

ALTERNATIVE TREATMENTS

Influence of Mediterranean Diet on Asthma Symptoms, Lung Function, and Systemic Inflammation: A Randomized Controlled Trial

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Objective. The rapidly increasing prevalence of asthma in developed countries suggests an environmental cause. The benefits of Mediterranean diet (MD) in cardiovascular disease have been tentatively attributed to its anti-inflammatory properties. Asthma is an inflammatory disease and MD is associated with reduced asthma risk in epidemiological studies, but there are no reported interventional studies of MD in asthma. **Methods.** In this 12-week open-label randomized trial, 38 adults with symptomatic asthma were allocated to high-intervention (HI), low-intervention (LI), and control groups. The first two groups were encouraged to adopt an MD and received multiple consultation sessions with a nutritionist, written advice, and vouchers for the purchase of appropriate foods. Food frequency questionnaires, asthma control questionnaires, asthma-related quality of life questionnaires (AQLQs), and spirometry were completed at the beginning and at the end of the study. **Results:** The MDt score increased in the HI group ($p < .001$), indicating successful alteration of dietary behavior. Statistically, nonsignificant improvements were seen in spirometry and several AQLQ subdomains in the two intervention groups. No changes were seen in the asthma control or in inflammatory markers. **Conclusions:** The trial intervention has successfully altered the dietary behavior among adults with asthma. Small but consistent improvements were seen in quality of life and spirometry among the intervention group. The use of the MD to treat asthma is feasible and warrants evaluation in a larger study, powered to examine clinical endpoints.

Keywords airways disease, asthma, Mediterranean diet

INTRODUCTION

The striking increase in the prevalence of asthma in developed countries in the last few decades (1), along with substantial inter-regional differences in asthma prevalence (2), suggests that environmental factors, in particular the Western lifestyle, predispose to asthma. Proposed explanations for this association include the “hygiene hypothesis,” which argues that reduced childhood exposure to microorganisms leads to an allergic diathesis (3), and the “dietary hypothesis,” which attributes the increase of secular dietary changes and adoption of a Western diet (4).

In epidemiological studies, a lower risk of asthma is associated with higher intake of fruits, vegetables, whole grains, nuts, fish, and dairy products (5–21) and lower intake of polyunsaturated fat (19, 22–26). However, results of interventional studies of supplementation with individual foods, antioxidants, or other nutrients have generally been negative (27–34). This failure has led to interest in a more holistic approach to study the health effects of dietary patterns.

The Mediterranean diet (MD) is characterized by high intake of fruits, vegetables, legumes, nuts, whole grains, and olive oil; moderately high intake of oily fish; moderate intake of dairy products (mainly cheese and yoghurt); and low intake of meat, poultry, and ω -6 fatty acids (35). Many MD staple foods are associated with reduced asthma risk and have become less widely consumed in contemporary Western countries. Prospective clinical trials have shown benefits of MD in cardiovascular disease (36–38) and glycaemic control (39). The mechanism is unclear, but may relate to anti-inflammatory properties of the diet (40–44), or exposure to beneficial gut or soil microorganisms as part of the rural lifestyle traditionally associated with MD (45, 46). The anti-inflammatory properties of MD have led epidemiologists to examine its association with asthma, an inflammatory disease. To date, however, no interventional studies have been published, and the readiness with which individuals will adopt MD in this clinical setting is unknown.

We designed and conducted a randomized trial with the primary aim of assessing the feasibility of inducing adherence to the MD in adults with asthma. Our secondary aims were to assess the effects of this diet on asthma symptoms, asthma-related quality of life, and systemic inflammation.

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METHODS

Subjects

Adults with symptomatic asthma were recruited through community advertisements. Asthma was defined by physician diagnosis and by at least one of the following: 12% postbronchodilator increase in forced expiratory volume in 1 second (FEV₁) or forced vital capacity (FVC); 20% increase in postbronchodilator peak expiratory flow rate (PEFR); or 15% morning PEFR variability during the run-in period. Subjects were required to be clinically stable over the preceding 6 weeks and were excluded if they already adhered to MD, had a smoking history of >10 pack years, had FEV₁ or FVC <60% of predicted, had more than one hospital admission with asthma in the past 12 months, or were taking long-term oral corticosteroids.

Study Design

This was an open-label randomized controlled trial. Participants gave informed consent, and the study hypothesis was openly discussed. Baseline data were collected at a screening visit. Following a 14-day run-in period, the participants who remained clinically stable were randomized into one of the three arms: a high-intervention (HI) group, who were encouraged to adopt MD and received intensive initial advice and 41-h consultation sessions with a dietitian; a low-intervention (LI) group, who received less intensive advice and spent 2 h with a dietitian; and a control group, who were offered one session with a dietitian, recipes, and free food at the end of the trial. Both intervention groups were provided with written advice, olive oil, and vouchers for the purchase of appropriate foods. The participants were able to contact dietitians for additional advice, if needed.

Follow-up visits occurred at 6 weeks and 12 weeks after randomization. The study coordinator contacted the participants by telephone between visits.

Procedures

A food frequency questionnaire (FFQ) that has been shown to be reproducible and valid (47) was completed by each participant at the screening and final visits. MD score (MDS) was calculated from FFQ using the method described by Panagiotakos et al. (48). Diet diaries¹ and asthma daily record cards were completed prior to each of the randomization and follow-up visits. The asthma-related quality of life questionnaire (AQLQ) (49) and asthma control questionnaire (ACQ) (50) were completed at randomization and at each follow-up visit.

Spirometry was performed at randomization and at each follow-up visit, using an electronic spirometer (Micro Loop CE 0120, CareFusion 232 Limited, Chatham Maritime, Kent, UK), before and after inhalation of 400 mcg of salbutamol via spacer. Fasting blood samples were drawn at randomization and the final visit.

Laboratory Analysis

Commercial ELISA kits (BD OptEIA™ Human ELISA Set, Becton and Dickinson, NJ, USA) were used to

measure interleukin-6 (IL-6), IL-10, interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α) in serum samples. The level of protein of interest in each sample was determined according to the manufacturer's instructions. Each sample was measured in duplicate wells side by side, and positive and negative controls were included in each plate. The final absorbance of each plate was read and calculated by an ELISA plate reader (BioTek Synergy 2, BioTek, Winooski, VT, USA).

Outcome Measures

Our primary endpoint was adherence to MD, assessed by MDS (48). Other outcome measures were designed to assess the effect of intervention on asthma symptoms (AQLQ), asthma control (ACQ), and inflammation (serum biomarkers).

We assessed clinical response using the endpoints of AQLQ, ACQ, and pre- and post-bronchodilator spirometry. A mean change of 0.5 per item in AQLQ is accepted as clinically significant (49).

Statistical Analysis

Mean and standard errors are presented for all the participants. Differences between control and intervention groups and percentage changes were adjusted for age and gender. Statistical analyses were carried out using SAS (51). All variables were checked for normality using the Shapiro–Wilk statistic, and statistical comparisons were made using *t* tests.

Ethical Approval

Ethical approval was obtained from the Auckland Ethics Committees.

RESULTS

Of 38 participants recruited, 35 completed the study. The control, LI, and HI groups were well matched at baseline (Table 1). Baseline ACQ scores indicated poor asthma control.

MDS increased significantly for the HI group ($p < .001$), and the HI participants reported consuming more fruits and fish, and less red meat and chicken, than controls. No significant differences were seen for other food types. MDS for the LI and control groups did not change during the study.

There were no changes in lung function or asthma control (ACQ) during the study (Table 2). AQLQ scores showed clinically significant increase of ≥ 0.5 (49) in several subdomains in the HI group, and in the environmental subdomain in the LI group, but these changes were not statistically significant.

Comparison of biochemical results showed that total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol fell significantly in the HI group at the end of the study ($p < .05$) (Table 3). However, there were no significant changes in any of the inflammatory biomarkers.

TABLE 1.—Baseline characteristics.

	Control	LI	HI
<i>n</i>	12	12	11
Age (years)	40.2 (3.99)	37.0 (3.99)	38.0 (4.16)
Male	33.3%	33.3%	18.2%
BMI (kg/m ²)	26.2 (1.16)	25.3 (1.16)	25.3 (1.21)
FEV ₁ (L)	2.67 (0.20)	2.94 (0.20)	2.38 (0.21)
FEV ₁ % predicted	76.7 (3.74)	83.1 (3.74)	73.0 (3.90)
FVC (L)	3.81 (0.20)	3.86 (0.20)	3.39 (0.21)
FVC % predicted	90.6 (3.42)	89.8 (3.42)	87.5 (3.57)
FEV ₁ /FVC ratio	69.5 (2.92)	75.8 (2.92)	67.8 (3.05)
Cholesterol (mmol/L)	4.85 (0.28)	4.90 (0.27)	5.45 (0.28)
HDL cholesterol (mmol/L)	1.56 (0.13)	1.65 (0.12)	1.64 (0.13)
Cholesterol:HDL ratio	3.32 (0.32)	3.25 (0.30)	3.44 (0.32)
LDL cholesterol (mmol/L)	2.78 (0.26)	2.83 (0.25)	3.25 (0.26)
Triglycerides (mmol/L)	1.08 (0.15)	0.95 (0.15)	1.25 (0.15)
Blood eosinophil count (× 10 ⁹ /L)	0.44 (0.07)	0.31 (0.06)	0.27 (0.07)
AQLQ symptoms score	4.9 (0.23)	5.4 (0.23)	5.1 (0.24)
AQLQ activity limitation score	5.2 (0.24)	6.0 (0.23)*	6.0 (0.25)*
AQLQ emotional function score	5.0 (0.34)	5.5 (0.34)	5.5 (0.25)
AQLQ environment stimuli score	4.6 (0.33)	5.1 (0.33)	5.3 (0.34)
AQLQ total score	5.0 (0.23)	5.6 (0.23)	5.5 (0.24)
ACQ score	2.1 (0.25)	1.7 (0.25)	1.6 (0.26)
MDS	29.0 (1.23)	32.1 (1.16)	26.4 (1.22)

Notes: ACQ – asthma control questionnaire; AQLQ – asthma-related quality of life questionnaire; BMI – body mass index; FEV₁ – forced expiratory volume in 1 second; FVC – forced vital capacity; HDL – high-density lipid; LDL – low-density lipid.

Mean (standard error), adjusted for age and gender.

**p* < .05 compared to the Control group.

TABLE 2.—Clinical outcome measures.

Variable	Baseline	Mean change in outcome measure		
		Control	LI	HI
MDS	29.2 (0.79)	0.44 (1.11)	1.19 (1.06)	6.62 (1.11)**
ACQ	1.7 (0.60)	−0.12 (0.17)	−0.11 (0.18)	−0.22 (0.18)
AQLQ				
Symptom domain	5.1 (0.14)	0.09 (0.27)	0.17 (0.28)	0.55 (0.28)
Activity domain	5.7 (0.15)	0.26 (0.21)	−0.08 (0.22)	0.30 (0.22)
Emotional domain	5.0 (0.19)	0.27 (0.32)	0.27 (0.34)	0.69 (0.34)
Environmental domain	5.3 (0.20)	−0.12 (0.28)	0.71 (0.29)*	0.64 (0.29)
Total score	5.3 (0.14)	0.15 (0.22)	0.17 (0.24)	0.49 (0.24)
FEV ₁ , prebronchodilator (L)	2.68 (0.121)	0.01 (0.06)	0.01 (0.06)	0.12 (0.06)
FVC, prebronchodilator (L)	3.70 (0.121)	0.00 (0.07)	0.00 (0.07)	0.11 (0.07)
FEV ₁ , postbronchodilator (L)	3.03 (0.13)	−0.09 (0.05)	−0.10 (0.05)	0.02 (0.05)
FVC, postbronchodilator (L)	3.92 (0.12)	0.06 (0.06)	−0.12 (0.06)	−0.02 (0.06)

Notes: ACQ – asthma control questionnaire; AQLQ – asthma-related quality of life questionnaire; FEV₁ – forced expiratory volume in 1 second; FVC – forced vital capacity; MDS – Mediterranean diet score.

Mean (standard error), adjusted for age and gender.

p* < .05 and *p* < .001 compared to control group.

Body weight and BMI did not change significantly during the study.

MDS did not correlate with lung function, AQLQ, ACQ, or any biochemical markers.

DISCUSSION

Because asthma is an inflammatory disease and because MD has anti-inflammatory properties and is rich in “asthma-protective” foods, there has been an interest in assessing the association between MD and asthma. Actual evidence of a protective effect is restricted to observational studies, almost exclusively involving children. Several

cross-sectional pediatric studies reported that adherence to MD is associated with reduced asthma risk (7, 17, 19, 20, 45, 52–56). A recent systematic review of the pediatric literature confirmed this and found that MD was associated with substantial reductions in risk of asthma [odds ratio (OR) = 0.22] and atopy (OR = 0.55) (56). Few studies have addressed this question in adults, but one cross-sectional study found that high adherence to MD was associated with a 78% reduction in risk of poor asthma control (45). Longitudinal and interventional studies are lacking, as is information about the effect of MD on markers of allergic inflammation. To our knowledge, this study is the first interventional study of MD in asthma to be published.

TABLE 3.—Biochemical markers.

Variable	Baseline ^a	Mean change in outcome measure		
		Control	LI group	HI group
TC (mmol/L)	5.1 (0.16)	0.26 (0.17)	0.04 (0.17)	−0.40 (0.18)*
HDL cholesterol (mmol/L)	1.6 (0.07)	0.06 (0.06)	−0.10 (0.06)	−0.08 (0.07)
LDL cholesterol (mmol/L)	2.7 (0.21)	0.20 (0.14)	0.01 (0.14)	−0.32 (0.16)*
Triglyceride (mmol/L)	1.1 (0.09)	0.05 (0.17)	0.21 (0.17)	−0.07 (0.20)
IL-6 (pg/mL)	15.4 (0.32)	−0.34 (0.65)	−0.49 (0.65)	−1.23 (0.68)
IL-10 (pg/mL)	19.5 (0.25)	−0.19 (0.60)	−0.44 (0.60)	−0.05 (0.62)
INF- γ (pg/mL)	8.4 (0.18)	−0.43 (0.35)	−0.55 (0.35)	−0.84 (0.26)
TNF- α (pg/mL)	40.5 (0.98)	−3.12 (2.36)	−0.11 (2.36)	−3.40 (2.47)
C-reactive protein (mg/L)	3.3 (0.74)	−0.62 (1.68)	2.86 (1.68)	2.10 (1.87)
Blood eosinophil count ($\times 10^9/L$)	0.3 (0.04)	−0.06 (0.05)	0.02 (0.04)	−0.01 (0.03)

Notes: HDL – high-density lipid; HI – high-intervention; IL – interleukin; LDL – low-density lipid; LI – low-intervention; TNF- α – tumor necrosis factor- α .
Mean (standard error), adjusted for age and gender.

* $p < .05$ compared to the Control group.

^a Not adjusted for age and gender.

Our aims in designing the study were first to produce an intervention that could successfully elicit a sustained alteration in dietary behavior and second to assess whether increased adherence to MD was associated with health benefits in asthma.

We succeeded in the first of these objectives. MDS increased in the HI group, providing evidence that our approach produced sustained changes in the dietary behavior over the course of the trial. Also supporting this conclusion are the data on food servings, which showed changes to a more Mediterranean eating habit in this group, with increased consumption of fruits, vegetables, fish, oil, nuts, seeds, legumes, grains, and cereals and decreased consumption of red meat, full-fat dairy, and hard cheese. Finally, TC and LDL cholesterol levels fell in the HI group, and ascorbic acid levels rose, consistent with the effects of a “Mediterraneanized” diet.

However, this behavioral change required substantial and sustained intervention; a lesser degree of intervention (the LI group) was not associated with dietary change. Subjects were asked to evaluate the dietary advice and support they received at the conclusion of the study, and all feedback were positive. This suggests that there was room for a further intensification of our approach (more hours of dietitian consultation), which might have amplified the observed clinical improvements in asthma.

Overall, these results provide valuable guidance on the type and intensity of intervention that would be required for a randomized trial of sufficient power to determine whether MD can improve asthmatic inflammation or asthma control.

Regarding our second objective—detection of clinical benefits associated with MD—results were equivocal. While clinically significant improvements were seen in a number of endpoints in the HI group, none of these improvements reached statistical significance. For example, clinically significant improvements in AQLQ were seen in the symptom, emotional, and environmental subdomains, and the total AQLQ score increased by 0.49

(borderline clinical significance). Again, none of these changes reached statistical significance.

We also observed a mean improvement of 120 mL in pre-bronchodilator FEV₁ in the HI group, accompanied by a reduction in bronchodilator reversibility. Reduced pre-bronchodilator FEV₁ is a feature of poor asthma control (57), so these changes in spirometry could be consistent with a small improvement in control. However, the observed changes in spirometry were below the accepted minimum clinically important difference for FEV₁ in asthma (58). No clinically or statistically significant changes were seen in ACQ score.

Besides the effects of MD on clinical endpoints, we were also interested in its effects on systemic inflammation, particularly the eosinophilic inflammation which characterizes allergic asthma. We found no evidence of an effect of MD on markers of eosinophilic inflammation (IL-10 and peripheral blood eosinophil count). Other studies have found no effect of MD on the levels of exhaled nitric oxide (ENO), a marker of eosinophilic airway inflammation (17, 32, 45), and the lack of an observed antieosinophilic effect in our study further suggests that MD may not act to improve asthma through this mechanism. We observed small decreases in some non-eosinophilic inflammatory cytokines in the HI group (IL-6 and INF- γ), but the changes were statistically nonsignificant.

Several possible explanations suggest themselves for this set of results. First, it may be that MD truly does not produce clinical improvements in asthma. Second, it may be that the clinically meaningful improvement seen in AQLQ and the modest improvement seen in FEV₁ are “real,” but they failed to reach statistical significance because the study was not powered for these endpoints. An alternative interpretation of the observed quality of life improvements is that MD improves general quality of life without specifically benefitting asthma. The increase in FEV₁ argues against this, however.

Third, it is possible that while MD influences the likelihood of developing asthma, it does not influence the

established asthma. This would, however, be at odds to its effects on other inflammatory diseases. Detection of a purely preventative effect of MD would require randomized trials in children, with many years of follow-up.

The final possibility is that the clinical benefit from MD is dependent on either duration or intensity of dietary changes, and that a more unequivocally positive result might have been obtained if the intervention had been more intense, or maintained over a longer period. This is possible, and the participants would probably have been receptive to a more intensive intervention (as noted above).

The only available information on the relationship between asthma control and intensity of MD adherence comes from the cross-sectional, observational studies. In several of these, adherence to MD was higher in controlled than in uncontrolled asthma, but the variety of scales and scores that were used to quantify MD adherence (45) makes the comparisons with the scoring system used in this study difficult (48). Additionally, many studies report outcomes by treatment group rather than by MD adherence. The situation is similar in the studies outside of asthma; MDS ≥ 36 was associated with lower systolic blood pressure, triglyceride, C-reactive protein, and IL-6 in one cross-sectional study (59).

Because the literature on MD in asthma is cross-sectional, it cannot provide guidance into the duration of dietary adherence that is needed for improvements in asthma control. (As an aside, in this case, duration is more important for the design of the randomized trial than for the treatment of individual patients, as if MD was found to be beneficial for asthma then patients would presumably be advised to adopt this intervention permanently, since it appears to be harmless and has numerous other proven health benefits.) Clinical trials of MD outside asthma might provide some guidance on required duration of treatment. In such trials, the cardiovascular benefits of MD seem to appear quickly, probably in under 6 months (36, 37, 44) and perhaps in as little as 6 weeks (60). We can also look at the trials of other dietary modifications in asthma: several such trials have shown benefits after a few weeks of treatment (27, 30, 61–63).

Taken together, these data suggest that the 3 months of follow up in this study was probably adequate to begin to capture a treatment effect, although the possibility remains that the effect might have increased with longer follow-up.

LIMITATIONS

The study was designed primarily to assess the feasibility of altering diet in adults with asthma and was not powered to detect the changes in clinical asthma endpoints (AQLQ, ACQ, and FEV₁). The study has yielded some suggestive results which consistently point in the direction of a beneficial effect from MD; however, few of these results are statistically significant, perhaps due to the small sample size.

A related issue is that our analysis has involved making a large number of statistical comparisons on a small sample

of measurements. We would expect to see 1 in 20 false positives using a significance level of 0.05. However, all statistically significant results remained significant after applying the Bonferroni correction for multiple analyses. Furthermore, almost all of the positive findings and trends seen in our results have pointed in the same direction.

Some other limitations should be acknowledged. The nature of the intervention means a double-blinded study design is impossible. The small number (three) of participants who withdrew during the study were not followed up, and their results were not included in analysis. Asthma exacerbations are an important clinical outcome, and these were not recorded; however, it is likely that the number of exacerbations that occurred during the 3-month follow-up period would have been too small to meaningfully analyze.

Finally, in an open-label study whose intervention is perceived by the participants as probably beneficial and very unlikely to be harmful, and which is easily available outside the study, there is a risk that control subjects will “cross-over” by choosing to avail themselves for the treatment (by altering their diet in this case). However, MD scores did not appreciably increase in either the control or LI groups, suggesting that this phenomenon was not important in this study. The maximum change in MDS score in the control and LI groups was 6, lower than the mean change observed in the HI group, which argues that excessive cross-over was not an important phenomenon.

CONCLUSION

In summary, this study is, to our knowledge, the first randomized controlled trial of MD for treatment of asthma in adults. Our high-intensity dietary intervention was successful in altering the eating habits of participants toward a Mediterranean pattern. Although our study was underpowered for examining clinical endpoints, we observed a consistent pattern of improvements in asthma-related quality of life and modest increase in spirometry among the participants in the HI group, a pattern that was not seen in the LI or control groups. We found no evidence that allergic inflammation was specifically affected by this diet.

Our results show that adoption of MD is feasible and may produce clinical improvements in asthma. In comparison to other asthma treatments, MD is free of adverse effects and has proven health benefits beyond asthma. This intervention should be further evaluated in a larger randomized trial.

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remains an inspiration to all who were privileged to spend time with him.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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NOTE

1. Diet diaries were completed for 3 days of each inter-visit period, chosen at random.

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