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Development of exchange lists for Mediterranean and Healthy Eating Diets: implementation in an intervention trial

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Abstract

Background: There has been little research published on the adaptation of diabetic exchange list diet approaches for the design of intervention diets in health research despite their clinical utility. The exchange list approach can provide clear and precise guidance on multiple dietary changes simultaneously. The present study aimed to develop exchange list diets for Mediterranean and Healthy Eating, and to evaluate adherence, dietary intakes and markers of health risks with each counselling approach in 120 subjects at increased risk for developing colon cancer.
Methods: A randomised clinical trial was implemented in the USA involving telephone counselling. The Mediterranean diet had 10 dietary goals targeting increases in mono-unsaturated fats, *n*-3 fats, whole grains and the amount and variety of fruits and vegetables. The Healthy Eating diet had five dietary goals that were based on the US Healthy People 2010 recommendations.
Results: Dietary compliance was similar in both diet arms, with 82–88% of goals being met at 6 months, although subjects took more time to achieve the Mediterranean goals than the Healthy Eating goals. The relatively modest fruit and vegetable goals in the Healthy Eating arm were exceeded, resulting in fruit and vegetable intakes of approximately eight servings per day in each arm after 6 months. A significant ($P < 0.05$) weight loss and a decrease in serum C-reactive protein concentrations were observed in the overweight/obese subgroup of subjects in the Mediterranean arm in the absence of weight loss goals.
Conclusions: Counselling for the Mediterranean diet may be useful for both improving diet quality and for achieving a modest weight loss in overweight or obese individuals.

Introduction

Research into improving the health effects of specific dietary patterns is challenged by the availability of methods to elicit defined dietary changes. A large number of studies have designed interventions using group, school or worksite based approaches or electronic media, although these have generally resulted in very modest increases in fruit and vegetable intakes (Ammerman *et al.*, 2002; Pomerleau *et al.*, 2005; Lin *et al.*, 2010; Harris *et al.*, 2011). Studies that have utilised intensive one-on-one counselling combined with self-monitoring have generally shown larger dietary changes, and this includes two cancer prevention research studies that targeted increases in fruit, vegetable and fibre intakes combined with decreases in total fat (Lanza *et al.*, 2001; Newman *et al.*, 2005). None of these intervention studies has used an exchange list approach for improving diet quality.

The Exchange Lists for Meal Planning booklet was first developed by the American Dietetic Association and the American Diabetes Association as a tool for diabetic meal planning (Franz *et al.*, 1987; Wheeler *et al.*, 1996, 2008). The exchange lists have been modified for use in other countries, although there has been surprisingly little research done to evaluate their effectiveness (Hung, 1989; Ziegler *et al.*, 1989; Shovic, 1994; Wheeler *et al.*, 1996; Bawadi & Al-Sahawneh, 2008). Only a handful of studies have modified the exchange lists to achieve low-fat diets and/or diets that target increased variety of fruits and vegetable (Boyar & Loughridge, 1985; Djuric *et al.*, 2002, 2009). The exchange list approach is potentially a method to achieve the USDA dietary recommendations (US Department of Agriculture and US Department of Health & Human Services, 2010), although this has not been tested. The exchange list approach was used in the present study to design two different diets that might be useful for colon cancer prevention.

Diet appears to plays a role in modulating risk of many cancers, and colon cancer is among the cancers for which diet has the biggest impact (American Institute for Cancer Research, 2011). One observational study of a large screening cohort found that persons who consumed diets with relatively more features of either the Mediterranean diet, the USDA Food Guide recommendations or the Dietary Approaches to Stop Hypertension (DASH) Eating Plan, all were preventive of colorectal adenomas in men, although only the USDA Food Guide pattern was preventive in women (Dixon *et al.*, 2007).

Although research on USDA-recommended diets has been more limited, extensive international research on Mediterranean diets has indicated its' cancer prevention potential (Simopoulos, 2004; Verberne *et al.*, 2010; Kontou *et al.*, 2011). Prior to the 1950s, risk of colorectal cancer was low in Greece, although the incidence has increased with the westernisation of the diet and incidence is higher among Greek immigrants to the USA and Australia (McMichael *et al.*, 1980; Paspatis *et al.*, 2001; Simopoulos, 2004; Fernandez *et al.*, 2005). In the USA, rates of colon cancer are among the highest in the world (World Cancer Research Fund/American Institute for Cancer Research, 2007). All the major components of the traditional Greek diet appear to be protective for colorectal cancer, including olive oil, fish, legumes, whole grains and fruits and vegetables (Gallus *et al.*, 2004). In comparison to the American diet, the Mediterranean diet has higher intakes of *n*-3 and *n*-9 fatty acids and lower intakes of *n*-6 polyunsaturated fats (Pauwels, 2011). The Mediterranean diet also contains much higher intakes of plant-based foods and monounsaturated fats (MUFA) and lower red meat intake (Pauwels, 2011).

In most of the Mediterranean diet intervention studies that have been conducted, the population being studied was living in southern Europe and a high MUFA food was provided. This is exemplified in two of the larger studies that were conducted with disease endpoints (De Lorgeril *et al.*, 1998; Estruch *et al.*, 2006). There have been relatively few intervention studies reported using a Mediterranean diet in American populations (Djuric *et al.*, 2008). Well-designed intervention studies can isolate and identify the effects of diet versus that of other lifestyle factors on health endpoints. Initially, we began studies to develop an exchange-list approach to elicit multiple dietary changes consistent with Mediterranean intakes (Djuric *et al.*, 2008). This approach was further expanded in the present study to include goals for dark green herbs (e.g. parsley, basil) and omega 3 fats obtained from fish and flax seeds to more fully mimic Greek-Mediterranean dietary intakes. In addition, an exchange list was devised to target Healthy People 2010 recommendations for fruits, vegetables, whole grains and saturated fats (Office of Disease Prevention & Health Promotion, 2005). With an exchange list, foods are classified into categories, and there are daily goals for consuming foods from each category. Any food within a category, in the specified serving size, can be used (or exchanged) to meet the daily intake goal for that category. Such an approach offers an individual flexibility in food choices for meeting dietary goals. The present study aimed to demonstrate the implementation of the exchange list counselling approach and to evaluate compliance to the Mediterranean diet versus compliance to a standard Healthy Eating diet in a randomised trial of persons at increased risk of colon cancer.

Materials and methods

Participants and eligibility

The Healthy Eating for Colon Cancer Prevention Study was approved by the University of Michigan Institutional Review Board (HUM00007622). The study was listed on the ClinicalTrials.gov website maintained by the National Institutes of Health (registration number NCT00475722). One hundred and twenty subjects were recruited as described previously (Djuric *et al.*, 2012). There were 61 participants in the Healthy Eating arm and 59 in the Mediterranean Diet arm, in the Ann Arbor, MI, and surrounding areas from July 2007 to November 2010 (Djuric *et al.*, 2012).

The overall objective of the Healthy Eating for Colon Cancer Prevention study was to design and evaluate implementation of novel exchange list diets that could be used in a biomarker study for individuals at high risk of colon cancer. The study collected blood and colon biopsy samples for investigation of cancer biomarker endpoints such as prostaglandins, epithelial proliferation and epithelial nuclear morphology. In a prevention study, one would target individuals at increased risk and it was therefore important to test the intervention in a high-risk population. Subjects at increased risk of colon cancer were eligible for the study. Eligibility was defined as having one-first-degree or two-second-degree relatives with colon cancer or a personal history of adenomatous polyps or early stage colon cancer in the past if they were at least 2 years after cancer treatment. Other inclusion criteria included good, general health, being at least 21 years old, body mass index (BMI) at least 18.5 and <35 kg m^{-2}. It was considered that it would be inappropriate to prescribe a diet that seeks to maintain current body weight in persons with class II obesity and higher. Exclusion criteria included being on a medically prescribed diet, following a diet that would require extensive counselling to correct nutritional deficiencies or taking supplements or medications that might interfere with the study such as vitamins and minerals above 250% of the recommended daily allowance and high doses of other supplements with potential antioxidant function such as glucosamine and chondroitin.

Dietary eligibility criteria were designed to exclude persons already following a Mediterranean diet or a low-fat diet. Eligible diets were at least 23% of energy intake from total fat with no more than 48% of fat as MUFA. Fruit and vegetable intakes to meet eligibility criteria were below two-thirds of the 2005 USDA recommended servings per day (Djuric *et al.*, 2012). This was enumerated excluding white potatoes after the first serving and iceberg lettuce. These vegetables can be consumed in large quantities but, because they are low in carotenoids, subjects were not excluded from participation if intakes of fruits and vegetable were too high because of the consumption of these two foods.

Eligible participants were stratified into categories based on sex, body mass index (<25 versus at or above 25 kg m^{-2}), regular use of nonsteroidal anti-inflammatory drugs (yes/no), and colon cancer risk status (prior colon cancer, prior adenoma or a positive family history of colon cancer) prior to randomisation to a Healthy Eating or Mediterranean diet for 6 months. Stratification was important to assure equal representation of participants with these characteristics in the two study arms. The full details of recruitment and retention to the Healthy Eating Study have been published elsewhere (Djuric *et al.*, 2012).

Dietary assessment

Dietary eligibility for recruitment to the study was assessed using 2 days of written records and one unannounced 24-h recall. Subjects were given written and verbal instructions on how to maintain a complete food record with sufficient detail for analysis. If details were missing, staff called the subject to verify details of foods eaten. The ability to provide a complete and plausible food record was part of the eligibility determination. Dietary recalls and food records also were collected at baseline, and at 3 and 6 months. Food records were completed by subjects on a Sunday and Monday, and subjects were called for an un-unannounced 24-h recall on one further weekday. All the dietary recalls were conducted using the five-pass method (Conway *et al.*, 2004). The recalls were carried out by trained staff but not by the study dietitian because it was felt that this would maximise objectivity in data collection. An additional 24-h recall was obtained at the first study visit, and all 4 days were averaged to obtain an estimate of baseline diet. The same assessments were repeated at 6 months. At 3 months, 2 days of written records and one unannounced 24-h recall were analysed before the visit to give each participant feedback on their progress. Mean nutrient intakes from the in-person recalls were similar to those calculated for the average of the three other days (Djuric *et al.*, 2012). It should be noted that an average of at least 3 days is generally required for accurate estimation of energy intake, although even a single recall can provide estimates of energy, fat and fruit/vegetable servings that were not significantly different from that of 4 days of food records (Basiotis *et al.*, 1987; Radakovich *et al.*, 2006).

For 5% of the 406 records completed, 1–2 days of data were missing as a result of inability to obtain a recall or failure to collect a written record. The food records and recalls were analysed using the Nutrition Data System for Research (NDSR) software, version 2010 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA). Records entered with previous versions of the software (2007–2009) were re-analysed with the 2010 nutrient database at study completion. Double entry of a random sample of 30 records was carried out for quality control and this revealed average differences of 10% or less for intakes of energy, vitamin E, vitamin C, calcium, percentage of energy intake from fat, total carotenoids, and whole grain servings.

Questionnaires and anthropometric assessments

A study questionnaire designed for this study captured demographic characteristics of subjects. A Health-Update

Questionnaire was used at 3 and 6 months to capture changes in medication use, health and physical activity levels. Physical activity was assessed using a validated questionnaire and metabolic equivalents were calculated (Johnson-Kozlow *et al.*, 2007). This questionnaire asked respondents about time spent walking at various speeds and performing mild, moderate and strenuous activities.

Self-efficacy for making dietary changes was assessed in all subjects at baseline and 3 months using seven behaviours targeted by both interventions, and answers were given on a Likert-type five-point scale (Likert, 1932). The seven items asked about confidence to find a way to eat a variety of fruits and vegetables, finding way to meet fat goals, finding time to buy needed foods, finding time to prepare foods, finding ways to stick to goals when others around you make it difficult, controlling the home environment, and meeting goals when eating out. Internal consistency of the scale was good with an overall Cronbach's alpha of 0.85.

Anthropometric measures were obtained at baseline, and at 3 and 6 months by trained staff of the Michigan Clinical Research Unit using a written protocol. Body weight was measured in light clothing, without shoes and rounded to the nearest quarter pound with a model 5005 Stand On Scale (Scale-Tronix, White Plains, NY, USA). Height was measured to the nearest 0.1 cm with a stadiometer and BMI was calculated as kg m^{-2}. Waist and hip circumference was measured to the nearest 0.1 cm. Blood pressure was measured using a sphygmomanometer by auscultation of the upper arm. All measures at baseline and 6 months were obtained in the morning after an overnight fast, whereas the 3-month visits were scheduled at the subject's convenience.

Dietary interventions

The Mediterranean and Healthy Eating interventions were delivered using individualised counselling with a registered dietitian. The schedule for counselling was weekly for the first month, biweekly for the next 2 months and monthly for the last 3 months. The counselling at baseline and 3-months was conducted face-to-face, and the remainder of the scheduled counselling was carried out by telephone calls that were structured to last approximately 20 min. All individual diet goals were based to maintain energy intake reported at baseline.

At the baseline visit, subjects were presented with exchange booklets written by study staff that listed foods in categories together with serving sizes, and their own individual goals were written in the booklet. The booklet information was also provided in an abbreviated form on a single, laminated page. Other printed materials provided were for buying fruits and vegetables, estimating portion sizes, and reading food labels. Subjects randomised to the Mediterranean diet treatment arm received study recipes, sample menus for 7 days and flax recipes from the Flax Council of Canada. Subjects in the Mediterranean arm were asked to keep food diaries until they became adept at meeting exchange goals, as determined by the dietitian from review of self-monitoring records, after which they could use a checklist format to track exchanges consumed from each targeted food category. Subjects in the Healthy Eating diet arm received only checklists from the start. These checklists were available both in printed format and as EXCEL files (Microsoft Corp., Redmond, WA, USA). Each group received a bimonthly newsletter written for that diet arm with news of the study progress, and information on seasonal foods and recipes.

The dietary counselling used Bandura's social cognitive theory that addresses self-efficacy, self- monitoring, social support, goal setting and developing problem solving strategies (Bandura, 1986). At every counselling session after baseline, a review of dietary intakes in the previous period was the main subject of discussion between the dietitians and the study participant, and this formed the basis for short-term goal setting. If a participant's intake of any vitamin or mineral was <67% of dietary reference intake values, however, they were given a list of foods that are rich in that nutrient to correct the deficiency.

Study participants were requested to keep self-monitoring records for 5–7 days before each counselling call and to mail them to the dietitian. The counselling session at by which a participant achieved all of their food exchange goals was recorded by the dietitian using a review of each participant's self-monitoring logs. The number of goals met was also recorded at 6 months.

Dietary goals

The goals for the Healthy Eating diet were based on the US Healthy People 2010 recommendations (Office of Disease Prevention & Health Promotion, 2005). The specific dietary goals are shown in Table 1. The saturated fat goal was given in grams per day, based on baseline energy intake, and subjects enumerated grams of saturated fat in the foods that they consumed on the tracker. Reducing saturated fat intake resulted in a small decrease in total fat intake by study participants, and participants therefore were able to reduce total fat intake to <30% of energy intake without additional counselling for maintaining total fat intake to below 30% of energy intake. A food list of high salt foods, that participants should avoid was provided, although subjects were not asked to track sodium intake.

The number of goals was greater in the Mediterranean arm (Table 1). The 'fat' goal was to maintain 30% of

Table 1 Summary of dietary goals that were tracked on self-monitoring forms in the two study arms

Diet arm	Dietary goal	Method of enumeration
Healthy eating*	Saturated fat <10% of energy intake	Saturated fat grams per day
	Fruit	Two servings per day†
	Vegetables	Two servings per day
	Dark green or orange vegetable	One serving per day
	Whole grains	At least three servings per day
Mediterranean‡	High MUFA foods	7–10 exchanges per day (5 g per exchange)
	High omega 3 food	Twice a week, 3 ounce serving size (with limits on fish with higher mercury)
	Dark green vegetable	One to two servings per day
	Orange and yellow vegetable	One to two servings per day
	Red vegetable	One to two servings per day
	Other vegetable	One to two servings per day
	Dark green culinary herbs	One serving per day, 1 tablespoon fresh or 1 teaspoon dried
	Allium vegetables	Use liberally at least once a day
	Fruit	One serving per day vitamin C fruit and one serving per day other fruit
	Whole grains, at least three servings per day	At least three servings per day

*The exchange book for the Healthy Eating diet included a list of sodium content of various types of foods, although sodium intake was not tracked.

†For both diets, one serving for fruits and vegetables was defined as one medium, one cup fresh, two cups leafy greens, ½ cup canned or cooked, ½ cup juice or ¼ cup dried. For grains, serving sizes were one ounce (12 chips or six crackers), one slice bread, ½ cup cooked grain, ¾ cup dry cereal, or three cups popcorn.

‡The exchange book for the Mediterranean diet included lists of foods high in omega 6 fats to either avoid, limit to twice a week or limit to twice a day and a high monounsaturated fats (MUFA) list. The total fruit and vegetable goal was seven to nine servings per day, depending on baseline energy intake, and variety was defined by use of five exchange groups for vegetables and two exchange groups for fruit.

energy intake from fat at the same time as reducing polyunsaturated fatty acid (PUFA) and saturated fatty acid (SFA) intakes by approximately 50% and 30%, respectively, and increasing MUFA intake by approximately 50%. Subjects in this group were asked to consume foods high in omega 3 fatty acids at least twice a week. The 'whole grain' goal was the same as in the Healthy Eating treatment arm. 'Fruit and vegetable' goals were for consumption of at least seven to nine food and drug administration servings per day, depending on energy intake, and to include culinary herbs and allium vegetables, as shown in Table 1.

Blood sample analysis

Blood samples were obtained at baseline and 6 months following after an overnight fast. Measures of total cholesterol, high-density lipoprotein (HDL), triacylglycerol (triglycerides) concentrations, were performed using a Cobas Mira Chemistry analyser from Roche Diagnostics Corp. (Indianapolis, IN, USA). High sensitivity C-reactive protein was measured using a latex immunoturbimeteric assay. Glucose was measured using a hexaokinase colorimeteric assay. C-peptide, insulin-like growth factor 1, growth hormone and its binding protein 3 were analysed using an Immulite chemiluminescent assay system purchased from Diagnostics Products Corporation (Los Angeles, CA, USA). C-peptide is more stable biomarker than insulin and is secreted in equal amount as insulin (Nesbitt *et al.*, 2006). All of these laboratory analysis and all assays were carried out by the Michigan Diabetes Research and Training Center Core Chemistry Laboratory. Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation (Friedewald *et al.*, 1972). The homeostasis model of assessment for insulin resistance (HOMA) was calculated from C-peptide and glucose using an online calculator from the University of Oxford (HOMA CALCULATOR, version 2.2; The Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK).

Statistical analysis

Alcohol intake was calculated from the study questionnaire using USDA values for standard sizes of wine (15.4 g per glass), beer (13.9 g per beer) and spirits (15.9 g per drink). All analyses were carried out using SPSS, version 18 (PASW Statistics, IBM Corporation, Chicago, IL, USA). Various aspects of dietary counselling were compared across the two dietary treatment arms using two-sample *t*-test or Fisher's exact test depending on whether the variable of interest was continuous or categorical (Table 2). Linear regression was used to evaluate predictors of the percentage of goals met at the end of the trial (Table 3). To evaluate changes over time in the

Table 2 Compliance with dietary counselling for subjects who completed 6 months of study

Variable	Healthy eating (n = 46)	Mediterranean (n = 47)	P-value*
Number of counselling calls	10.3 (0.6)	10.6 (1.0)	0.106
Total minutes counselling[†]	212 (67)	245 (45)	0.008
Number of sessions to meet goals[‡]	5.2 (1.8)	6.9 (2.2)	<0.001
Record-keeping[§]	81% (22%)	80% (22%)	0.883
Self-efficacy score at baseline	31 (4)	31 (3)	0.802
Self-efficacy score at 3 months	31 (3)	31 (3)	0.399
Percentage of goals met at 6 months	88% (23%)	82% (18%)	0.159
Participants meeting ≥ 70% of goals at 6 months, number and percent	41 (89%)	40 (85%)	0.759
Participants meeting 100% of goals at 6 months, number and percent	31 (67%)	15 (32%)[¶]	0.001

Data shown are the mean (SD), or number and percentage for subjects who completed 6 months.

*Differences between arms were analysed by two-sample *t*-tests or by Fisher's exact test for proportions.

[†]The sum total of minutes spent on counselling calls over 6 months. This does not include the in-person study visits at baseline and 3 months.

[‡]This excludes one subject in the Mediterranean arm who never met all goals. Goal attainment was judged by the study dietitian from review of self-monitoring records.

[§]The percentage of self-monitoring records that were kept and returned to the study dietitian.

[¶]Only two of the 25 subjects who did not meet all Mediterranean goals at 6 months had never met those goals at any point when under study.

dietary intakes, regression analyses were carried out under a linear mixed models framework. Linear mixed model regression analysis is an intent-to-treat analysis that provides valid results in presence of drop-outs and incorporates all available data at every given time point. Separate models were used for each of the nutrients as outcome, with a three-level variable time (baseline, 3 months, 6 months) as the primary within-subject factor and diet group assignment as the primary between-subject factor. The variable of interest was the group × time interaction that indicates any difference in the pattern of change over time across groups. Regression models were controlled for covariates that can affect dietary intakes including age, sex and BMI. To isolate the effect of diet quality, energy intake was used as a time-dependent covariate for nutrient intakes. Residuals were checked for normality of the distribution and the outcome was appropriately transformed as needed prior to the final model fit (as indicated in the footnote of Table 4) on which the inference is based. Clustering within subjects was incorporated by means of an unstructured variance–covariance matrix. Models also were constructed using the data stratified by baseline weight status (normal or overweight/obese).

Table 3 Predictors of dietary goal attainment at 6 months

Predictor of dietary goal attainment	Beta	P-value
Record-keeping	0.476	<0.001
Self-efficacy at baseline	0.342	<0.001

The two factors shown accounted for 37% of the variance in goal attainment (P < 0.001). The model was controlled for diet arm assignment, sex, baseline age and baseline body mass index status (normal weight or not), all of which were not significant predictors of goal attainment.

Results

Study subjects

Recruitment and retention of subjects to the study was described previously (Djuric *et al.*, 2012). Briefly, 59 subjects were randomised to the Mediterranean arm of the study and 60 subjects to the Healthy Eating arm. Most of the subjects were Caucasian (88%), mean age was 53 years and most were female (72%). Only one subject had a personal history of colon cancer and the rest of the subjects either had a strong family history of colon cancer (64%) or a previous adenoma (27%), or both (9%) (Djuric *et al.*, 2012). None of these characteristics differed significantly between the two diet arms (Djuric *et al.*, 2012). There were 93 participants of the original 120 who completed the whole 6 months of study participation (46 in the Healthy Eating arm and 47 in the Mediterranean arm).

Counselling adherence

Measures of compliance and dietary goal achievement are shown in Table 2. Subjects in both arms received a similar number of contacts over 6 months of study (Table 2). Compliance with the record-keeping requirements was similar in both arms, with an average of 80% of the requested records being returned. The period that elapsed before the counselling session at which subjects were able to achieve all of their dietary goals, however, differed significantly by study arm (Table 2). The time required to meet goals was, on average, 48 days in the Healthy arm and 82 days in the Mediterranean arm.

At the 6-month time point, the food records and 24-h recalls were used to assess the number of dietary goals met for each participant. The percentage of goals met at

Table 4 Dietary intakes over time in the two study groups

Nutrient or food	Healthy eating Baseline (*n* = 61)	Healthy eating 3 months (*n* = 49)	Healthy eating 6 months (*n* = 47)	Mediterranean Baseline (*n* = 59)	Mediterranean 3 months (*n* = 50)	Mediterranean 6 months (*n* = 47)
Energy (kJ day^{-1})*	8970 (2715)	7648 (2129)†	7945 (1899)†	8372 (2401)	8732 (2782)	8493 (2748)
Total fat (% of energy)*‡	35 (6)	27 (6)†	28 (7)†	35 (6)	36 (6)	33 (6)
Total protein (g per day)	84 (24)	77 (24)	81 (22)	77 (22)	84 (29)	83 (24)
Carbohydrate (g per day)*‡	261 (83)	260 (69)†	265 (71)†	247 (81)	256 (93)	261 (96)
Saturated fat (g per day)	30 (13)	18 (10)†	18 (7)†	26 (9)	19 (9)†	19 (8.5)†
MUFA (g per day)*‡	32 (12)	22 (10)†	24 (10)†	30 (12)	46 (16)†	39 (18)†
n-6 PUFA (g per day)‡§	15 (6)	12 (5)	13 (2)	16.0 (7.6)	13.2 (6.7)†	11.8 (4.7)†
n-3 PUFA (g per day)‡§	1.8 (0.8)	1.7 (1.1)	1.8 (0.8)	1.9 (1.1)	2.9 (2.4)†	2.4 (1.7)
Long chain *n*-3 fats (g per day)	0.13 (0.20)	0.26 (0.52)	0.24 (0.32)	0.15 (0.26)	0.41 (0.57)	0.35 (0.43)
Trans fats (g per day)*‡	3.6 (2.0)	2.3 (1.6)†	2.1 (1.4)†	3.6 (2.7)	1.5 (1.4)†	1.9 (1.9)†
Fruit per vegetable (servings per day)*	4.55 (1.84)	7.64 (3.17)†	7.60 (3.43)†	4.47 (1.72)	9.42 (3.12)†	8.20 (3.32)†
Total carotenoids (mg per day)	11.0 (6.0)	22.3 (13.5)†	19.2 (8.6)†	11.2 (6.4)	25.5 (13.4)†	22.1 (13.3)†
Variety (fruit per vegetable per day)	3.2 (1.2)	4.5 (1.8)†	4.4 (1.8)†	3.4 (1.5)	5.3 (1.4)†	4.9 (1.7)†
Whole grains (servings per day)	1.8 (1.6)	3.3 (1.7)†	3.4 (1.6)†	1.9 (1.7)	3.4 (1.8)†	3.4 (2.1)†
Fibre (g per day)	22 (8)	29 (11)†	30 (10)†	22 (8)	36 (16)†	33 (13)†
Red meat (servings per day)	1.9 (1.6)	1.4 (1.5)	1.0 (1.2)†	1.5 (1.3)	1.2 (1.6)	0.9 (1.1)†
Legumes (servings per day)	0.25 (0.38)	0.16 (0.27)	0.30 (0.44)	0.20 (0.27)	0.35 (0.49)	0.41 (0.55)
Glycaemic load*‡	200 (69)	188 (54)†	189 (58)	190 (73)	168 (82)†	179 (79)†
Sodium (g per day)*‡	3.48 (1.17)	3.05 (1.19)	3.04 (0.98)	3.30 (1.13)	2.77 (1.39)†	3.06 (1.12)†
Calcium (mg per day)	934 (340)	921 (376)	978 (387)	843 (36)	1041 (403)†	1026 (331)†

Data are shown as the raw mean (SD) for all available data.

*A significant group × time interaction was present for indicated variables from mixed linear regression models using variables transformed to achieve normality, as described in the Materials and methods. Covariates in the analyses were energy intake (except in the case of energy and percentage fat), sex, baseline body mass index status (normal weight or not) and baseline age. One subject in the Healthy arm who completed food records for the 6 months visit did not attend the 6-month study visit. The transformations used before analysis were log for saturated fat, polyunsaturated fatty acid (PUFA), fibre, sodium, calcium, legumes and glycaemic load; square root for whole grain servings, fruit and vegetable servings, and total carotenoids; fourth root for momounsaturated fatty acid (MUFA), and long chain omega 3 fats; and the reciprocal square root for energy.

†Significantly different than baseline for that diet arm.

‡A significant fixed effect of group was present in the model.

§The *n*-6 PUFA intake was the sum of 18 : 2 and 20 : 4. The *n*-3 PUFA intake was the NDSR variable 'omega 3 fatty acids', which is the sum of 18 : 3, 18 : 4, 20 : 5, 22 : 6 and 22 : 5.

¶Significantly different than 3 months for that diet arm.

6 months in each arm was good, at approximately 80% in each arm, although the number of subjects meeting all goals at 6 months was considered by the team to be low, especially in the Mediterranean arm. This could be a result in part to the fact that the omega 3 goal was for a weekly, not a daily, intake, making it difficult to discern goal-meeting from 4 days of diet data. There also was some deterioration of dietary intakes of target nutrients in the Mediterranean arm from 3 to 6 months. Because dietary goals were just being met by 2½ months, on average, better compliance to this diet might require a greater frequency of counselling contacts or more time for subjects to become adept at it.

Subjects of normal weight did not differ from subjects who were overweight or obese with regard to session number at which goals were reached, number of calls or minutes of counselling time (not shown). The percentage of dietary goals met at 6 months was, however, greater for the 33 normal weight subjects (90% goal met; SD 13) versus the 60 overweight or obese subjects (82% goals met; SD 24%; $P = 0.036$ by a two-sample t-test). Record-keeping was also slightly greater in the normal weight versus overweight or obese subjects (86% versus 78%, respectively; $P = 0.082$). There were no significant differences by sex in counselling adherence, although the session number at which goals were reached in the Mediterranean arm was borderline different for men (5.9 sessions) versus women (7.3 sessions; $P = 0.053$ determined by the two-sample t-test).

A brief scale was used to measure self-efficacy for making dietary changes (see Materials and methods). This scale was devised to measure the seven behaviours targeted by both interventions, and this revealed no significant differences in mean scores by diet arm (Table 2). In addition, there were no significant differences from baseline to 3 months in either diet arm, as determined from paired t-tests (not shown). Although self-efficacy for making dietary changes did not change appreciably over time, it was a significant predictor of reaching dietary goals in a linear regression model. Self-efficacy at baseline and record-keeping percentage over 6 months were significant predictors of goal attainment at 6 months (Table 3). Diet arm assignment, number of counselling calls, length of time spent on telephone counselling, sex, education, current smoking status, age, marital status, baseline intake of fruits and vegetables, baseline BMI, and baseline obesity were not significant predictors of meeting dietary goals at 6 months.

Food and nutrient intakes over time

Changes in nutrient intakes were evaluated using mixed linear regression models consistent with intention-to-treat principles (Table 4). Variables that exhibited significant fixed effects of diet group assignment and group × time interaction are annotated in Table 4. Significant fixed effects of BMI status (normal weight or overweight/obese) were evident for saturated fat, *trans* fats, carotenoids, fibre and calcium. Significant fixed effects of sex were evident for energy, saturated fat, n-6 PUFA and fibre. There was a significant group × time interaction for several dietary variables. Energy was significantly decreased from baseline in only the Healthy Eating group and carbohydrate intakes were significantly increased only in the Mediterranean group. MUFA intake decreased in the Healthy group and increased in the Mediterranean group. *Trans* fats, total fruit and vegetable servings, glycaemic load and sodium all changed in the same direction in both arms, but the pattern of change in the Mediterranean group was different over time, which resulted in a significant interaction effect (Table 4).

Subjects in the Healthy arm reported a reduction in total energy, percentage of energy from fat and saturated fat intake over 6 months of intervention, which was maintained quite well from 3–6 months. In the Mediterranean arm, there was some deterioration of diet in the last 3 months of study. It is interesting to note that MUFA intakes decreased in the Healthy Eating arm and increased in the Mediterranean arm. Intakes of n-6 and n-3 fatty acids also differed by diet arm, with significant interaction effects being present in each case. Although *trans* fats were not targeted by the intervention, there was a significant decrease in the Mediterranean arm only.

Both diet groups reported increased intakes of whole grains and fibre, and a decrease in red meat intake. Glycaemic load decreased significantly in both diet arms. Carbohydrate intake increased in the Healthy arm significantly over time in the mixed regression model, although this was not reflected in the simple means of all available data shown in Table 4. The Mediterranean arm was unique in the significant decrease in sodium and the increase in calcium, even though these were not specifically targeted by the intervention. Sodium intake was not decreased in the Healthy arm.

The goal for consuming five servings of fruits and vegetables per day in the Healthy Eating arm was surpassed, resulting in statistically similar fruit and vegetable intakes in the two study arms (7.6 versus 8.2 servings per day in the Healthy and Mediterranean arms, respectively, at 6 months). The significant group × time interaction indicated that total fruit and vegetable intake changed over time differently in the two study arms, perhaps as a result of the decrease in the Mediterranean arm from 3 to 6 months. The somewhat higher total fruits and vegetable intakes in the Mediterranean arm were mainly a result of vegetable intakes (not shown).

Variety of fruit and vegetable intakes was scored and assessed by adding one point for each different type of fruit or vegetable that was consumed in a quantity that was at least half of a serving per day. The variables included in the variety count were six types of fruit intake (citrus, citrus juice, other fruits, other fruit juice, avocado, and fried fruit) and eight different types of vegetable intake (deep green, deep yellow, tomato, white potato, other starchy vegetables, other vegetables, fried vegetables not including potatoes, and vegetable juice). Variety of fruit and vegetables intakes appeared to be similar between diet arms as well, although enumeration of allium vegetables and herb intakes was not available in the NDSR software. Increases in dark green and yellow vegetables were similar between the two arms and significant in each case, although citrus intake increased significantly only in the Mediterranean arm (data not shown). Tomato intakes did not differ significantly over time, although there was a trend for a decrease in the Healthy arm and an increase in the Mediterranean arm (not shown).

Changes in anthropometric variables and blood markers of health risks

There was little change in anthropometric variables. There was a small mean weight loss in both arms, 0.92 and 1.58 kg in the Healthy and Mediterranean arms, respectively, although this was not statistically significant. In stratified analyses, there was a significant weight loss in overweight/obese subjects randomised to the Mediterranean arm ($P < 0.05$) (Fig. 1). Mean hip circumference decreased in the Mediterranean arm from 41.1 to 40.0 inches. Diastolic blood pressure decreased significantly in the Healthy arm (from 76 to 72 mm of mercury).

There were no significant effects of either intervention on blood lipids, growth hormone or measures related to insulin status. In stratified analyses, HDL decreased and LDL did not change significantly (Fig. 1). C-reactive protein, however, decreased at 6 months in overweight/obese subjects randomised to the Mediterranean arm (Fig. 1).

Discussion

Dietary interventions that target the entire eating pattern as a whole have good potential for the prevention of many cancers and can deliver a combination of preventive compounds. This may be important because interventions with single food components have not shown consistently beneficial results (Alberts *et al.*, 1997; Bingham *et al.*, 2003; Peters *et al.*, 2003; Ebrahimi *et al.*, 2009). In the present study, exchange lists were derived to target either Healthy Eating and Mediterranean patterns. Goal attainment was reasonably good for participants on both diets and large dietary changes were observed in both study arms. However, it did take individuals more time to meet the dietary goals in the Mediterranean versus the Healthy arm, perhaps because the Mediterranean diet had more goals and therefore required larger changes from baseline (Table 2). Predictors of compliance to dietary goals were record-keeping and baseline self-efficacy

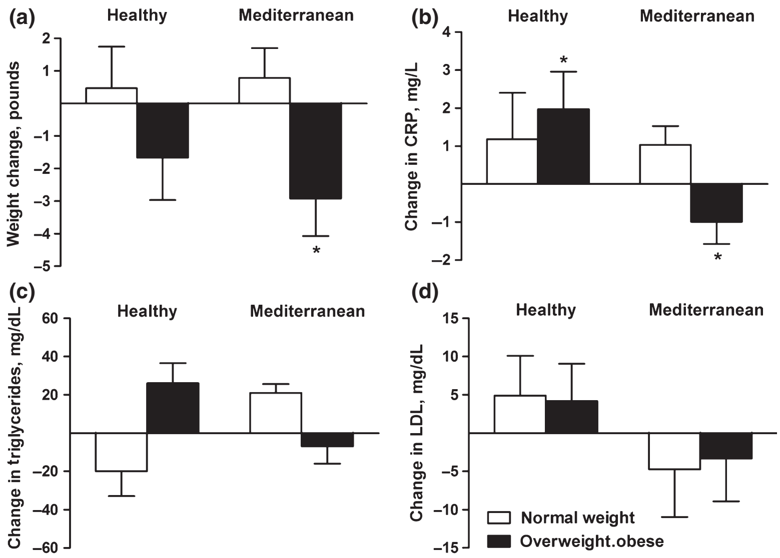

Figure 1 Change in (a) body weight, (b) C-reactive protein, (c) triglycerides and (d) low density lipoprotein (LDL) after 6 months in the Healthy Eating and Mediterranean arms in subjects who were either normal weight or overweight/obese at baseline. Data shown are the mean (SE). Mixed models regression indicated that the decrease in body weight and C-reactive protein in the Mediterranean arm for overweight/obese subjects (starred) was statistically significant after controlling for baseline age and sex ($P < 0.05$).

for making dietary changes (Table 3). It therefore may be important to increase counselling efforts directed at self-efficacy and record-keeping to improve compliance. Compliance is always a concern in clinical trials. In the Polyp Prevention Trial, for example, there was no significant effect of a low-fat, high fibre intervention overall, although the subset of subjects with excellent adherence did have a lower polyp recurrence rate (Sansbury *et al.*, 2009).

The present study yielded several unexpected results. The Mediterranean intervention resulted in an increase in calcium and decreases in both *trans* fats and sodium (Table 4). The latter could result from a lower use of ready-made food products, many of which have a dietary fat content that is not consistent with the Mediterranean goals. One of the other interesting results was that the higher goals for fruit and vegetable intakes in a greater variety in the Mediterranean diet arm did not result in significantly higher intakes than the more modest goals fruit and vegetable goals in the Healthy arm (Table 4). This indicates that the exchange list goals derived in the present study for fruit and vegetable consumption that are consistent with Healthy People 2010 goals might be sufficient to increase both quantity and variety of intakes.

Given the similarity between the two diets arms in fruit and vegetable intakes, the major difference between the two interventions was found in dietary fat intakes. The Mediterranean intervention uniquely increased mean dietary intakes of both MUFA and *n*-3 fats, with decreases in *n*-6 fats. This is potentially important because prostaglandin E_2 (PGE_2) is formed from arachidonic acid, *n*-6, and cyclooxygenase 2 is induced by high *n*-6 fatty acid diets (Rao *et al.*, 2001). PGE_2 is strongly and positively associated with colon cancer risk (Dubois & Smalley, 1996). On the other hand, *n*-3 and *n*-9 fatty acids, the main types of fats found in Mediterranean diet, have protective effects and have been associated with decreased PGE_2 levels and COX-2 expression (Singh *et al.*, 1997; Bartoli *et al.*, 2000; Broughton & Wade, 2002). In addition, the mean, calcium intake was significantly increased only by the Mediterranean intervention, which is encouraging because a recent supplementation trial has indicated a preventive potential for calcium (Ahearn *et al.*, 2011).

The other important difference between the two interventions was a significant weight loss in overweight or obese subjects randomised to the Mediterranean diet. This was achieved despite the fact that the dietary counselling was designed to maintain baseline weight. Mean reported energy intakes did not change significantly in the Mediterranean study arm (Table 4). The reasons for the observed weight loss with the Mediterranean diet are not clear. One of the factors might be related to increased post-prandial oxidation of MUFA versus SFA, which would favour weight loss in the Mediterranean versus the Healthy diet (DeLany *et al.*, 2000; Piers *et al.*, 2003).

Other Mediterranean interventions were typically carried out with individuals who had cardiovascular or diabetes risks, and counselling for energy restriction was provided for individuals who were not of normal weight, such as the studies of Esposito *et al.* (2004, 2011). In the Medi-Ravage study, energy restriction was not used and there was a slight, nonsignificant weight loss (Vincent-Baudry *et al.*, 2005). Our Mediterranean intervention was unique in that it provided more specific guidance for increasing the consumption of more categories of fruits and vegetables. Our study also achieved relatively large increases in dietary MUFA (Djuric, 2011; Esposito *et al.*, 2011).

The subjects recruited for the present study were healthy, which could have limited effects of the dietary interventions in both arms of the study on blood measures of insulin resistance and plasma cholesterol concentrations. There was, however, a significant decrease in C-reactive protein in the overweight/obese subjects randomised to the Mediterranean arm, although we cannot determine whether this was a result of weight loss or the change in dietary composition. Another limitation of the present study is that persons at increased colon cancer risk might be more motivated than the general population. On the other hand, intensive interventions such as this may be most appropriate in populations with defined health risks such as that in the present study. The strengths of the present study include the randomised design and the novel intervention methods with good participant compliance. Weaknesses include a reliance on self-report for dietary assessments and the fairly short time frame of intervention (6 months).

In conclusion, the present study implemented two different exchange-list dietary intervention strategies in individuals at increased risk of colon cancer. The intervention that was based on Healthy People 2010 goals resulted in increases in the quantity and variety of fruits and vegetables similar to the more elaborate Mediterranean intervention, indicating that more modest goals for fruit and vegetables could be adequate. The Mediterranean intervention was unique in increasing intakes of MUFA and *n*-3 fatty acids. Self-monitoring and self-efficacy were key for goal attainment. The Mediterranean diet did not have weight loss goals, although it resulted in a significant weight loss and a decrease in serum C-reactive protein in the subjects who were overweight or obese at baseline. Given the difficulty in achieving and maintaining weight loss, the present results indicate that the Mediterranean exchange list approach should be more fully explored in studies of weight loss and weight loss maintenance.

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Conflict of interests, source of funding and authorship

The authors declare no conflicts of interest with this research.

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ES wrote the paper, performed data management and analysed data. MC conducted research and analysed data. LA constructed databases and analysed data. YL performed data management and statistical analysis. NT wrote the paper and verified data. MR conducted research. AS designed the research and analysed data. MTR, DB and DKT designed the research. ZD designed the research, obtained funding, wrote the paper and had primary responsibility for the final content. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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