Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study[1–3]

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ABSTRACT

Background: We hypothesized that favorable changes in dietary patterns would lead to a reduction in body size and an improvement in metabolic status.

Objective: The objective was to study changes in diet patterns relative to changes in body size, blood pressure, and circulating concentrations of lipids, glucose, insulin, adiponectin, and other cytokines in the context of a 1-y randomized intervention study.

Design: For 1 y, 187 men aged 45 ± 2 y, ≈50% of whom met the criteria of the metabolic syndrome, were randomly assigned to a diet protocol ($n = 45$), an exercise protocol ($n = 48$), a protocol of diet plus exercise ($n = 58$), or a control protocol ($n = 36$). A previously defined a priori diet score was created by summing tertile rankings of 35 food group variables; a higher score generally reflected recommended dietary changes in the trial (mean ± SD at baseline: 31 ± 6.5; range: 15–47).

Results: Over the study year, the diet score increased by ≈2 ± 5.5 in both diet groups, with a decrease of an equivalent amount in the exercise and control groups. The weight change was −3.5 ± 0.6 kg/10-point change in diet score ($P < 0.0001$), similarly within each intervention group, independently of the change in energy intake or baseline age and smoking status. Weight change was attenuated but remained significant after adjustment for intervention group and percentage body fat. Subjects with an increased diet score had more favorable changes in other body size variables, systolic blood pressure, and blood lipid, glucose, insulin, and adiponectin concentrations. Change in diet score was unrelated to resistin and several cytokines.

Conclusion: The change toward a more favorable diet pattern was associated with improved body size and metabolic profile. *Am J Clin Nutr* 2009;89:509–17.

INTRODUCTION

Because people eat food that contains thousands of constituents, which may affect health, it is desirable to study the effects of dietary patterns in addition to the effects of single nutrients on health (1, 2). A healthy dietary pattern is associated with a reduced incidence of cardiovascular disease (3) and diabetes (4). Lockheart et al (5) defined an a priori healthy diet pattern score in which a high score corresponds to a healthy diet rich in whole grains, fruit, vegetables, nuts, fish, chicken, and some dairy products and with a low content of red meat, high-fat milk, butter, margarine, high-energy drinks, and sweet or salty snacks. In Lockheart et al's case-control study (5), a high a priori diet score was associated with a low risk of myocardial infarction.

A dietary pattern providing a higher energy intake than energy expenditure (positive energy balance) will lead to weight gain, which may have adverse health effects. However, because of food synergy (1, 2), the quality of the diet may also influence metabolism beyond energy balance, including the way in which energy-containing food constituents are metabolized. Thus, diet quality may influence body fatness and whole-body metabolism, beyond the influence of energy in the food consumed.

A cross-sectional study reported that a healthy diet pattern is associated with reduced body weight, blood pressure, blood lipid concentrations, and inflammatory and endothelial factors (6). Adipokines and related factors have recently gained attention because of their association with chronic diseases by playing a part in the process of atherosclerosis (7–9), although there have been few studies of them in relation to diet (9–14). Nettleton et al (15) implemented the a priori diet score defined by Lockheart et al (5) in the Multi-Ethnic Study of Atherosclerosis. After adjustment for several factors, the score was cross-

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sectionally inversely related with body mass index, waist circumference, and plasma concentrations of fasting insulin and triglycerides and positively related with HDL-cholesterol concentrations. Furthermore, subjects with a high a priori diet score had low concentrations of C-reactive protein (CRP), interleukin (IL)-6, and homocysteine.

Whether changes in the diet pattern would alter the risk of cardiovascular disease and diabetes cannot be determined from cross-sectional studies alone. In the context of a 1-y randomized trial of diet and exercise change, we hypothesized that the 1-y change in the a priori diet score defined by Lockheart et al (5) would be favorably associated with concurrent change in weight, waist circumference, body fat, blood pressure, and plasma concentrations of cholesterol, triglycerides, fasting glucose, fasting insulin, and some adipokines (leptin, adiponectin, and resistin). Moreover, we anticipated that diet associations would be independent of changes in energy intake, would occur within each intervention group, and would explain a part of the known intervention effects. We also investigated without hypothesis the association of change in diet score with changes in cytokines [IL-6, IL-8, tumor necrosis factor-α (TNF-α)], CRP, growth factors [hepatocyte growth factor (HGF) and nerve growth factor (NGF)], and plasminogen activator inhibitor 1 (PAI-1).

SUBJECTS AND METHODS

Study design and subjects

Data from the Oslo Diet and Exercise Study (ODES) were analyzed (16, 17). ODES was an unmasked randomized 2 × 2 factorial primary prevention trial with a duration of 1 y, performed in 1990–1992 in 219 participants (198 men and 21 women). The participants were 41–50 y of age and had several risk factors for diabetes and cardiovascular diseases. The experimental design, recruitment of participants, and laboratory analyses were described in detail elsewhere (16). The ethical principles of the Helsinki Declaration were followed, and the trial was approved by the local ethics committee. Participants were randomly allocated to 4 intervention groups: diet, exercise, diet and exercise, and control. The diet intervention was similar in the diet and diet and exercise groups, and the exercise intervention was similar in the exercise and the diet and exercise groups. There was little contact with the control group during the yearlong intervention period. Measurements were made at baseline and after 12 mo.

The diet intervention included individual dietary counseling with the participant, while the participant's spouse was present, at baseline, month 3, and month 9 of the trial, which was tailored to each participant's dietary habits and risk factor profile (total cholesterol, HDL cholesterol, triglycerides, blood pressure, and body weight). It was recommended that energy intake be spread more or less evenly throughout the day, Increased consumption of fish and fish products, vegetables, and fiber-rich products was recommended, as was a reduction in the intake of sugar and saturated fat and moderate salt restriction in those with higher blood pressure. After each of the 3 counseling sessions, an individualized dietary program including the 5–10 most important points was provided. Target weight reduction was discussed, which was usually 0.5–2 kg/mo in the most overweight participants. Participants were asked to record their body weight once each week. Energy intake was reduced in the diet groups, but not in the control or exercise groups. There was a reduction in total fat intake in the diet groups only, and plasma docosahexaenoic acid increased in the diet groups but changed little or not at all in the control and exercise groups (16, 17).

The exercise program entailed supervised group workouts, such as aerobics, circuit training, and fast walking and jogging 1 h per session 3 times/wk. The instructors recorded attendance at each session, and an average 1.8 h/wk of exercise time throughout the year was logged (17). Furthermore, participants were asked to record their physical activity performed elsewhere. There was no change in physical activity habits in the diet and control groups (17).

Laboratory procedures

Anthropometric measurements were performed with the participant wearing only underclothes. Body weight was measured by using a Lindel's balance scale (Samhald, Klippan, Sweden). Height was measured at the same time while the subjects were shoeless. Waist circumference was measured at the umbilical level while the subjects were standing. Two recordings were made, and the mean of the 2 values was used in the analysis. Percentage body fat was measured with a Futrex 5000A (Futrex Inc, Gaithersburg, MD), which is based on a near-infrared spectrophotometry technique. Three recordings of supine blood pressure were made at 1-min intervals with an automatic oscillometer (Dinamap Vitastat, Criticon, Tampa, FL). The mean of the 2 last measurements was used for analysis.

Blood samples were drawn between 0800 and 1000 after the subjects had fasted and abstained from smoking overnight. Total cholesterol, HDL cholesterol, triglycerides, glucose, and insulin were measured in frozen serum or plasma. Cholesterol, triglycerides, and glucose concentrations were derived with enzymatic methods (16). HDL cholesterol was measured with a Heparin-manganese method. LDL cholesterol was estimated by using the Friedewald equation. A radioimmunoassay method was used to measure insulin (Linco Research, St Charles, MO). Laboratory procedures for factor VII activity, adipokines, cytokines, growth factors, CRP, and PAI-1 were described elsewhere (13, 16). The prevalence of the metabolic syndrome was calculated according to the definition of the National Cholesterol Education Program (18).

Diet assessment

Diet was assessed at baseline and year 1 of the intervention with a 5-page optically readable 180-item food-frequency questionnaire, which had been extensively validated (19, 20). For example, fruit and vegetable intakes from the questionnaire correlated with 14 d weighed records ($r = 0.33$ and 0.45, respectively) from 100 Norwegian men aged 20–55 y (19). Spearman correlation coefficients (125 Norwegian men aged 20–55 y) between the questionnaire and 14-d weighed food records ranged from 0.42 for percentage of energy from fat to 0.66 for sugar intake (median $r = 0.51$) (20). Correlations between fatty acids per questionnaire and the relative amounts of adipose tissue fatty acids ranged from 0.38 to 0.52 for linoleic acid, α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (20); these finding also suggest the validity of our

measure of fish intake. Portion sizes were self-estimated by given alternatives in household measures. A similar questionnaire was used in the case-control design, in which the healthy diet pattern score defined a priori was found to be inversely related to acute myocardial infarction (5). The same nutrient analysis and food-grouping program was used to evaluate the diet questionnaire in ODES and in the case-control study.

This a priori diet score, expanding a concept originally proposed by Steffen et al (14), was created by summing tertile rankings of 35 food group variables (**Table 1**). Food groups were postulated to be beneficial ($n = 22$), neutral ($n = 4$), or adverse ($n = 9$) for health. For each food group postulated to have a benefit, the a priori diet score received 2 points for being in the highest tertile, 1 point for being in the middle tertile, and 0 points for being in the lowest tertile. For each food group postulated to be adverse, the a priori diet score received 0 points for being in the highest tertile, 1 point for being in the middle tertile, and 2 points for being in the lowest tertile. Food groups rated as neutral did not contribute to the a priori diet score. The theoretical maximum score was 62, with an observed range of 15–47. Although developed after the ODES was completed, this a priori diet score matched well with the recommended changes in the diet intervention groups.

Statistical analysis

Of the 219 subjects randomly allocated to groups, 209 (188 men and 21 women) completed all measures, except that adipokines, cytokines, CRP, growth factors, and PAI-1 were not quantified in women because of their small sample size. All women were excluded for this reason. One man was excluded from the analyses because of undiagnosed diabetes, first confirmed by a high fasting blood glucose concentration at the 1-y examination, which left 187 participants for the analyses. All analyses were performed by using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Dependent variables were 1-y changes in weight, waist circumference, percentage body fat, systolic and diastolic blood pressure, and plasma concentrations of cholesterol (total, HDL, and LDL), triglycerides, fasting glucose, fasting insulin, adipokines (leptin, adiponectin, and resistin), cytokines (IL-6, IL-8, and TNF-α), CRP, growth factors (HGF and NGF), and PAI-1. Of dual primary interest was the predictive ability of the intervention group and the change in diet score and the extent to which the intervention group and change in diet score explained each other's predictive power. Because of the study design, the change in the a priori diet score varied substantially between intervention groups, with more positive changes in the diet groups than in the control and exercise groups. The regression equations for each dependent variable included either intervention group, change in diet score, or both. Because a goal of ODES was a loss of body weight and fat, changes in diet score could also be confounded with change in energy intake. Adjustment for changes in energy intake and baseline age and smoking status had little effect on any of the regression equations; adjusted equations are presented.

For each intervention group, the proportion of change in the dependent variable compared with control was calculated with and without adjustment for diet score. Furthermore, the proportion of the change in the outcome variable explained by a 10-point change in the a priori diet score was calculated, with and without adjustment for intervention group.

Finally, we examined ability to predict mean weight in intervention group-specific quartiles of the a priori diet score within each intervention group. This was done to assess visually closeness of the observed means to the predictions based on the regression equation (goodness of fit). In this graph, intervention effects beyond the changes in the diet score appear as differences in the vertical direction, whereas diet score effects beyond the intervention effects appear in the horizontal direction. A regression line was fitted across diet change within each intervention group as a visual interpretive aid, rather than with a focus on interaction between intervention groups.

RESULTS

Baseline characteristics, as previously reported (8, 17, 21, 22), were similar across the randomized intervention groups; the mean ($\pm$SD) values for the 187 men were as follows: age, 45 $\pm$ 2.5 y; weight, 91 $\pm$ 12.5 kg; waist circumference, 103 $\pm$ 9.0 cm; body mass index (in kg/m^2), 28.6 $\pm$ 3.4; and percentage body fat, 24.4 $\pm$ 3.4%. Systolic/diastolic blood pressure was 131/88 $\pm$ 11/8 mm Hg; plasma total, HDL, and LDL cholesterol concentrations were 6.3 $\pm$ 0.8, 1.0 $\pm$ 0.16, and 4.3 $\pm$ 0.8 mmol/L, respectively; and the triglyceride, fasting glucose, and fasting and postload insulin concentrations were 2.3 $\pm$ 1.4 mmol/L, 5.5 $\pm$ 0.6 mmol/L, and 136 $\pm$ 68 and 785 $\pm$ 522 pmol/L. Other variables measured (13) included leptin (9.5 $\pm$ 6.4 ng/mL), adiponectin (12.4 $\pm$ 8.3 μg/mL), resistin (7.8 $\pm$ 2.9 ng/mL), TNF-α (4.8 $\pm$ 2.4 pg/mL), IL-6 (2.9 $\pm$ 4.8 pg/mL), IL-8 (2.6 $\pm$ 2.1 pg/mL), CRP (3.8 $\pm$ 4.6 μg/mL), NGF (48.1 $\pm$ 96.8 pg/mL), HGF (1180 $\pm$ 704 pg/mL), PAI-1 (18.7 $\pm$ 13.8 U/mL), factor VII activity (129.5 $\pm$ 38.1%), and monocyte chemoattractant protein-1 (244 $\pm$ 117 pg/mL). The sample by design generally tended to have some component of the metabolic syndrome, and about half of the participating men fulfilled the criteria.

Weight, waist circumference, and plasma leptin concentration (8) decreased in the diet groups, and percentage body fat mass decreased in the diet and exercise groups (17, 21). The diet groups also showed a reduction in blood pressure and plasma concentration of glucose and insulin (22–25). The plasma adiponectin concentration was stable in the diet and exercise groups, whereas there was a decrease in the control group (13). TNF-α unexpectedly increased in the diet group and the exercise group, compared with the control group, as also previously reported (13). Other adipokines, cytokines, CRP, growth factors, and hemostatic factors did not change much during the 1 y of intervention (13).

Energy intake was 10.6 $\pm$ 2.9 MJ/d; it tended to decrease in both diet groups, but showed little change in the exercise and control group (**Table 2**). The mean ($\pm$SD) a priori diet score was 31 $\pm$ 6.5. Over the year of intervention, the a priori diet score increased by $\approx$2 $\pm$ 5.5 in both diet groups, whereas it decreased by an equivalent amount in the exercise and control groups. A few individuals in the diet group reduced their a priori diet score, such that the median change in the lowest quartile of change in the score was -6 in the diet group, -3.5 in the diet plus exercise group, -8 in the exercise group, and -8 in the control group. In contrast, the median increase in the highest

TABLE 1
Mean intake of specific food groups (in the lowest and highest quartiles of change in the a priori diet score) at baseline (BL) and over 1 y and the mean difference in intake

	A priori diet score change, lowest quartile (−14 to −5)			A priori diet score change, highest quartile (5–16)		
Food group[1]	BL	1 y	Difference ± SE	BL	1 y	Difference ± SE
	g/d			*g/d*		
Whole-grain breads (+) (whole-meal bread, bran bread, dark rolls, dark crisp bread)	131	95	−36 ± 12[2]	57	130	73 ± 14[2]
Whole-grain breakfast cereals (+) (breakfast cereal, muesli, 4-grain cereal, rolled oats)	12	9	−3 ± 3	11	17	6 ± 3[2]
Refined grains (0) (refined wheat flour, parboiled and polished rice, macaroni, spaghetti, light crisp bread, white bread, school bread, Vienna bread, light rolls, waffles)	125	120	−6 ± 11	152	86	−66 ± 14[2]
Cruciferous vegetables (+) (broccoli, Brussels sprouts, cabbage, Chinese cabbage, cauliflower, sauerkraut)	49	34	−15 ± 5	31	48	16 ± 4[2]
Tomatoes (+) (tomatoes, tomato puree)	11	8	−3 ± 1[2]	7	14	7 ± 2[2]
Lettuce (+)	2	2	0 ± 1	3	2	−2 ± 1
Other vegetables (+) (carrots, rutabaga, onion, cucumber, red pepper, frozen vegetables, mixed vegetables)	101	74	−26 ± 6[2]	67	87	21 ± 6[2]
Fruit (+) (all fruit, orange, banana, grape, apple, berries, tinned fruit)	164	125	−40 ± 17[2]	135	185	50 ± 30
Fruit juice (+) (orange juice)	49	37	−13 ± 16	48	100	52 ± 23[2]
Eggs (0)	23	22	−1 ± 2	22	16	−6 ± 2[2]
Chicken (+)	17	12	−5 ± 2[2]	15	22	7 ± 2[2]
Organ meats (−) (liver, liver pate, blood sausage)	8	8	−1 ± 1	7	4	−3 ± 1[2]
Red and processed meats (−) (meat, pork, beef, lamb, wild, bacon, cold meats, sausage, ground meat, hamburger, meatballs, hot dog)	121	87	−34 ± 11[2]	113	89	−24 ± 7[2]
High-fat fish (+) [herring (regular, pickled, sour), herring salad; mackerel (regular, spring, fall, smoked, with tomato), fish oil, cod liver oil]	20	19	−1 ± 4	14	37	23 ± 5[2]
Low-fat fish (+) (fish, cod, haddock, pollack, tuna, sardines, trout, caviar, caviar topping, fish pudding, fish balls, cod fish sticks)	116	90	−27 ± 7[2]	75	105	30 ± 7[2]
Nonhydrogenated vegetable oil (+) (vegetable cooking oil)	1	1	0.5 ± 0.2[2]	1	1	0.7 ± 0.2[2]
Dressings, mayonnaise, sauce (+) (salad dressing, light Italian dressing, regular dressing, remoulade, Bearnaise sauce)	8	5	−3 ± 1[2]	5	8	3 ± 1[2]
Butter and margarine (−) (margarine, margarine mixture, butter, soy margarine, Smoregod, Bremykt, Brelett[3])	36	24	−12 ± 4	34	22	−12 ± 3[2]
Cheese and yogurt (+) (yogurt, light yogurt, white cheese, white cheese 45% fat, desert cheese 60% fat, cheese 30% fat, melt cheese light, melt cheese 45% fat, brown cheese, brown cheese 33% fat, cream cheese 20% fat)	42	42	0 ± 6	47	64	17 ± 8[2]
Low-fat milk (+) (2%-fat milk, skim milk)	383	310	−72 ± 31[2]	330	319	−10 ± 46
High-fat dairy (−) (milk, whole milk, whole sweet milk, whipping cream, sour cream, ice cream, chocolate ice cream)	80	65	−15 ± 7[2]	84	42	−42 ± 22[2]
Condiments (0) [sugar (farin and refined), sweet sandwich filling, marmalade, strawberry jam, salt]	38	24	−15 ± 5[2]	26	18	−8 ± 4[2]
Chips and snacks (−) (potato chips)	3	3	0 ± 1	2	1	−1 ± 0.3[2]

(*Continued*)

TABLE 1 *(Continued)*

Food group[1]	A priori diet score change, lowest quartile (−14 to −5) BL	1 y	Difference ± SE	A priori diet score change, highest quartile (5–16) BL	1 y	Difference ± SE
Nuts (+) (peanuts, peanut butter)	4	2	−2 ± 2	5	7	1 ± 3
Potatoes (0) (potatoes, fried potatoes, instant potatoes, French fries, potato cake)	134	130	−5 ± 8	133	137	3 ± 12
Pizza (−) (frozen pizza)	13	10	−4 ± 2	14	11	−4 ± 2
Soup (+) (clear soup powder mix, fish soup powder mix)	3	2	−1 ± 0.4[2]	2	2	1 ± 0.5
Sweets (−) (chocolate, chocolate candy, butter cookies, cake, marble cake, layer cake, small cake, cookies, instant pudding)	28	25	−4 ± 3	31	25	−6 ± 7
Coffee (−) [coffee (brewed, instant, filtered)]	484	488	4 ± 29	594	549	−45 ± 45
Tea (+) (tea, black tea)	211	137	−74 ± 23[2]	130	149	19 ± 19
Wine (+) (table wine)	29	24	−6 ± 4	22	20	−2 ± 3
Beer (+) (light beer, regular beer, strong beer)	229	232	3 ± 16	179	126	−54 ± 45
Liquor (+) (liquor)	53	63	11 ± 21	54	52	−2 ± 6
Low-energy drinks (+) (water)	126	100	−27 ± 10[2]	84	85	2 ± 9
High-energy drinks (−) (soft drinks, sports drinks)	147	144	−3 ± 17	150	90	−60 ± 23[2]

[1] Postulated health effects are categorized as beneficial (+), neutral (0), or adverse (−). Formation of the diet score from the food groups is described in Subjects and Methods.

[2] $P < 0.05$ for change within group. Change quartiles were computed without regard to intervention assignment.

[3] Smoregod, Bremykt, and Brelett (Fjordland AS, Oslo, Norway) are Norwegian brand names for butter/margarine spreads.

quartile of change was 9 in the diet group, 9 in the diet plus exercise group, 4 in the exercise group, and 4 in the control group.

Body size

After adjustment for change in energy intake and baseline age and smoking status, weight loss was 5–7 kg in the diet groups and 2 kg in the exercise only group, as compared with a 3.5-kg/10-point change in the diet score (**Table 3**; diet score changes are detailed in the tables, whereas intervention changes are provided in the text only). The diet score explained little of the intervention group effect, whereas the diet effect was attenuated by the intervention groups by 39%. With further adjustment for percentage body fat, 67% of the diet score effect was explained, although the diet score slope remained statistically significant.

Correspondingly, the decrease in waist circumference was 5–7 cm in the diet groups and 3 cm in the exercise only group, whereas it was 3 cm per 10-point change in the diet score. Again, the diet score explained little of the intervention group effect, whereas the diet effect was attenuated by the intervention groups by 46%, and additional adjustment for percentage body fat led to a 78% reduction in the diet score effect, implying that the change in diet score may have acted on the waist via its action on body fat. Percentage body fat decreased by 1–2% in each intervention arm and per 10-point change in the diet score. Diet was attenuated by 23% after adjustment for intervention effects, whereas the intervention effects were attenuated by 0–31% by mutual adjustment. Plasma leptin decreased by 1.5–3.1 ng/mL in each intervention arm and per 10-point change in the diet score. Decreases in the diet score effect were attenuated by 27% after adjustment for intervention effects, whereas the intervention effects were changed by 7 to −22% after adjustment for diet score. The plasma concentration of adiponectin increased with diet score change (2.6 ± 1.20 μg/mL; $P = 0.03$); this change was attenuated by 23% and lost statistical significance after adjustment for intervention group and by 46% by further adjustment for percentage body fat.

Blood pressure

Systolic blood pressure decreased by 5–6 mm Hg in the diet groups, by 2 mm Hg in the exercise only group, and by 3 mm Hg per 10-point change in the diet score. The intervention effect was unaffected by adjustment for the diet score. The diet score effect was attenuated to nonsignificance by 45% after adjustment for intervention group and by 66% with further adjustment for percentage body fat. Diastolic blood pressure was unaffected by intervention or diet score, except for a 4.4-mm Hg decrease in the diet and exercise group.

TABLE 2
Baseline and 1-y changes in a priori diet score and energy intake by intervention group[1]

Variable	Diet group ($n = 45$)	Diet + exercise group ($n = 58$)	Exercise group ($n = 48$)	Control group ($n = 36$)
A priori diet score, baseline	30.7 ± 6.5	30.2 ± 6.2	32.2 ± 6.3	29.6 ± 7.1
A priori diet score, 1-y change	1.2 ± 6.2[2]	2.2 ± 5.3[3]	−2.6 ± 5.3	−1.7 ± 5.1
Energy, baseline (MJ/d)	11.0 ± 3.5	10.5 ± 2.6	10.6 ± 2.6	10.3 ± 3.2
Energy, 1-y change (MJ/d)	−2.2 ± 2.6[4]	−1.7 ± 2.8[2]	−0.5 ± 2.8	−0.5 ± 3.1

[1] All values are means ± SDs.
[2–4] Significantly different from both the control and exercise groups: [2]$P < 0.05$, [3]$P < 0.001$, [4]$P < 0.01$.

Blood lipids

Changes in total and LDL cholesterol (**Table 4**) occurred in the diet and exercise intervention group and were about −0.3 mmol/L per 10-point change in the diet score. For total cholesterol, 29% of the diet and exercise group effect and 15% of the diet score effect were explained by mutual adjustment; 35% of the diet score effect was explained by further adjustment for percentage body fat. The percentage explained by these adjustments was somewhat greater in the case of LDL cholesterol. HDL cholesterol increased by 0.13 mmol/L in the diet and exercise group and by 0.05 mmol/L per 10-point change in the diet score. The diet and exercise intervention effect did not change much after adjustment for diet score, whereas the diet score effect was explained by the adjustment for intervention group. Triglycerides were related only to the diet and exercise intervention, 19% of which was explained by adjustment for percentage body fat.

Glucose and insulin

Fasting glucose decreased by ≈0.18 mmol/L per 10-point change in the diet score—a finding that persisted after adjustment for intervention group, but was attenuated to nonsignificance by 33% by further adjustment for percentage body fat, which suggests mediation of the diet score effect by loss of body fat. Fasting insulin decreased by 25 pmol/L in the diet and exercise group and by 22 pmol/L per 10-point change in the diet score. These findings were unexplained by mutual adjustment or by adjustment for percentage body fat. Findings for postload insulin were similar to those for fasting insulin.

TABLE 3
Adjusted changes in body size and blood pressure variables per 10-point change in the a priori diet score[1]

	B	SE	*P*
Change in body weight (kg)			
Not adjusted for intervention	−3.46	0.57	<0.0001
Adjusted for intervention	−2.1	0.55	0.0002
Adjusted for intervention and change in percentage body fat	−1.15	0.47	0.02
Change in waist circumference (cm)			
Not adjusted for intervention	−2.8	0.58	<0.0001
Adjusted for intervention	−1.5	0.56	0.009
Adjusted for intervention and change in percentage body fat	−0.6	0.47	0.18
Change in percentage body fat (%)			
Not adjusted for intervention	−1.3	0.31	<0.0001
Adjusted for intervention	−1	0.33	0.003
Change in leptin (ng/mL)			
Not adjusted for intervention	−1.5	0.41	0.0003
Adjusted for intervention	−1.1	0.43	0.01
Adjusted for intervention and change in percentage body fat	−1	0.44	0.03
Change in adiponectin (ng/mL)			
Not adjusted for intervention	2.6	1.2	0.03
Adjusted for intervention	2.0	1.4	0.13
Adjusted for intervention and change in percentage body fat	1.4	1.4	0.32
Change in systolic blood pressure (mm Hg)			
Not adjusted for intervention	−2.9	1.12	0.01
Adjusted for intervention	−1.6	1.24	0.2
Adjusted for intervention and change in percentage body fat	−1	1.27	0.41
Change in diastolic blood pressure (mm Hg)			
Not adjusted for intervention	−1.4	0.98	0.1
Adjusted for intervention	−0.8	1.06	0.48
Adjusted for intervention and change in percentage body fat	−0.2	1.07	0.84

[1] Each row represents a separate regression analysis of change in the dependent variable (indicated in the section heading) on change in the a priori diet score, adjusted for change in energy intake and baseline age and smoking status, with further adjustment as stated.

TABLE 4
Changes in plasma lipids, glucose, and insulin according to intervention group and per 10-point change in the a priori diet score[1]

	B	SE	*P*
Change in total cholesterol (mmol/L)			
Not adjusted for intervention	−0.34	0.09	<0.0001
Adjusted for intervention	−0.29	0.09	0.003
Adjusted for intervention and change in percentage body fat	−0.22	0.09	0.02
Change in LDL cholesterol (mmol/L)			
Not adjusted for intervention	−0.28	0.09	0.002
Adjusted for intervention	−0.23	0.1	0.02
Adjusted for intervention and change in percentage body fat	−0.15	0.1	0.12
Change in HDL cholesterol (mmol/L)			
Not adjusted for intervention	0.05	0.02	0.01
Adjusted for intervention	0.01	0.02	0.46
Adjusted for intervention and change in percentage body fat	0	0.02	0.8
Change in triglycerides (mmol/L)			
Not adjusted for intervention	−0.2	0.17	0.25
Adjusted for intervention	−0.1	0.19	0.61
Adjusted for intervention and change in percentage body fat	−0.09	0.19	0.65
Change in fasting glucose (mmol/L)			
Not adjusted for intervention	−0.18	0.06	0.002
Adjusted for intervention	−0.17	0.06	0.01
Adjusted for intervention and change in percentage body fat	−0.12	0.06	0.06
Change in fasting insulin (pmol/L)			
Not adjusted for intervention	−21.6	6.11	0.001
Adjusted for intervention	−20.1	6.69	0.003
Adjusted for intervention and change in percentage body fat	−22.5	6.87	0.002
Change in insulin after glucose challenge (pmol/L)			
Not adjusted for intervention	−134.1	50.97	0.01
Adjusted for intervention	−125.1	54.94	0.02
Adjusted for intervention and change in percentage body fat	−120.3	56.77	0.04

[1] Each row represents a separate regression analysis of change in the dependent variable (indicated in the section heading) on change in the a priori diet score, adjusted for change in energy intake and baseline age and smoking status, with further adjustment as stated.

Other variables

Plasma concentrations of resistin, IL-6, IL-8, TNF-α, CRP, HGF, NGF, and PAI-1 were unrelated to the diet score.

Change in energy intake

Change in energy intake was positively related to change in body weight (0.15 ± 0.06 kg per 500 kcal/d; $P = 0.01$), waist circumference (0.1 ± 0.06 cm per 500 kcal/d; $P = 0.1$), plasma leptin (0.08 ± 0.04 ng/mL per 500 kcal/d; $P = 0.05$), and systolic blood pressure (0.3 ± 0.11 mm Hg per 500 kcal/d; $P = 0.01$), but not to change in percentage body fat. The associations of change in energy intake with changes in body weight, waist circumference, plasma leptin, and systolic blood pressure strengthened after adjustment for the diet score and became significant for diastolic blood pressure, fasting glucose, and postload insulin, but were all close to zero after adjustment for intervention group. Change in energy intake was unrelated to any of the other outcome variables studied.

Intervention group–specific changes

The closeness of the observed data to our models (goodness of fit) and the nature of the associations with diet score are shown in **Figure 1** as the mean change in weight by change in a priori diet score within each intervention group, adjusted for the change in energy intake and in baseline age and smoking. There was good fit to the linear model, with similar slopes of weight across diet score in the diet, diet plus exercise, exercise, and control groups of −2.7 ± 1.0 ($P = 0.01$), −4.5 ± 1.0 ($P \leq 0.0001$), −3.0 ± 1.1 ($P = 0.005$), and −3.5 ± 1.2 ($P = 0.004$) kg per 10-point change in the a priori diet score, respectively (P for interaction = 0.9). The regression slope for diet score adjusted for intervention group presented in Table 3 is a weighted average of the 4 diet score slopes (horizontal), whereas the vertical differences are the intervention group effects after adjustment for the diet score. Thus, the association of diet score with weight apparently existed

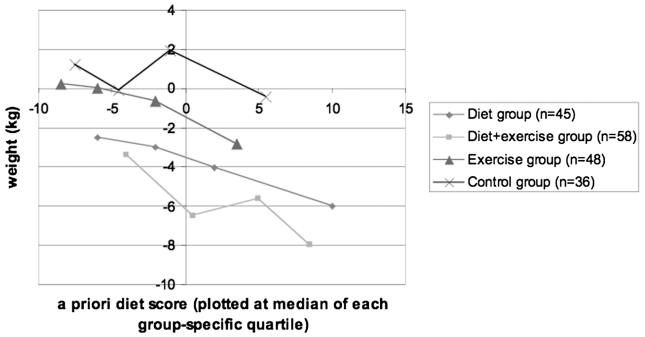

FIGURE 1. Change in weight by change in a priori diet score by intervention group.

for the control group (no change in energy intake or expenditure), the diet group, the exercise group, and the diet plus exercise group. There was similarly no significant interaction for any of the outcome variables examined, except that HDL cholesterol increased significantly in the exercise only group and nonsignificantly in the diet group, but decreased nonsignificantly in the control and diet plus exercise groups (P for interaction = 0.006).

Specific food-group changes in those who changed their diet score

Participants with an increase in diet score tended to increase intakes of whole-grain foods, fruit and vegetables, chicken, fish, oils, dressings, cheese and yogurt and to decrease intakes of refined grains, eggs, organ and red meats, butter and margarine, high-fat dairy products (milk and ice cream), chips and snacks, and high-energy drinks (Table 1). Participants with a decrease in diet score tended toward the reverse changes, although they did not change refined grains and decreased red meats, low- and high-fat milk, condiments, soup, tea, and low-energy drinks.

DISCUSSION

On the basis of change in a clinically relevant a priori diet score (5), we found a change in several body size and biochemical markers over the 1-y randomized clinical trial of diet and exercise. The diet score was created after the study was completed but nevertheless captured a portion of the diet change recommendations in our study. This study showed a beneficial effect of change in diet score on change in weight, waist circumference, body fat, systolic blood pressure, and plasma concentrations of total and LDL cholesterol, fasting glucose, fasting and postload insulin, and leptin, independent of energy intake and the intervention group the subjects were in. The a priori diet score, although correlated with the study diet recommendations, explained only part of the intervention effects on body size and biochemical markers. Change in energy intake showed relatively small associations only with body size–related variables, leptin, and systolic blood pressure. There was little diet change in the exercise and controls groups and substantial change in the 2 diet groups. However, diet advice was general, and compliance with different aspects of the diet recommendation was variable. Thus, the diet changed variably in the different participants, and the association between diet change and metabolic change could be studied. Similarly, energy expenditure changed by a fairly constant amount in the exercise groups and little in the nonexercise groups.

The intervention had an effect on percentage body fat. The diet score associations with waist circumference, systolic blood pressure, LDL cholesterol, and glucose were explained by changes in percentage body fat. Thus, the change in body fat may have played a mediating role; diet quality affected body composition and subsequently affected these outcome variables.

A nested case-control study among 656 type 2 patients with diabetes and 694 controls among women in the Nurses' Health Study monitored the association between a dietary pattern derived by reduced rank regression for its association with markers of inflammation. The results showed a strong association between the dietary pattern score (diet relatively high in refined grains, diet soft drinks, and processed meats) and IL-6, CRP, and incident diabetes (4). Furthermore, some cross-sectional studies have investigated associations between inflammatory markers and dietary patterns derived by using factor analysis (6) or based on healthy eating concepts (26) or on selected food groups (27). Nettleton et al (6) reported that subtle differences in dietary pattern composition, realized by incorporating measures of inflammatory processes, affect associations with markers of subclinical atherosclerosis. Salas-Salvadó et al (27) reported that consumption of fruit, cereals, virgin olive oil, and nuts was associated with lower serum concentrations of inflammatory markers, especially those related to endothelial function, in Spanish subjects with a high risk of cardiovascular disease. Boynton et al (26) observed limited evidence that healthy eating patterns contribute to reduced inflammation in overweight and obese postmenopausal women.

In a 4-wk intervention study in obese subjects, Rankin and Turpyn (28) showed that a low-carbohydrate diet increased serum CRP, whereas a high-carbohydrate diet reduced it. In a 12-wk supplementation study, fish oil, which tends to be found in healthy diet patterns, modulated the ability of monocytes to stimulate endothelial cells in vitro (29). This effect of marine fatty acids is one example of how a healthy diet pattern might contribute to a more favorable metabolic profile.

It is of interest that diet quality, expressed by a higher a priori diet score, affected weight and other body size measures. Even though definitive measures of energy expenditure were not available, participants were asked either to maintain their habitual physical activity or to engage in a supervised exercise program, and it appears that this diet effect on body size operated via pathways other than the classic energy balance. Although there is little evidence from human studies, possible mechanisms exist. One might consider diet-induced changes in hormones and enzymes that could alter the amount of energy expended in uptake, transport, or fat storage, for example. Uncoupling of oxidative phosphorylation may take place as a result of omega-3 fatty acid supplementation, as suggested by enhanced mRNA expression of uncoupling proteins in rodents (30). Enhanced uncoupling would lead to increased energy expenditure and hence less fat storage. Another mechanism might relate to increased vitamin D intake in a healthy diet pattern; a positive correlation has been observed between plasma vitamin D and insulin sensitivity (31), which is relevant to our finding of reduced plasma insulin and both fasting and postload insulin sensitivity.

On the other hand, we observed little to no association of either the a priori diet score or the study intervention with inflammatory, adipokine, cytokine, growth factor, and hemostatic markers in our present analyses or in previous studies of the same population (13). Many of these biochemical markers operate in a relatively late stage of atherogenesis and may be altered by the disease processes themselves. Thus, the markers might relate to a healthy diet in people with atherosclerotic disease, who would have more variable activation of these pathways.

A strength of our present study was our ability to evaluate the reversibility of changes in body size and biochemical markers. Reversibility is an important aspect of causal inference, namely that change in diet results in change in outcomes. Because this observational study was embedded in a randomized trial, change in diet was more varied than would generally be seen in free-living subjects and diet was carefully monitored. Thus, the

present study is substantially stronger than the more common cross-sectional design that has been used previously to address this type of question. The study had limitations, one of which was that it was conducted in men only in a particular cultural context and another was that the sample studied was restricted to those who were eligible for the randomized study. Residual confounding was possible; for example, we could not adjust for socioeconomic status because we did not measure it.

In conclusion, we offer evidence that a clinically relevant diet score is associated with body size and biochemical markers, beyond the apparent effects of exercise and changes in energy expenditure. The specific diet score studied may not capture the full scope of such diet effects. Because the outcome variables studied are important in several chronic diseases, the findings are consistent with an important role for diet quality in chronic disease modulation.

The authors' responsibilities were as follows—SAA and CAD: provided plasma and serum from the Oslo Diet and Exercise Study; DRJ and DS: formulated the study strategy; MHR-A: conducted the interleukin-8, tumor necrosis factor-α, monocyte chemoattractant protein-1, hepatocyte growth factor, nerve growth factor, C-reactive protein, and resistin analyses; DS: carried out the statistical analyses; DRJ: supervised the statistical analyses; and DRJ and DS: drafted the manuscript. All authors contributed to the revision of the manuscript. None of the authors had a personal or financial conflict of interest.

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