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Inflammatory cytokines mediate the effects of diet and exercise on pain and function in knee osteoarthritis independent of BMI

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SUMMARY

Objective: Diet restriction and exercise form key treatments for osteoarthritis (OA) related symptoms in overweight and obese individuals. Although both interventions are known to influence systemic low-grade inflammation, which is related to pain levels and functional limitations, little is known about the potential changes in systemic inflammation as a working mechanism of diet restriction and exercise in knee OA.

Design: Data from the Arthritis, Diet, and Activity Promotion Trial (ADAPT) were used. Through causal mediation analyses, the proportion of the effect of a 18 months diet and exercise intervention explained by the 18 months change in interleukin (IL)-6, TNF-α, soluble IL-6 receptor, soluble IL-1 receptor, CRP, and BMI were assessed, using self-reported pain and function as outcomes.

Results: The change in inflammatory factors accounted for 15% of the total effect on pain and was totally independent of the change in BMI. The change in inflammatory factors accounted for 29% of the effect on function, with the change in BMI adding only 4% to the total mediated effect.

Conclusions: The change in inflammatory factors after the diet and exercise intervention was a 'medium' size mediator of the effect on pain and a 'strong' mediator for the effect on function in overweight and obese individuals with knee OA. The change in BMI added minimally to the mediated effect on function. These results highlight the relevance of changes in systemic inflammation as drivers for clinically relevant effects after diet and exercise in overweight and obese individuals with knee OA.

Introduction

In overweight and obese individuals with knee osteoarthritis (OA), the effects of combined diet restriction and exercise exceed the effects of either treatment alone.[1–3] A recent meta-analysis showed no significant effects of diet restriction only interventions on pain relief, but moderate effects of diet restriction plus exercise interventions.[1] Both diet restriction and diet restriction plus exercise showed moderate effects on improvements in function.[1] Although diet restriction and exercise are advocated in many international guidelines for the primary treatment of osteoarthritis (OA) related pain and disability of the knee in overweight and obese patients, the effects on improvements in pain and function are only modest.[1,4] For exercise therapy, part of this low effectiveness is attributed to the lack of understanding of its mechanisms of action. A systematic review on potential working mechanisms of exercise therapy for knee and hip

OA revealed that only six out of the potential 94 studies actually evaluated the association between a mediating factor and the improvements in pain/function.[5] Unfortunately, all six studies used unadjusted simple correlations instead of proper mediation analyses to evaluate the mediating effects.[5] Knowing the working mechanisms of exercise therapy for OA patients could help in

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designing more effective protocols that optimally trigger the mechanisms of action, resulting in larger effects on pain and function.

In recent years, the role of systemic low-grade inflammation in the pathogenesis of OA has been acknowledged.[6–8] In OA patients, higher systemic concentrations of pro-inflammatory cytokines are associated with more pain and worse function.[9] Since exercise and weight loss therapies are known to reduce systemic concentrations of pro-inflammatory cytokines, the anti-inflammatory effects of these interventions are suggested as a potential working mechanism.[10–12] Unfortunately, only a few studies evaluating a diet restriction and exercise interventions among OA patients have monitored the effects on serum cytokine concentrations.[1,5] Those studies doing so never evaluated the mediating effects of changes in cytokine concentrations on patient reported outcomes after the intervention.

Therefore, the objective of the current study was to evaluate the mediating effect of the change in serum cytokine concentrations on the change in pain and function, using data from the Arthritis, Diet, and Activity Promotion Trial (ADAPT)[2] and cutting edge Causal Mediation Analyses[13,14] to study the potential of cytokine modulation as a working mechanism of diet restriction and exercise for overweight and obese knee OA patients.

Methods

The current study used data from the Arthritis, Diet, ADAPT, which was described in detail before.[2] In short, in this trial subjects willing to undergo testing and intervention procedures were included, using the following criteria: age ≥60 years, BMI ≥28 kg/m^2, knee pain on most days of the month, a sedentary activity pattern, and radiographic evidence of OA (KL grade 1–3) based on weight-bearing radiographs. Eligible subjects were randomized to either; an exercise group (E) that received exercise therapy 3 times per week, a diet group (D) that received a dietary intervention aimed to achieve and maintain a 5% body weight reduction, a diet and exercise group (D+E) that received both the diet and the exercise therapy, or a healthy lifestyle group that served as usual care control group (C) that received an education module on OA and healthy living. All interventions were 18 months in duration. All participants gave informed consent prior to baseline testing and all procedures of ADAPT were in accordance with the Helsinki Declaration.

Patient selection

Since ADAPT showed significant effects on pain and function only in D+E, compared to the healthy lifestyle group, and only after 18 months of follow-up,[2] the current study only evaluated the mediating effects of the intervention within D+E, compared to group C, after 18 months. For the analyses, subjects with baseline and 18 months cytokine and outcome data (see below) available were selected.

Demographics

At baseline, age, gender, race (white/non-white), current smoking status (yes/no), and alcohol consumption ('never' vs '<1 serving/months' or more) were determined. At baseline and after 18 months the BMI was determined using measured body weight and height (without shoes).

Outcome measures

At baseline and after 18 months, all participants completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire.[15] Outcome measures of interest were the change from baseline to 18 months for the pain and function subscales.

Inflammatory cytokines

A fasted serum sample was collected via venipuncture at baseline and after 18 months. Fasting serum concentrations of interleukin (IL)-6, tumor necrosis factor (TNF)-α, soluble IL-6 receptor (IL-6sR), soluble IL-1 receptor (IL-1sR), and C-reactive protein (CRP) were measured by enzyme-linked immunosorbent assays. All samples were measured in duplicate, and the average of the two values was used for data analyses. Duplicate samples that did not provide a CV <15% were reanalyzed, and all values were averaged for data analyses.[12] Inter- and intraassay CVs for IL-6 were 7.3% and 3.5%, respectively; those for TNF-αwere 11.8% and 6.2%%, respectively; and those for the soluble receptor assays were <5%. The inter- and intraassay CVs for the CRP assay were 8% and 6.7%, respectively.[12] Changes in inflammatory cytokines (delta) were calculated by subtracting the baseline values from the 18 months values. Selection of inflammatory cytokines was based on their involvement in knee OA, the association to weight loss and their systemic release after exercise.[8–12,16]

Statistical analyses

Baseline demographics were calculated (presented as means ± standard deviation or percentages) and tested for significant differences between groups to compare the randomized groups after removal of participants without follow-up data. Also, baseline characteristics were compared between participants with and without follow-up data to assess selective dropout. First, the individual effect of each of the five inflammatory factors was determined, using the Causal Mediation Analysis in a model containing only one single mediator (Fig. 1A).[13,14,17] For this a series of linear regression analyses were run to determine the regression coefficient for the exposure-mediator relation (α), where the group assignment was used as independent variable (D+E vs C) and the change in inflammatory factor over 18 months as the mediator. In the next series of linear regression analyses, the regression coefficient for the exposure-outcome (β) and the regression coefficient for mediator-outcome (γ) relations were determined by adding the exposure and mediator to the same model. All analyses used the change in WOMAC pain and in WOMAC function over the 18 month intervention period as outcome measures. Finally, for each inflammatory factor the percentage mediated was calculated by dividing the indirect effect through the mediator (α times γ) over the total effect, which is the sum of the indirect and direct effect (β).[13,17] Since group assignment was randomized, its associations with the mediator and with the outcome were unbiased. The association between the mediator and the outcome is non-randomized and hence is subjective to confounding. To allow for causal interpretation of the estimates, all analyses were adjusted for potential mediator-outcome confounders (baseline BMI, gender, age, race, smoking status and alcohol consumption).[14] Ideally also muscle strength was used as confounder, but due to a high percentage of missing values, this was omitted.

For those inflammatory factors showing a percentage mediated > 0%, a multi-mediator model (Fig. 1B) was composed. The α for each inflammatory factor was taken from the single-mediator models described above. The β^+ (now adjusted for multiple

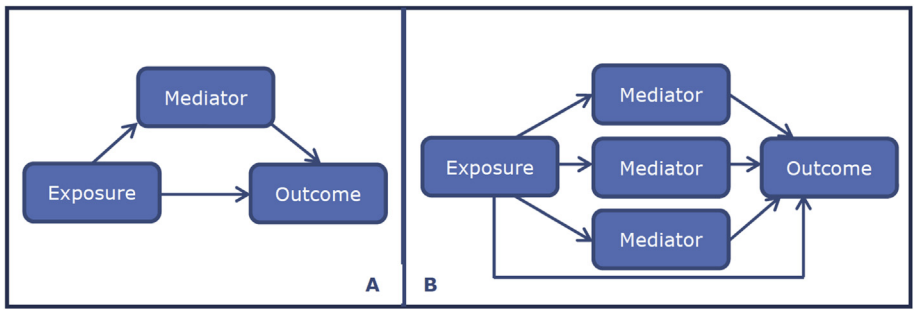

Fig. 1. Mediator analyses models for a single (panel A) and multiple (panel B) mediators.

mediators) and the γ^+ for each inflammatory factor were obtained by constructing a new regression analysis containing the independent variable and all selected mediators. Again, all analyses used the change in WOMAC pain and in WOMAC function as outcome measures and all analyses were adjusted for baseline BMI, gender, age, race, smoking status and alcohol consumption. Percentage mediated by the selected mediators was calculated by summing the indirect effects (α times γ^+) of all selected mediators and divide it by the sum of all indirect effects and the direct effect (β^+).Since the intervention studied (D+E) included both an exercise and a dietary intervention and changes in body weight are known to effect both inflammatory cytokine concentrations and self-reported measures of pain and function, in the final step the 18 month change in BMI was added as a mediator to the multi-mediator models. This enabled the evaluation of the percentage of change in pain and function mediated by the change in BMI in addition to the change in the selected inflammatory cytokines.

Results

Baseline characteristics are given in Table I. There were no statistical significant differences in baseline characteristics between those subjects excluded and those included in the present analyses ($P \geq 0.1$) nor between the randomized groups among the subjects included in the present analyses ($P \geq 0.1$). On average, subjects were 68.5 ± 6.2 years old and had a BMI of 33.5 ± 4.7 kg/m^2. Over 18 months, mean change in WOMAC pain was −0.78 ± 3.5 for C and −2.68 ± 3.2 for D+E and mean change in WOMAC function was −2.22 ± 9.7 for C and −6.75 ± 11.5 for D+E.

Table I
Baseline characteristics

	Control group (N = 55)	Diet + exercise group (N = 44)
BMI (kg/m^2)	34.0 ± 4.9	32.9 ± 4.4
Age (yr)	68.9 ± 5.9	67.9 ± 6.7
Gender (%F)	62%	80%
Race (%white)	80%	75%
Smoking (%yes)	4%	5%
Alcohol consumption (yes)*	66%	71%
WOMAC pain (0–20)	6.6 ± 3.6	7.3 ± 3.1
WOMAC function (0–68)	24.3 ± 11.9	23.3 ± 11.7
KL-grade†		
- grade 1	11%	16%
- grade 2	18%	18%
- grade 3	55%	50%
- grade 4	5%	9%
[IL-6] (pg/mL)	4.84 ± 3.1	4.59 ± 2.8
[TNF-α] (pg/mL)	4.29 ± 8.7	4.26 ± 8.0
[IL-1sR] (pg/mL)	13,192 ± 4,153	13,370 ± 4,497
[IL-6sR] (pg/mL)	36,853 ± 10,725	37,344 ± 12,176
[CRP] (mg/L)	0.61 ± 0.66	0.71 ± 0.81

* Alcohol consumption: never vs '<1 serving/months' or more.
† Numbers do not add up to 100% due to missing radiographs. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. KL: Kelgren & Lawrence. IL: interleukin. TNF: Tumor Necrosis Factor. CRP: C-reactive protein.

Mediating effects of single factors

The regression coefficients (α) and the 95% confidence intervals (CI) for D+E over C were −0.165 (95% CI -0.503 to 0.174) for delta IL-6, -0.029 (95% CI -0.644 to 0.587) for delta TNF-α, −279.430 (95% CI -742.838 to 183.978) for delta IL-1sR, −43.150 (95% CI -650.830 to 564.529) for delta IL-6sR, and −0.184 (95% CI -0.396 to 0.029) for delta CRP. The regression coefficients and the 95% CI for D+E over C (β) and each of the mediators (γ) on the change in WOMAC pain and in WOMAC function are noted in Table II. Since for every mediator a single regression analysis was done, containing the exposure, mediator and confounders, Table II presents five different regression coefficients for the D+E.

For the models containing delta IL-6sR, the indirect and direct effect had opposite directions. Hence, no percentage mediated could be calculated. For change in WOMAC pain and in WOMAC function, percentage mediated through delta IL-6 was 5% and 8%, through TNF-α 0% and 1%, through delta IL-1sR 2% and 6%, and through delta CRP 8% and 10%, respectively.

Mediating effects of multiple factors

Given the results presented above, delta IL-6, delta TNF-α, delta IL-1sr and delta CRP were selected for the multi-mediator model. Table III presents the regression coefficients for D+E, each of the selected mediators and the confounders on the change in WOMAC pain and in WOMAC function. Since only one regression analysis

Table II
Regression coefficients (95% confidence intervals) for the exposure-outcome and the mediator-outcome relations in the single mediator models

	Delta WOMAC pain	Delta WOMAC function
Exposure	−0.705 (−1.178 to −0.232)	−1.499 (−2.996 to −0.003)
Delta IL-6	0.223 (−0.069 to 0.514)	0.818 (−0.102 to 1.739)
Exposure	−0.739 (−1.211 to −0.266)	−1.620 (−3.107 to −0.133)
Delta TNF-α	0.102 (−0.058 to 0.263)	0.467 (−0.039 to 0.973)
Exposure	−0.724 (−1.204 to −0.244)	−1.532 (−3.050 to −0.015)
Delta IL-1sR	$6.338\ 10^{-5}$ ($-15.2\ 10^{-5}$ to $27.9\ 10^{-5}$)	$36.3\ 10^{-5}$ ($-31.7\ 10^{-5}$ to 0.001)
Exposure	−0.747 (−1.218 to −0.276)	−1.650 (−3.148 to −0.151)
Delta IL-6sR	$-12.5\ 10^{-5}$ ($-28.7\ 10^{-5}$ to $3.8\ 10^{-5}$)	$-36.1\ 10^{-5}$ (-0.001 to $15.5\ 10^{-5}$)
Exposure	−0.683 (−1.162 to −0.203)	−1.472 (−3.000 to 0.055)
Delta CRP	0.322 (−0.143 to 0.787)	0.880 (−0.6000 to 2.360)

Exposure: D+E compared to C. All analyses were adjusted baseline BMI, gender, age, race, smoking status and alcohol consumption.

Table III
Regression coefficients (95% confidence intervals) for the exposure-outcome and the mediator-outcome relations and the confounders in the multi-mediator model

	Delta WOMAC pain	Delta WOMAC function
Exposure	−0.632 (−1.117 to −0.147)	−1.235 (−2.742 to 0.272)
Delta IL-6	0.192 (−0.123 to 0.506)	0.801 (−0.177 to 1.778)
Delta TNF-α	0.098 (−0.064 to 0.260)	0.472 (−0.033 to 0.977)
Delta IL-1sR	12.3 10^{-5} (-9.7 10^{-5} to 34.2 10^{-5})	0.001 (-8.86 10^{-5} to 0.001)
Delta CRP	0.223 (−0.272 to 0.718)	0.474 (−1.066 to 2.014)
Confounders		
BMI	−0.029 (−0.185 to 0.126)	0.027 (−0.456 to 0.510)
Gender*	−0.208 (−1.824 to 1.407)	−0.972 (−5.996 to 4.052)
Age	−0.146 (−0.265 to −0.027)	−0.172 (−0.542 to 0.199)
Race	0.652 (−1.133 to 2.437)	−2.248 (−7.799 to 3.303)
Smoking status†	−1.537 (−5.045 to 1.971)	1.734 (−9.176 to 12.644)
Alcohol consumption‡	−0.379 (−1.896 to 1.138)	1.850 (−2.869 to 6.568)

Exposure: D+E compared to C.
* Male vs female.
† Current smoker vs non-current smoker.
‡ Never vs '<1 serving/months' or more.

was done containing the exposure with all selected mediators and the confounders, Table III only presents one regression coefficient for D+E.

For these models, the percentage mediated was 15% for the change in WOMAC pain and 29% for the WOMAC function scores.

Change in BMI as potential additional mediator

After 18 month, the change in BMI was −0.74 ± 1.7 kg/m^2 for C and −1.41 ± 2.3 kg/m^2 for D+E. The regression coefficient of D+E over C on delta BMI was −0.248 (95% CI -0.528 to 0.032) and the regression coefficients for delta BMI on change in WOMAC pain and WOMAC function were −0.005 (95% CI -0.365 to 0.355) and 0.295 (95% CI -0.822 to 1.412), respectively. The regression coefficients of D+E and of the other mediators in the model were changed only marginally by introducing the change in BMI as mediator to the model (data presented in Appendix). The percentage mediated by the combination of mediators was 15% for the change in WOMAC pain and 34% for the WOMAC function scores. Within this model, the indirect effect through the mediator delta BMI was only 0% and 4% for the change in WOMAC pain and function, respectively.

Discussion

The current study found that the significant improvement in pain and function after a diet and exercise intervention among overweight and obese individuals with knee OA is partly mediated by changes in a combination of inflammatory factors IL-6, TNF-α, IL-1sR and CRP. Moreover, the multi-mediator model that also included the 18 months change in BMI as a mediator showed that the mediating effects of the inflammatory factors are only minimally explained by BMI changes.

The combination of changes in IL-6, TNF-α, IL-1sR and CRP over the intervention period explained 15% of the change in WOMAC pain scores and 29% of the change in WOMAC function scores. These numbers are within the range for a 'medium mediator' (≥13%) to a 'strong mediator' (≥26%).[18] This suggests that interventions that can significantly lower the concentrations of these inflammatory factors have the potential for a significant impact on the reported pain and function for knee OA patients. The higher percentage mediated for WOMAC pain over WOMAC function scores suggests that the effects of D+E on pain were mediated through other factors to a larger extend. As mediation analyses on treatment effects after D+E in knee OA patients are scarce, there is little known about the reasons for these differences on pain and function or in general what drives the effects of D+E on patient reported knee OA symptoms. Next to the proposed mediating effects of the change in inflammatory factors, other mediating factors like joint loading, muscle strength, psychological factors, and pain sensitivity have been suggested and could account for parts of the treatment effects.[1,5,19]

Previously, Lee *et al.*[20] reported significant reductions in IL-6, TNF-α and CRP concentrations after an 8 week exercise program among 19 older women. Interestingly, all factors were reduced in both the aerobic exercise group and the combined exercise group (aerobic + strengthening). Only the change in CRP was significantly different between groups, with a stronger reduction in the combined exercise group. Another small intervention study ($n = 43$) among knee OA participants reported no significant changes in IL-6 or TNF-α concentrations after a 6 week isokinetic exercise program or a 6 week aerobic exercise program.[21] Changes in CRP concentrations did tend to reduce similarly after both interventions ($P = 0.09$ and $P = 0.07$ respectively). Unfortunately, these very small studies are rare examples of studies evaluating changes in inflammatory factors after exercise therapy. The 2015 systematic review on potential working mechanisms of exercise therapy for OA patients identified only nine studies that measured a variety of inflammatory factors, of which only one (the Intensive Diet and Exercise for Arthritis trial) measured any of the factors reported here.[5] Not surprisingly, this study was the successor of the current trial that reported significant reductions in WOMAC pain and function after D+E compared to E or D alone, with concurrent stronger reductions in IL-6 concentrations in D+E compared to E, but not when compared to D.[3]

One of the best described anti-inflammatory effects of exercise is the release of IL-6.[16, 22, 23] In an interesting review, Petersen and Pedersen describe the IL-6 produced by contracting skeletal muscle fibers as the driver of the anti-inflammatory effect of exercise.[22] The concentration of circulating IL-6 increases in an exponential fashion (up to 100-fold) in response to exercise and stimulated the release of other anti-inflammatory factors, like IL-1ra and IL-10. Interestingly, the production of IL-6 depends on the type of muscle contraction (faster increase after concentric than after eccentric contractions),[23,24] the duration of the exercise (a longer duration leads to a higher IL-6 production),[23] the mass of activated muscles (greater mass leads to a higher IL-6 production),[22,24] and the intensity of the exercises (moderate exercise intensity have better results than low or high intensities).[22] Whether the IL-6 production after exercise is similar in OA patients is unknown. If so, an exercise protocol taking these parameters into account should lead to a higher IL-6 production, hence a stronger anti-inflammatory effect and potentially to greater effectiveness on patient-reported outcomes.[10] However, given the pleiotropic nature of IL-6 and the opposite effects to weight loss (reduced IL-6 production probably due to reduced TNF-α production by less fat mass[22]) and to exercise (enhanced due to the production by contracting muscles[22]), showing and interpreting the mediating effect of IL-6 after undergoing diet and exercise will be challenging.

The current analyses used Causal Mediation Analyses to determine the mediating effect of different inflammatory factors. For correctly applying this method and allowing causal interpretation, four assumptions are made.[13,14] Assumption one is that there is no unmeasured confounding of the exposure-outcome relation. Since the present study used randomized exposure groups, no confounding of the exposure-outcome relation is assumed. Assumption two is no unmeasured mediator-outcome confounding. Current analyses were adjusted for baseline BMI gender, age, race, smoking status and alcohol consumption. Although these

confounders will not cover all potential confounders for the relation between inflammatory factors and pain/function in OA patients, the majority of the known factors are taken into account. Assumption 3, no unmeasured exposure-mediator confounding, is also taken care of due to the randomization of the exposure. Assumption four is no effect of the exposure that confounds the mediator-outcome relation. This is the reason for controlling the regression analyses for baseline BMI and adding change in BMI over the intervention period (dependent of the exposure) to the set of mediators, as advised by literature,[13,14] in the multi-mediator models. Altogether, all assumptions for unbiased mediation analyses were met satisfactorily. This allows for causal interpretation of the results, which was not possible from previously presented anti-inflammatory effects of diet and exercise and the association to BMI using data from the same trial.[12] Current result warrant external validation for confirmation of the mediating effects of inflammatory factors after a diet restriction and exercise therapy intervention in overweight and obese individuals with knee OA.

The current study has some limitations. First, despite the large number of participants in the original ADAPT study, the present study only reports on 99 patients. Data from patients randomized to the diet and to the exercise groups were omitted, as no significant effect on pain and function were reported for these groups. Not much is known on required sample sizes for properly powered mediation analyses. Based on the empirical estimates, Fritz and MacKinnon indicated that a total sample of 90 participants would be required for 80% power with medium effect sizes (based on Cohen's criteria[18]) for the exposure-mediator and mediator-outcome relations.[25] Hence, with reported percentages mediated well above the indicated cut-offs for medium mediators in the multi-mediator models, the analyses seem to be powered properly. Second, the inflammatory factors analyzed for their mediating effects are not the only ones that have been reported to have an influence on pain/function in OA patients. Potentially, other inflammatory factors not measured in the current trial are also significant contributors to the effect of diet and exercise on pain and function in OA patients. Third, as indicated before, there is always the potential of unmeasured confounding of the mediator-outcome relation in mediation analyses. This could bias the presented mediator-outcome relations and therewith the presented strength of the proposed mediators. Nevertheless, since the analyses were adjusted for baseline BMI, gender, age, race, smoking status, and alcohol consumption and the final multi-mediator model even included the change in BMI, it seems most potential confounding is taken care of in the current analyses. Moreover, showing the mediating effects of objectively obtained measures strengthens the potential for a true working mechanism. Finally, the presented percentage mediated have to be seen within the modest difference in intervention effects between D+E and C; the absolute difference between D+E and C was 2.3 for WOMAC function (on a 0–68 scale) and 1.1 for WOMAC pain (on a 0–20 scale).[2] Moreover, as the 95% confidence interval for each mediator-outcome relation in the multi-mediator models included zero, there was potential overestimation of the percentage mediated.

Conclusions

In conclusion, the present analyses showed that the diet and exercise induced change in inflammatory factors is a 'medium' size mediator of the effect on pain in overweight and obese knee OA patients. The change in inflammatory factors accounted for 15% of the effect on pain and was totally independent of change in BMI. The change in inflammatory factors was a 'strong' mediator for the effect in function. The change in inflammatory factors accounted for 29% of the effect on function, with the change in BMI adding only 4% to the total mediated effect. Potentially, focusing diet restriction and exercise interventions on optimal reduction in inflammatory factors will enhance the effects of these interventions on patient reported pain and physical function.

Authors' contributions

JR contributed to the conception and design of the current study, data analyses, interpretation of the results, and drafting the manuscript. GDM, BN and RL contributed to the conception and design of the original trial, the interpretation of the current results, and critically revised the manuscript. SBZ contributed to the interpretation of the current results, and critically revised the manuscript. SM contributed to the conception and design of the original trial, the conception and design of the current study, the interpretation of the current results, and critically revised the manuscript. All authors approved the final version of the manuscript.

Competing interests

All authors declare no conflicts of interest.

Role of the funding source

N/A.

Appendix

Table

Regression coefficients (95% confidence intervals) for the exposure-outcome and the mediator-outcome relations and the confounders in the multi-mediator model including 18 months change in BMI

	Delta WOMAC pain	Delta WOMAC function
Exposure	−0.633 (−1.128 to −0.139)	−1.167 (−2.702 to 0.369)
Delta IL-6	0.192 (−0.124 to 0.508)	0.800 (−0.182 to 1.782)
Delta TNF-α	0.098 (−0.066 to 0.261)	0.478 (−0.030 to 0.986)
Delta IL-1sR	12.3 10^{-5} (-10.0 10^{-5} to 34.6 10^{-5})	0.001 (-12.5 10^{-5} to 0.001)
Delta CRP	0.223 (−0.276 to 0.721)	0.489 (−1.058 to 2.037)
Delta BMI	−0.005 (−0.365 to 0.355)	0.295 (−0.822 to 1.412)
Confounders		
BMI	−0.030 (−0.190 to 0.130)	0.055 (−0.442 to 0.553)
Gender*	−0.210 (−1.843 to 1.422)	−0.848 (−5.916 to 4.221)
Age	−0.146 (−0.266 to −0.026)	−0.164 (−0.537 to 0.210)
Race	0.654 (−1.147 to 2.455)	−2.365 (−7.957 to 3.228)
Smoking status†	−1.541 (−5.086 to 2.003)	2.001 (−9.004 to 13.006)
Alcohol consumption‡	−0.379 (−1.906 to 1.147)	1.850 (−2.889 to 6.589)

Exposure: D+E compared to C.

* Male vs female.

† Current smoker vs non-current smoker.

‡ never vs '<1 serving/months' or more.

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