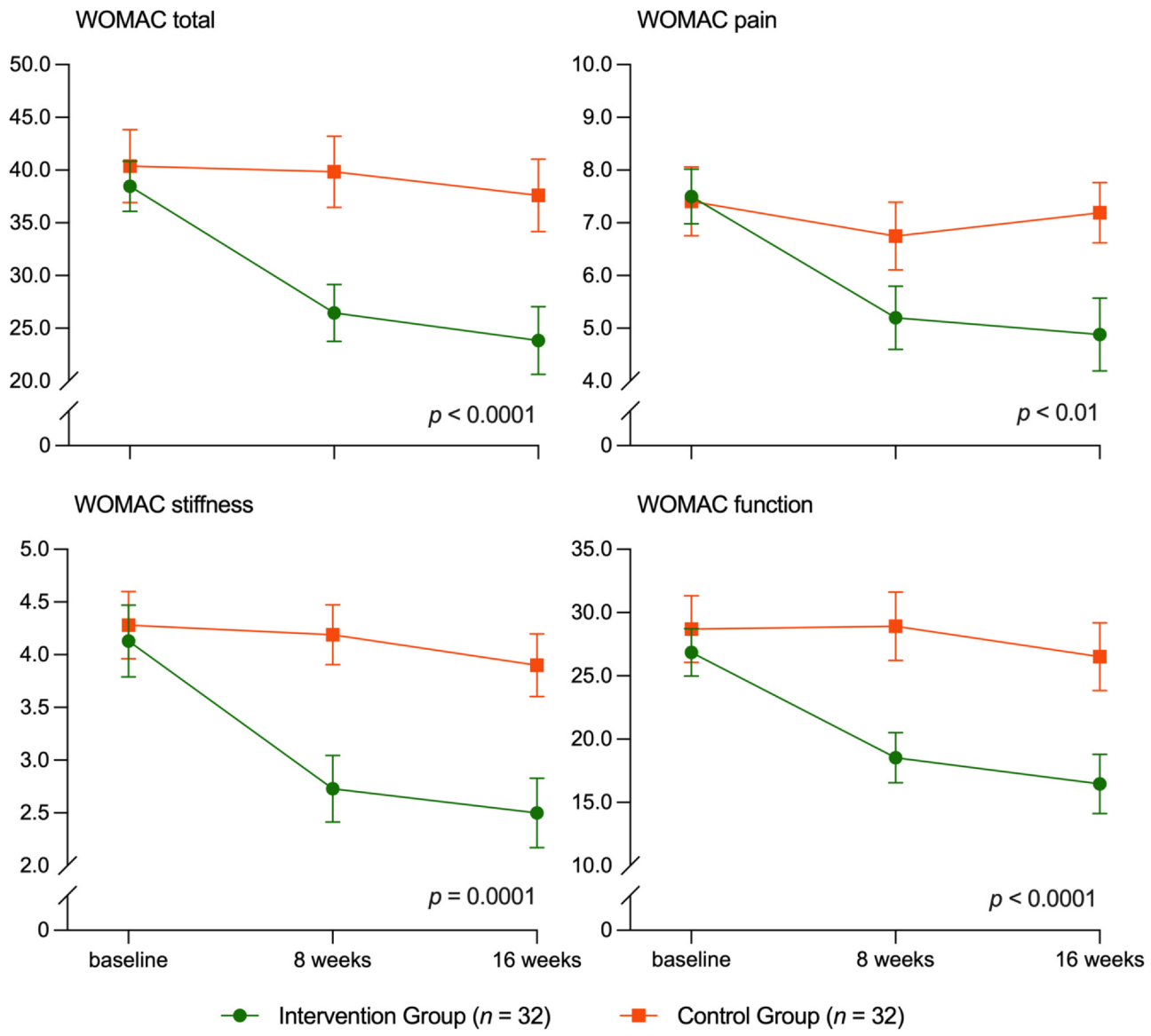

Fig. 2

Osteoarthritis and Cartilage

Change in WOMAC total and subscores (pain, stiffness, and physical function) for the intervention group ($n = 32$) when compared with the control group ($n = 32$). Higher WOMAC scores are worse. Graphs show mean ± standard error.

between-group differences may in part have been caused by attention effects.

However, improvement also occurred in objective measures. In addition, the adherence to the lifestyle components was not measured by objective means, thus providing room for potential misreporting. The small improvement in physical activity may be due to the high baseline levels of approximately 200 minutes per week and the use of self-reported data. Also, for stress-reducing activities, self-reported data were used. Although dietary intake was measured using a validated method, many participants did not keep the diary resulting in missing values. In addition, food diaries result in underreporting, especially in individuals with a higher BMI.[53]

Another limitation is that COVID-19 measures, in addition to the accidently underestimated sample size, resulted in a relatively small sample size of 66 instead of 150 participants which can limit precision estimates and generalizability. Also, selection bias is a potential limitation, as only highly motivated individuals who chose to personally apply for the intervention were included.

Finally, the present study is too small and short to be able to measure possible structural effects on osteoarthritic joints. Our focus on the systemic aspects of OA also resulted in less appreciation of the unique disease mechanisms and pathologies of hip and knee OA separately. Yet, it is noteworthy that weight loss is associated with less progression of OA.[54] In this respect, it will be of interest to see in how far the present favorable results can be maintained in the ongoing 2-year observational extension study.[24] In this extension study, cost effectiveness will also be investigated.

In conclusion, the multidisciplinary "Plants for Joints" program relieved pain, reduced stiffness, improved physical function, decreased inflammation, and improved metabolic status in patients

Characteristic	Intervention group ($n = 32$)			Control group ($n = 32$)		
	Mean (SD)			Mean (SD)		
	Baseline	8 weeks	16 weeks	Baseline	8 weeks	16 weeks
Diet	$n = 31$	$n = 23$	$n = 25$	$n = 26$	$n = 18$	$n = 25$
Energy, kcal	1755 (310)	1616 (226)	1638 (259)	1800 (568)	1810 (545)	1863 (575)
Fat, g	75 (21)	64 (16)	70 (16)	81 (32)	79 (29)	80 (33)
Saturated fat, g	25 (9)	13 (5)	14 (5)	27 (13)	24 (12)	25 (13)
Saturated fat, energy%	13 (3)	7 (2)	8 (2)	13 (4)	12 (4)	11 (4)
Carbohydrate, g	170 (37)	178 (29)	169 (36)	174 (48)	175 (48)	188 (45)
Carbohydrate, energy%	39 (6)	44 (6)	41 (6)	40 (7)	40 (9)	42 (8)
Protein, g	74 (16)	57 (12)	60 (12)	71 (24)	73 (34)	69 (26)
Protein, g/kg body weight	0.8 (0.2)	0.7 (0.1)	0.7 (0.2)	0.7 (0.3)	0.7 (0.4)	0.7 (0.3)
Fiber, g	23 (7)	37 (9)	35 (9)	24 (7)	27 (10)	29 (11)
Fiber, g/1000 kcal	13 (4)	23 (4)	22 (5)	14 (5)	16 (5)	16 (6)
Self-reported physical activity	$n = 31$	$n = 29$	$n = 32$	$n = 32$	$n = 32$	$n = 31$
Physical activity, min/wk	195 (110)	210 (119)	202 (129)	208 (141)	226 (123)	196 (129)
Self-reported stress reducing activities	$n = 31$	$n = 29$	$n = 32$	$n = 32$	$n = 32$	$n = 31$
Stress reducing activities, min/wk	30 (30)	39 (27)	40 (33)	31 (28)	40 (30)	39 (29)

SD = standard deviation, kcal = kilocalories, energy% = percentage of total energy in kilocalories.

Table 3

Osteoarthritis and Cartilage

Lifestyle descriptives "Plants for Joints" OA trial

with MSOA compared to usual care. This program offers an additional and sustainable treatment option for patients with MSOA.

Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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CRediT authorship contribution statement

Study conception & fundraising: WW and DvS. Study design & statistical analysis: WW, CW, MvdP, ML, MG, JT, LR, HM, PW and DvS. Patient recruitment: WW, CW, MvdP, MG. WW drafted the manuscript. DvS supervised the overall project. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors report no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.05.014.

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