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A multidisciplinary lifestyle programme for patients with rheumatoid arthritis and metabolic syndrome-associated osteoarthritis: economic evaluation alongside the 'Plants for Joints' randomized controlled trials

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Objective: To evaluate the cost-effectiveness of the 'Plants for Joints' intervention for rheumatoid arthritis (RA) and metabolic syndrome-associated osteoarthritis (MSOA) patients over 16 weeks.

Method: Data from two randomized controlled trials were analysed. The first included 77 RA patients (intervention = 40; control = 37) and the second 64 MSOA patients (intervention = 32; control = 32). The intervention comprised a 16 week lifestyle programme including a whole-food plant-based diet, exercise, and stress management; control participants received usual care. Data from both trials were analysed together and separately. Costs were measured from societal and healthcare perspectives. Effects were expressed in quality-adjusted life-years (QALYs).

Results: The intervention cost €886/patient. Intervention group participants gained more QALYs than the control group (0.009; 95% confidence interval −0.004 to 0.023), equivalent to 3.3 additional days in 'perfect health' (0.009 × 365). Healthcare costs were higher in the intervention group, while societal costs were lower. None of these differences was statistically significant. From a societal perspective, the intervention had a moderate to high probability of being cost-effective compared with usual care, while the probability was low from a healthcare perspective. Stratified analyses indicated that the probability of cost-effectiveness was higher in RA than in MSOA patients. This difference became less pronounced after excluding outliers.

Conclusion: The Plants for Joints intervention demonstrated a relatively high probability of cost-effectiveness from a societal perspective, although this was lower from a healthcare perspective. If these benefits are sustained in the long term, this intervention may reduce the disease and economic burden of arthritic conditions.

Arthritic diseases are chronic rheumatic conditions characterized by progressive joint damage and potential extra-articular complications, which can lead to permanent disability and an elevated mortality rate compared with the general population (1). Globally, the prevalence of arthritic diseases is significant (2, 3), with millions affected worldwide, contributing to a substantial number of years lived with disabilities (4, 5). Beyond the significant human suffering associated with arthritic diseases, their economic burden is substantial (6, 7). A review of 27 studies found that the annual combined direct and indirect costs of rheumatoid

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arthritis (RA) range from US$2400 to US$84 000 per patient, with most estimates falling between US$10 000 and US$30 000. A significant portion of these costs typically stems from drug expenses (6). In contrast, pharmaceutical treatment options for osteoarthritis are more limited, and other healthcare use and productivity losses constitute the majority of its costs. The total economic burden of osteoarthritis is amplified by its high prevalence, which exceeds 20% in some developed countries (8).

While the exact causes of arthritic diseases remain unclear, their onset and progression have been linked to various environmental and lifestyle factors (e.g. smoking, poor diet, obesity, lack of exercise, psychological stress) (9–13). These unhealthy lifestyle factors, along with metabolic syndrome and microbiome dysbiosis, may also contribute to other chronic diseases through the shared mechanism of systemic chronic inflammation (14). This shared pathway may help to explain why individuals with arthritic diseases, such as RA, experience a higher prevalence of comorbid conditions, including coronary heart disease and diabetes mellitus, compared with the general population (15). Addressing and preventing unhealthy lifestyle habits could therefore not only reduce the incidence and burden of arthritic diseases, but also help to mitigate their associated comorbidities (16–21).

In response to the growing need for effective treatments, the 'Plants for Joints' intervention, a multidisciplinary lifestyle programme designed to alleviate symptoms in patients with RA or metabolic syndrome-associated osteoarthritis (MSOA), was developed (22). After 16 weeks, the intervention demonstrated a significant reduction in disease activity and improved metabolic status in RA patients (16). In addition, individuals with MSOA experienced decreased stiffness, pain relief, and enhanced physical function compared with those receiving usual care (23). After a year, these improvements were largely sustained, with a net decrease in medication use (24). However, given the limited resources available in healthcare, decision makers require insights into not only the effectiveness of interventions, but also their cost-effectiveness. Therefore, this study aimed to evaluate the cost-effectiveness of the Plants for Joints intervention in comparison to usual care for patients with RA and MSOA, using a 16 week randomized controlled trial (RCT) design.

Method

The Plants for Joints project consisted of two RCTs designed to assess the effectiveness and cost-effectiveness of the multidisciplinary lifestyle intervention compared with usual care in individuals with (i) RA or (ii) MSOA. In this economic evaluation, data from both trials were analysed together and separately. A comprehensive description of the Plants for Joints project has been published elsewhere (22), and a brief overview is provided in the following subsections.

Design

Both the RA and MSOA trials had a parallel design and were conducted as 16 week, observer-blind, open-label RCTs. The RCTs took place from May 2019 to December 2021 at the Reade outpatient clinic for rehabilitation and rheumatology in Amsterdam, the Netherlands. Study visits occurred at baseline, and at 8 and 16 weeks. After the RCT phase, control group participants also followed the intervention. After completion of the intervention, all participants were followed in a 2 year extension study, during which they received continued online support and six additional thematic, optional meetings to promote adherence. The Medical Ethical Committee of the Amsterdam UMC approved the study protocol (EudraCT number NL66649.048.18). The protocol was prospectively registered with the International Clinical Trial Registry Platform (number NL7800) and published (22). All participants provided written informed consent. This economic evaluation adhered to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (25).

Recruitment, selection, and randomization

Subjects aged 18 years and older were recruited through healthcare professionals or enrolled via a dedicated webpage. The main inclusion criteria were as follows.

RA trial: RA diagnosis according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) 2010 criteria, with low to moderate disease activity, as measured by the 28-joint Disease Activity Score (2.6 ≤ DAS28 ≤ 5.1), and either unchanged use of disease-modifying anti-rheumatic drugs (DMARDs) for the past 3 months or no use of DMARDs.

MSOA trial: osteoarthritis in the hip and/or knee, diagnosed according to the clinical criteria of the ACR (without an age criterion), and metabolic syndrome as defined by the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) criteria.

The main exclusion criteria for both trials included: insufficient e-health competencies to complete digital questionnaires and maintain an online food diary, currently following a predominantly plant-based diet, underweight [body mass index (BMI) < 18.5 kg/m^2], pregnancy, and unwillingness to abstain from smoking for at least the duration of the RCT, if applicable (22). In both trials, participants were randomized across study groups in a 1:1 ratio with a variable block randomization in block sizes of 2 and 4.

Intervention and control condition

At the beginning of the programme, intervention group participants received individual intake consultations with a dietitian and a physical therapist to assess general health, current dietary habits, and physical activity levels. During the programme, groups of six to 12 participants met 10 times for sessions lasting for 2–3 h. The programme actively promoted peer education and peer support. Intervention group participants received both theoretical and practical education on a whole-food, plant-based diet, physical activity and exercise, and stress management, all based on previous protocols and guidelines. This included a whole-food, plant-based dietary plan based on the protocols by Ornish et al (26) and Barnard et al (27), slightly adapted to align with the 2015 Guidelines on Healthy Nutrition from the Health Council of the Netherlands; personal physical activity goals in accordance with the 2017 Dutch physical activity guidelines (which recommend 150 min per week of moderately intense activity and 2 days per week of muscle and bone-strengthening activities); and psychoeducation on the health effects of stress, stress-management techniques, and coaching on sleep, based on the protocols by de Brouwer et al (20, 22). In addition, participants in the intervention group received a cooking class and instructional videos to support the practical adoption of the plant-based diet, at-home exercise routines, and a detailed weekly menu. They also received daily supplementation with methylcobalamin (1500 µg) and cholecalciferol (50 µg) to meet nutritional requirements not covered by diet alone. In contrast, control group participants received usual care and were advised not to alter their lifestyle habits. Usual care includes regular visits to the rheumatologist or rheumatology nurse, leading to treatments, such as medication and physiotherapy, and primary or secondary care for other conditions.

Measurements

At baseline, various clinical and sociodemographic characteristics were assessed, such as age, gender, body weight, and BMI.

For the economic evaluation, the primary outcome of interest was the Quality-adjusted life-year (QALY), estimated in accordance with the Dutch guideline for economic evaluations in healthcare (28). To derive QALYs, health-related quality of life was assessed using the 5-level EuroQol 5 Dimensions (EQ-5D-5L) at baseline, 8 weeks, and 16 weeks. The EQ-5D-5L measures health across five dimensions, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each rated on five levels of severity, ranging from no problems to extreme problems. Each unique combination of responses defines a specific health state, which was converted into a utility value anchored between 0 (representing death) and 1 (representing perfect health), using the Dutch value set (29). QALYs were then calculated by multiplying the duration spent in each health state by its corresponding utility value.

Costs were measured from a societal perspective and included the 16 week cost of the Plants for Joints intervention, other healthcare use, informal care use, as well as productivity losses from paid and unpaid work. Intervention costs were micro-costed, meaning that detailed data were gathered about the kinds of resources used during the 16 week intervention period and their respective unit prices. Data on other healthcare use, informal care, and productivity losses were collected through online questionnaires administered at baseline, and at 8 and 16 weeks. Each questionnaire covered an 8 week recall period, ensuring complete coverage of the 16 week follow-up. The questions were based on the iMTA Medical Consumption Questionnaire (iMCQ), Productivity Cost Questionnaire (iPCQ), and Valuation of Informal Care Questionnaire (iVICQ), but were specifically tailored to the patient population (30–32). Other healthcare use included the use of primary healthcare services (e.g. visits to a general practitioner) and secondary healthcare services (e.g. hospital admissions). Medication costs were not included, because medication use was kept stable during the 16 week study period. Healthcare use was valued with prices derived from the Dutch Manual of Costing (28) or prices of professional organizations if the former were unavailable. Informal care (i.e. unpaid care provided by family, friends, and/or other kinds of volunteers) and productivity losses from unpaid activities (e.g. voluntary work) were valued with a recommended Dutch shadow price (28). Productivity losses from paid work included both absenteeism (i.e. absence from work) and presenteeism (i.e. being less productive while being at work), and were valued at the average cost of labour in the Netherlands (28). Costs were expressed in 2024 euros. Discounting of costs and effects was not required owing to the trial's 16 week duration.

Statistical analyses

Analyses were performed by intention-to-treat. Descriptive statistics were used to compare baseline characteristics between intervention and control group participants. Missing data were addressed through multiple imputation, stratified by treatment group. Multivariate imputation by chained equation with predictive mean matching was used to generate 10 complete datasets with the R mice package. Each dataset was analysed separately, as outlined below, and pooled estimates were calculated using Rubin's rules (33).

In the main analysis, data from both trials were analysed together. This was done because cost data tend to be heavily skewed, and hence typically require larger samples sizes compared with clinical outcomes.

First, we descriptively analysed the aggregated and disaggregated mean costs per group, along with the unadjusted mean differences between groups. Then, seemingly unrelated regression (SUR) was used to estimate the differences in total costs and effects (ΔC and ΔE). A key advantage of SUR is its ability to model two regression equations (i.e. one for ΔC and one for ΔE) simultaneously, allowing for the correlation between them to be accounted for. Both regression equations were corrected for baseline and type of arthritic disease (i.e. RA or MSOA). Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the adjusted difference in total costs by that in effects (ΔC/ΔE). The uncertainty surrounding the ICERs and 95% confidence intervals (CIs) for cost differences was estimated using bias-corrected and accelerated (BCA) bootstrapping with 5000 replications. This uncertainty was visually represented by constructing cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). CEACs provide a summary measure of the joint uncertainty of costs and effects, indicating the probability of the Plants for Joints intervention being cost-effective compared with usual care at varying willingness-to-pay (WTP) thresholds (i.e. the maximum amount of money that decision makers are willing to pay per unit of effect). In the Netherlands, decision makers are willing to pay €20 000/QALY for conditions with a mild disease burden (e.g. asthma), €50 000/QALY for conditions with a moderate disease burden (e.g. RA), and €80 000/QALY for conditions with a severe disease burden (e.g. chronic kidney disease) (34). All analyses were conducted in R studio using codes developed by Ben et al (35).

Sensitivity analyses

Six sensitivity analyses were performed to assess the robustness of the results: (i) a crude analysis (i.e. unadjusted for baseline values and type of arthritic disease); (ii) an analysis from the healthcare perspective (i.e. only including costs accruing to the formal Dutch healthcare sector); (iii) an analysis using classification and regression tree (CART) imputation; (iv) an analysis stratified by type of arthritic disease (i.e. RA or MSOA) [this sensitivity analysis was conducted in accordance with item 19 of the CHEERS statement (characterize distributional effects) and to present the results of the separate trials within the Plants for Joints project (25)]; (v) an analysis excluding outliers [outliers were identified through visual inspection of histograms and were defined as cases with exceptionally high secondary healthcare costs (i.e. >€10 000) and/or sick-leave costs (i.e. >€15 000); and (vi) an analysis focusing on waist circumference (cm) and unhealthy low-density lipoprotein cholesterol (LDL-C) levels (i.e. >2.6 mmol/L; yes/no) [this sensitivity analysis was performed to examine whether the cost-effectiveness of the Plants for Joints intervention, expressed in QALYs, was consistent with its cost-effectiveness based on clinical outcomes].

Results

Participants' characteristics

Initially, 149 participants were included in the study (RA = 83; MSOA = 66). In the RA trial, six participants dropped out shortly after randomization and were lost to follow-up: one from the intervention group owing to pregnancy; and five from the control group owing to pregnancy (n = 1), a disease flare (n = 1), or dissatisfaction with group allocation (n = 3). In the MSOA trial, two participants dropped out shortly after randomization: one from the intervention group owing to unrelated health issues and diet intolerance; and one from the control group owing to health problems and limited e-health literacy. These dropouts were excluded from the analyses and had baseline characteristics similar to those of the included participants.

Eventually, 141 participants were included in the main analysis (RA = 77; MSOA = 64), with 72 participants (RA = 40; MSOA = 32) randomized to the control group and 69 participants (RA = 37; MSOA = 32) to the intervention group. A total of 53 participants (RA = 34; MSOA = 19) had one or more missing EQ-5D-5L and/or cost items at one or more measurement points. Notably, missing EQ-5D-5L data at baseline (RA = 24; MSOA = 24) resulted from the questionnaire being added to the study instrumentarium after the study had already commenced (i.e. it can assumed to be missing completely at random, meaning that it is independent of both observed and unobserved data).

With the exception of the difference in utility values, which was adjusted for in the analyses, baseline differences between participants in the intervention and control groups were negligible (Table 1). Participants in the RA trial were, on average, younger, more often female, and had lower BMI, lower LDL-C levels, lower glycosylated haemoglobin (HbA_{1c}) levels, and higher utility values, as well as a lower systolic and diastolic blood pressure, compared with those in the MSOA trial. More detailed, disease-specific baseline characteristics, as well as flowcharts depicting participant progression through the two Plant for Joints trials, are provided in the Appendix A (23, 24).

Effects

In both trials combined, participants in the intervention group gained slightly more QALYs over the 16 week period (mean: 0.217; range: 0.053–0.281; median: 0.229; sem: 0.006) compared with the control group (mean: 0.197; range: −0.020 to 0.299; median: 0.213; sem: 0.009). This corresponded to an adjusted mean difference (MD) of 0.009 QALYs (95% CI: −0.004 to

Table 1. Baseline patient characteristics.

Characteristic	Total		MSOA trial		RA trial	
	Intervention group (n = 72)	Control group (n = 69)	Intervention group (n = 32)	Control group (n = 32)	Intervention group (n = 40)	Control group (n = 37)
Age (years)	59.4 ± 11.4	57.7 ± 10.1	63.3 ± 6.8	63.4 ± 6.1	56.4 ± 13.4	52.8 ± 10.3
Female sex	64 (89)	61 (88)	28 (85)	26 (79)	36 (90)	35 (95)
Weight (kg)	84.7 ± 17.6	82.6 ± 17.6	94.6 ± 17.5	95.3 ± 14.3	76.8 ± 13.2	71.5 ± 11.9
WC (cm)	100.2 ± 14.4	99.5 ± 16.9	109.2 ± 13.6	112 ± 13	93.0 ± 10.1	88.8 ± 12.0
BMI (kg/m^2)	29.8 ± 5.7	29.0 ± 6.3	33.2 ± 5.2	33.4 ± 5.7	27.1 ± 4.6	25.1 ± 3.7
LDL-C (mmol/L)	3.3 ± 1.3	3.6 ± 1.2	3.7 ± 1.5	3.7 ± 1.3	2.9 ± 1.0	3.5 ± 1.1
HbA_{1c} (mmol/L)	38.0 ± 6.8	40.6 ± 9.3	41.1 ± 7.0	43.7 ± 10.2	35.5 ± 5.6	37.8 ± 7.4
SBP (mmHg)	141 ± 19	139 ± 22	146 ± 19	149 ± 20	137 ± 19	131 ± 20
DBP (mmHg)	89 ± 11	89 ± 12	92 ± 11	94 ± 9	87 ± 11	86 ± 13
EQ-5D-5L utility value*	0.683 [0.021]	0.611 [0.022]	0.667 [0.030]	0.583 [0.050]	0.700 [0.027]	0.635 [0.039]

Data are shown as mean ± sd, n (%), or mean [sem].
*Results are based on multiple imputed data as some baseline utility values were missing.
MSOA, metabolic syndrome-associated osteoarthritis; RA, rheumatoid arthritis; WC, waist circumference; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, glycosylated haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; EQ-5D-5L, 5-level EuroQol 5 Dimensions.

0.023), equivalent to an additional 3.3 days in perfect health (i.e. 0.009×365) over the 16 week study period. However, this difference was not statistically significant. When stratified by trial, the QALY gain was greater in the MSOA trial (MD: 0.015; 95% CI: 0.000 to 0.029) than in the RA trial (MD: 0.005; 95% CI: −0.016 to 0.026). Of these, only the difference observed in the MSOA trial reached statistical significance.

Costs

The 16 week cost of the Plants for Joints intervention amounted to €886 per patient. This included the costs of the intake and follow-up consultations, group sessions, a cooking class, coordination of the intervention by a registered dietitian, and intervention materials (Table 2). Participants in the intervention group incurred lower total societal costs over the 16 week period (mean: €7126; range: €887–33 935; median: €4492; sem: €928) compared with the control group (mean: €10 218; range: €28–38 451; median: €7669; sem: €1108). In both trials combined and separately, the cost of primary care, informal care, unpaid productivity losses, absenteeism, and presenteeism was, on average, lower in the intervention group compared with the control group, whereas the cost of secondary care was, on average, higher. Total healthcare costs were, on average, higher in the intervention group compared with the control group. Notably, the total healthcare cost difference was largest in the MSOA trial, whereas the total societal cost difference was largest in the RA trial (Table 3). These differences are crude (i.e. not adjusted for baseline values or type of arthritic disease) and, except for certain differences in informal care, unpaid productivity, and presenteeism costs, were not statistically significant.

Cost-effectiveness

In both trials combined, the ICER for QALYs was −91 562, indicating that the Plants for Joints intervention was, on average, €91 562 cheaper compared with usual care per QALY gained. The cost-effectiveness plane in Figure 1(A) shows that the Plants for Joints

Table 2. Specification of the cost of the 16 week Plants for Joints intervention.

	Cost per participant (€)
Cooking class	94.63
Intake (individual consultation with registered dietitian)	96.88
Follow-up consultation with registered dietitian or physiotherapist	58.13
10 group meetings of 3 h + 1 h preparation and location	332.14
Closing evaluation with registered dietitian	96.88
Coordination by registered dietitian	77.50
Materials (binder with information, weekly menus, recipes)	25.00
Content development and videos	75.00
Short consultation with medical doctor	30.00
Total	886.14

Table 3. Mean costs in the intervention and control groups, and corresponding crude cost differences.

Cost category	Total costs (€)			MSOA trial costs (€)			RA trial costs (€)		
	Intervention group (n = 72)	Control group (n = 69)	Cost difference	Intervention group (n = 32)	Control group (n = 32)	Cost difference	Intervention group (n = 40)	Control group (n = 37)	Cost difference
Intervention costs	886 (0)	0 (0)	886 (0)	886 (0)	886 (0)	0	886 (0)	0 (0)	886 (0)
Primary care costs	435 (66)	516 (72)	−81 (−293 to 131)	570 (113)	678 (130)	−109 (−3082 to 244)	328 (73)	376 (69)	−48 (−284 to 187)
Secondary care costs	1078 (350)	496 (160)	582 (−284 to 1448)	1637 (711)	674 (325)	963 (−653 to 2579)	630 (236)	341 (90)	289 (−525 to 1103)
Informal care costs	407 (136)	1873 (225)	−1466 (−2282 to −640)	466 (253)	1807 (498)	−1341 (−2478 to −204)	360 (139)	1930 (467)	−1570 (−2773 to −367)
Unpaid productivity costs	1043 (245)	2231 (398)	−1188 (−2262 to −113)	1580 (471)	1791 (526)	−211 (−1762 to 1339)	614 (212)	2611 (584)	−1997 (−3418 to −576)
Absenteeism costs	1121 (420)	1555 (543)	−434 (−1838 to 970)	743 (598)	808 (429)	−65 (−1577 to 1447)	1424 (585)	2201 (934)	−777 (−3012 to 1458)
Presenteeism costs	2156 (325)	3547 (441)	−1391 (−2666 to −117)	1592 (397)	2144 (440)	−552 (−1847 to 742)	2607 (483)	4761 (670)	−2154 (−4085 to −223)
Total healthcare costs	2399 (368)	1012 (187)	1387 (−445 to 2330)	3093 (743)	1352 (364)	1740 (24 to 3457)	1844 (255)	717 (132)	1127 (232 to 2021)
Total societal costs	7126 (928)	10 218 (1108)	−3092 (−6335 to 151)	7473 (1437)	7903 (1278)	−430 (−4453 to 3593)	6849 (1225)	12 220 (1689)	−5372 (−10 121 to −623)

MSOA, metabolic syndrome-associated osteoarthritis; RA, rheumatoid arthritis. Data are shown as mean (SEM) for costs per group and mean (95% CI) for cost differences between groups.

intervention dominates usual care by being, on average, less costly and more effective. The CEAC in Figure 1 (B) shows that at the lower bound of the Dutch WTP threshold for QALYs (i.e. €20 000/QALY), the Plants for Joints intervention had a 0.736 probability of being cost-effective compared with usual care. This probability increased to 0.842 at the upper bound of the Dutch WTP threshold (€80 000/QALY) (Table 4).

Sensitivity analyses

The sensitivity analyses revealed some differences compared with the main analysis. When the analyses were not adjusted for baseline and type of arthritic disease, the results were more favourable, showing higher probabilities of the Plants for Joints intervention being cost-effective compared with usual care. From the healthcare perspective, the intervention was, on average, more costly and more effective than usual care. Consequently, it no longer dominated usual care and was associated with substantially lower probabilities of cost-effectiveness. When using CART imputation or complete-cases only, cost reductions and QALY improvements were slightly smaller, resulting in slightly lower probabilities of cost-effectiveness. Stratified analyses indicated that the probability of the Plants for Joints intervention being cost-effective compared with usual care was higher in RA patients than in MSOA patients. However, when outliers were excluded (n = 6, RA = 3, MSOA = 3), this difference in probability of cost-effectiveness was much less pronounced. For waist circumference and LDL-C levels, the Plants for Joints intervention also dominated usual care, meaning that it was, on average, less costly and more effective, and associated with moderate to high probabilities of being cost-effective as well.

Discussion

Main findings and interpretation of the findings

The findings of this study suggest that the Plants for Joints intervention dominated usual care from the societal perspective, being, on average, both less costly and more effective. In contrast, from the healthcare perspective, the intervention was, on average, more costly while still more effective. However, it is important to emphasize that the differences in societal costs and QALYs were not statistically significant, and the observed QALY gain (0.009) was well below commonly accepted thresholds for a minimally clinically important difference (e.g. 0.074) (36), and therefore not considered clinically meaningful.

Despite the small QALY gain, the intervention demonstrated a relatively substantial average cost saving of €866 from the societal perspective, which

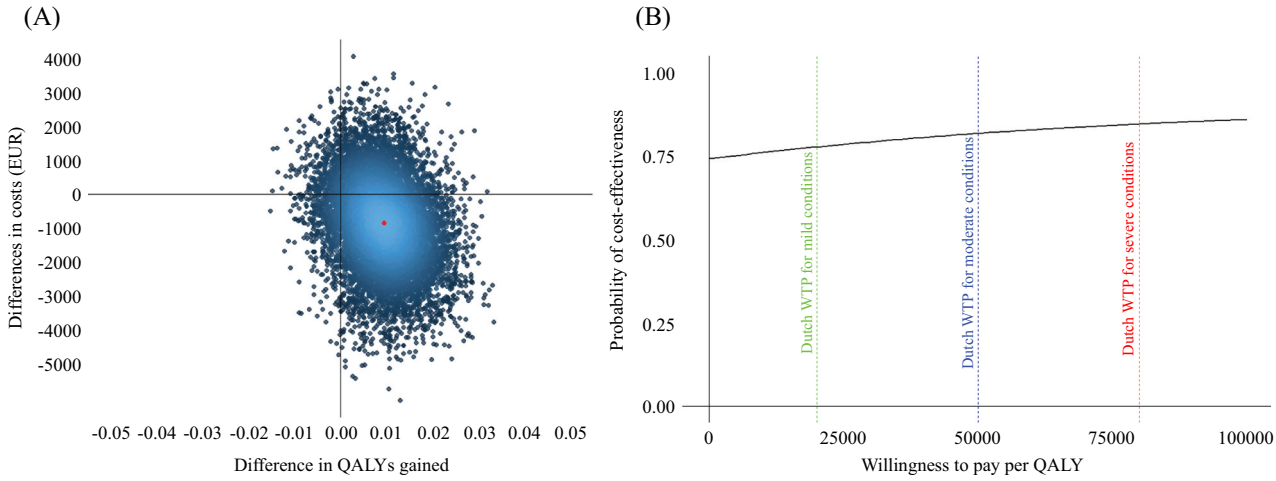

Figure 1. (A) Cost-effectiveness plane and (B) cost-effectiveness acceptability curve of the main analysis. WTP, willingness to pay; QALY, quality-adjusted life-year.

contributed to a high probability of cost-effectiveness over the 16 week study period, but this was not the case from a healthcare perspective. Specifically, at the Dutch WTP threshold for conditions with a moderate disease burden, such as arthritic diseases (i.e. €50 000 per QALY), the probability of cost-effectiveness was 0.813 from the societal perspective, compared with only 0.047 from the healthcare perspective.

Stratified cost-effectiveness analyses indicated a higher probability of cost-effectiveness for RA patients compared with MSOA patients. Although this difference became somewhat less pronounced after excluding outliers, it is notable that it was partly driven by substantially lower unpaid productivity costs in the RA intervention group relative to the control group. These reduced costs may reflect genuine improvements in functional ability, consistent with previously observed clinical effects (16, 23). However, given the relatively small sample sizes of the individual trials, this finding should be interpreted with caution and warrants further investigation.

The finding that the Plants for Joints intervention had a moderate to high probability of cost-effectiveness from the societal perspective is consistent with previous clinical results (16, 23), which demonstrated clinically meaningful improvements in disease activity in individuals with RA, as well as reductions in pain and stiffness, and improvements in physical function in those with MSOA. In line with these clinical outcomes, the intervention was also found to be, on average, less costly and more effective, with moderate to high probabilities of cost-effectiveness, for waist circumference and LDL-C.

While the intervention demonstrated promising economic value, it remains unclear which specific component(s) contributed most to this outcome (i.e. dietary, physical activity, psychological, peer support, and/or supplementation). Although adherence data indicated that the most substantial behavioural change occurred in the dietary domain and a mediation analysis suggested that the effects were not explained by weight reduction (16, 23, 37), the potential contributions of the other components cannot be ruled out.

The relatively short follow-up duration of the study (16 weeks) may not capture the long-term effects and cost-effectiveness of the Plants for Joints intervention. Although longer-term cost and utility data were available from the 2 year extension study, they could not be used to assess long-term cost-effectiveness because of the lack of a control group. These data do suggest, however, that the effects may persist beyond the 16 week study period. For example, a net reduction in medication use was observed 1 year after completion of the programme, with 50% of participants with RA reducing or discontinuing DMARDs by an average of 62% (24, 36, 37). In addition, a post-hoc analysis showed that EQ-5D-5L utility values in the intervention group remained consistently above baseline throughout the 2 year follow-up (e.g. T0: 0.683; T8: 0.754).

Taken together, if the added benefits of the Plants for Joints intervention over usual care are sustained in the long term, as suggested by the 2 year extension study data, it could offer a sustainable and cost-effective solution for managing arthritic diseases from a societal perspective.

Comparison with the literature

To the best of our knowledge, this is the first economic evaluation comparing a multidisciplinary lifestyle intervention consisting of a plant-based diet, physical activity, and sleep and stress management, with usual care in patients with RA or MSOA. Nonetheless, several previous studies have evaluated the cost-effectiveness of other lifestyle interventions compared

Table 4. Cost-effectiveness results.

	ΔC (€) (95% CI)	ΔE (95% CI)	ICER (ΔC/ΔE)	P(CE) Dutch WTP for mild conditions €20 000/QALY	P(CE) Dutch WTP for moderate conditions €50 000/QALY	P(CE) Dutch WTP for severe conditions €80 000/QALY
Main analysis	−866 (−3553 to 1820)	0.009 (−0.004 to 0.023)	−91 562	0.736	0.813	0.842
Sensitivity analyses						
Uncorrected analysis	−3092 (−6335 to 151)	0.025 (0.002 to 0.049)	−120 699	0.969	0.988	0.991
Healthcare perspective	1400 (443 to 2358)	0.009 (−0.004 to 0.023)	151 596	0.002	0.047	0.169
Classification and regression tree imputation	−498 (−2711 to 1716)	0.007 (−0.004 to 0.018)	−69 973	0.670	0.761	0.798
Complete-case analysis (n = 88)	−179 (−3122 to 2365)	0.008 (−0.004 to 0.018)	−23 622	0.595	0.654	0.715
RA trial	−2424 (−6214 to 1366)	0.005 (−0.016 to 0.026)	−506 567	0.895	0.886	0.877
MSOA trial	975 (−2117 to 4068)	0.015 (0.000 to 0.029)	66 769	0.268	0.438	0.548
Main analysis excluding outliers	−1543 (−4046 to 959)	0.009 (−0.005 to 0.023)	−175 013	0.901	0.916	0.924
RA trial excluding outliers	−2718 (−6399 to 964)	0.006 (−0.006 to 0.027)	−425 526	0.926	0.923	0.918
MSOA trial excluding outliers	−299 (−2882 to 2284)	0.011 (−0.003 to 0.025)	−27 278	0.651	0.729	0.788
				P(CE) 0/cm reduction	P(CE) 250/cm reduction	P(CE) 500/cm reduction
Waist circumference	−881 (−3530 to 1767)	−4.3 (−6.5 to −2.1)	206	0.74	0.92	0.98
				P(CE) 0/person with healthy LDL	P(CE) 5000/person with healthy LDL	P(CE) 10 000/person with healthy LDL
LDL dichotomous	−881 (−3526 to 1764)	0.17 (−0.03 to 0.31)	−5 268	0.74	0.89	0.95

MSOA, metabolic syndrome-associated osteoarthritis; RA, rheumatoid arthritis; ΔC, difference in total costs; ΔE, difference in effects; CI, confidence interval; ICER, incremental cost-effectiveness ratio; P(CE), probability of being cost-effective; WTP, willingness to pay; QALY, quality-adjusted life-year; LDL, low-density lipoprotein.

with usual care in osteoarthritis patients (38–40). For instance, in a systematic review of 23 studies, Mazzei et al found that exercise interventions, with or without educational and/or dietary components, were cost-effective or cost-saving compared with physician-delivered usual care or education at conventional WTP thresholds across various health systems (39). A more recent study by Kopp et al confirmed these findings by demonstrating that a community-based diet and nutrition programme for patients with knee osteoarthritis and obesity could be cost-effective when WTP thresholds exceed $62 000/QALY (38). It is important to note, however, that the study by Kopp et al was conducted in Canada, had an extensively longer follow-up duration than the current study (lifetime), did not include costs related to informal care, presenteeism, and unpaid productivity, and relied on a mathematical model, rather than empirical data (25, 38). Knoop et al, on the other hand, did not find evidence that stratified exercise therapy, supplemented by a dietary intervention for patients with obesity, was cost-effective compared with usual exercise therapy in patients with knee osteoarthritis (40). However, the dietary guidance in their study was less intensive than in the current study and was primarily focused on weight loss. The study by Knoop et al included the same cost categories as the current study and was also conducted in the Netherlands, but had a longer follow-up duration (12 months vs 16 weeks) (40). Even though various studies suggest that RA patients may also benefit from lifestyle interventions (41–43), very few studies have assessed the cost-effectiveness of such interventions. Sørensen et al, however, found an individually tailored lifestyle intervention consisting of motivational counselling and text messages to have a high probability of being cost-effective in RA patients compared with usual care at a WTP of €30 000/QALY (44). Their study, however, was conducted in Denmark, had a longer follow-up duration than the current study (22 months), and was only conducted from the healthcare perspective.

Strengths and limitations

This study is the first economic evaluation to compare a plant-based diet intervention with usual care in patients with RA or MSOA. It was conducted alongside an RCT and used state-of-the-art statistical methods (25, 35). Moreover, our study followed an estimation-based approach, meaning that we focused on mean differences and the probability of cost-effectiveness, rather than testing a particular hypothesis. While some scholars advocate for incorporating hypothesis testing in economic evaluations (46), the estimation approach allows for decision making under uncertainty and reflects the probabilistic nature of healthcare choices (47).

However, this study also has its limitations. First, 53 patients (38%) had one or more missing cost and/or EQ-5D-5L value at one or more measurement point. Although missing data are inevitable in trial-based economic evaluations (46, 47), the proportion of missing data was comparable to that of similar studies (40), and multiple imputation was applied to address this. Still, having a complete or more complete dataset is always preferable. Secondly, the 16 week follow-up period of the study may have been insufficient to capture the long-term effects and cost-effectiveness of the Plants for Joints intervention. Although cost and utility data were collected in a 2 year extension study, the absence of a control group in that phase precluded a formal assessment of long-term cost-effectiveness. To address this gap, an RCT with extended follow-up or a model-based economic evaluation is warranted (45). Thirdly, as with nearly every clinical trial, our study was powered based on the primary clinical effect outcome rather than cost-effectiveness outcomes, such as costs. This approach is common practice in health economics, because costs are heavily right-skewed and would therefore require extremely large sample sizes, which may be infeasible and/or unethical. To address this issue, we used estimation methods (e.g. reporting the probability of cost-effectiveness) rather than hypothesis testing to interpret our outcomes (46, 47). Fourthly, the current study was conducted in the Netherlands, and hence the results may not be generalizable to other countries with different healthcare systems and cost structures. Future research should consider conducting similar studies in diverse settings to enhance the external validity of the findings. Fifthly, this study was conducted during the coronavirus disease 2019 (COVID-19) pandemic, which necessitated adaptations to the original intervention delivery format. Specifically, group sessions that were initially intended to be held in person were moved online during periods of strict public health measures, and later transitioned to a hybrid format. Although previous research suggests that these different formats yielded comparable outcomes (37), the change in delivery may have influenced participant engagement and experience, and could potentially limit the generalizability of the findings to non-pandemic settings.

Conclusion

The Plants for Joints intervention demonstrated a moderate to high probability of being cost-effective over 16 weeks from a societal perspective, but not from a healthcare perspective. The probability of cost-effectiveness was greater for RA patients than for MSOA patients, although this difference diminished after excluding outliers. If the benefits persist in the long term, the intervention could sustainably reduce the disease and economic burden of arthritic diseases.

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Statement of informed consent

All participants provided written informed consent.

Disclosure statement

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Appendix A

Table A1. Baseline characteristics: rheumatoid arthritis trial.

Characteristic	Intervention group (n = 40)	Control group (n = 37)
Age (years)	56.4 ± 13.4	52.8 ± 10.3
Female sex	36 (90)	35 (95)
RF positive	20 (50)	29 (78)
ACPA positive	24 (60)	26 (70)
Seropositive	26 (65)	31 (84)
Disease duration (years)	10 ± 9	8 ± 8
BMI (kg/m^2)	27.1 ± 4.6	25.1 ± 3.7
DAS28	3.90 ± 0.7	3.78 ± 0.7
Erosive disease	23 (58)	15 (43)
Medication for RA		
Methotrexate monotherapy	12 (30)	4 (11)
Methotrexate combination therapy	10 (25)	6 (16)
Other csDMARD monotherapy	4 (10)	2 (5)
Other csDMARD combination therapy	4 (10)	0 (0)
bDMARD	4 (10)	6 (16)
tsDMARD	0 (0)	4 (11)
No medication	6 (15)	15 (41)
Previous medication for RA		
csDMARD treatment count	1 (0–4)	0 (0–4)
bDMARD treatment count	0 (0–4)	0 (0–5)
tsDMARD treatment count	0 (0–0)	0 (0–1)
Glucocorticoids	9 (23)	9 (24)
Only csDMARD treatment	10 (25)	8 (22)
1 bDMARD treatment	6 (15)	2 (5)
≥2 bDMARD treatments	4 (10)	4 (11)
No prior treatment	5 (13)	13 (35)
Medication for diabetes	2 (5)	1 (3)
Medication for hypertension	6 (15)	3 (8)
Medication for hyperlipidaemia	4 (10)	3 (8)

Data are shown as mean ± sd, n (%), or median (range).
RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; Seropositive, positive for RF or ACPA; BMI, body mass index; DAS28, 28-joint Disease Activity Score; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; bDMARD, biological disease-modifying anti-rheumatic drug; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug. Previous medication for DMARD treatment refers to the median number of DMARDs used before baseline medication.

Table A2. Baseline characteristics: metabolic syndrome-associated osteoarthritis trial.

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

Data are shown as mean ± sd or n (%).
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
For all WOMAC scores, lower scores are favourable.

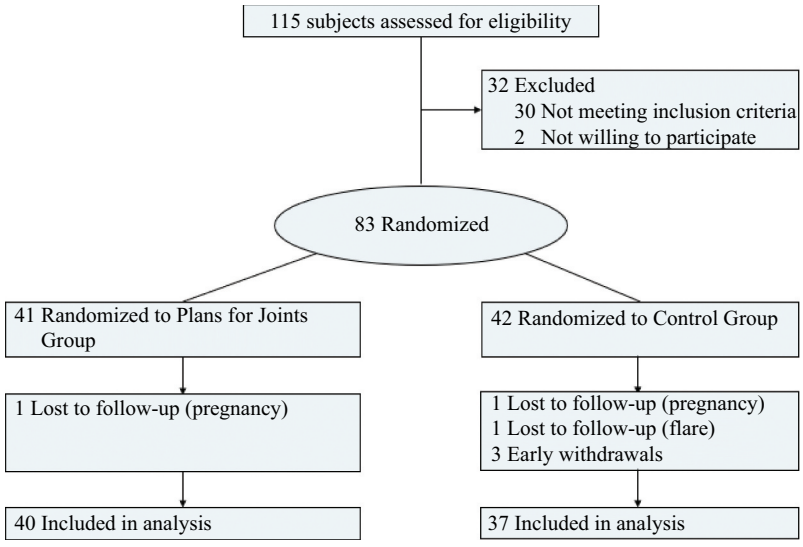

Figure A1. Flowchart of the rheumatoid arthritis trial.

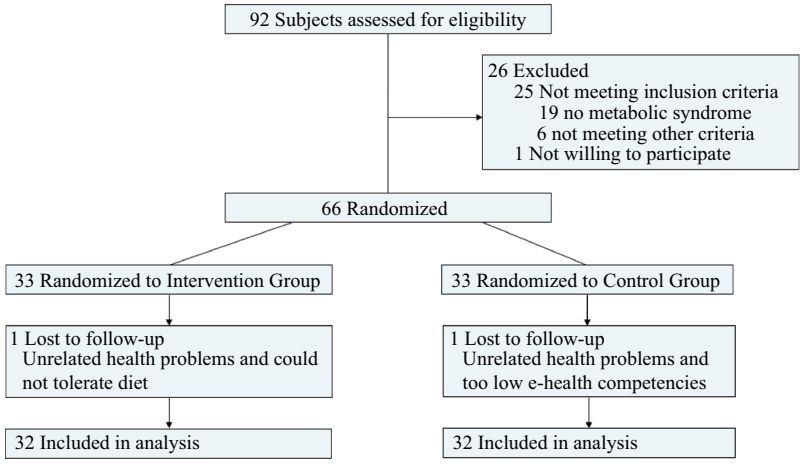

Figure A2. Flow-chart of the metabolic syndrome-associated osteoarthritis trial.