British Journal of Nutrition (2004), **92**, 809–818
DOI: 10.1079/BJN20041262

A substitution model of dietary manipulation is an effective means of optimising lipid profile, reducing C-reactive protein and increasing insulin-like growth factor-1

Adrian H. Heald[1]*, Cheryl Golding[2], Reena Sharma[1], Kirk Siddals[1], Sara Kirk[2], Clare Lawton[3], Simon Anderson[1], J. Martin Gibson[1] and Janet E. Cade[2]

[1]*Department of Diabetes and Endocrinology, Salford Royal Hospitals NHS Trust, Hope Hospital, Stott Lane, Salford M6 8HD, UK*
[2]*Nutritional Epidemiology Group and*
[3]*Department of Psychology, University of Leeds, 71–75 Clarendon Road, Leeds LS2 9P, UK*

(Received 8 February 2004 – Revised 1 June 2004 – Accepted 16 July 2004)

There are two key methods in which fat intake may be manipulated; the 'substitution model' and the 'reduction model'. However insufficient information is known about the mechanisms of dietary fat reduction in individuals who have successfully reduced their fat intake, to be clear as to which strategy offers the greatest chance of success. Our objective was to ascertain the most effective dietary intervention for improving cardiovascular risk profile. Eighty female volunteers (high fat consumers) were recruited. Each subject was randomly allocated into one of the following groups. Substitution of high-fat foods was made with reduced-fat products, by the reduction of high-fat foods, by a combination of substitution and reduction strategies, or no advice was given. Each intervention lasted 3 months. Anthropometric measures and fasting blood samples were taken at baseline and follow-up. The substitution intervention resulted in weight loss (mean −1·4 (95 % CI −2·4, −0·2) kg) and reduced percentage body fat (mean −1·3 (95 % CI −2·0, −0·5) %). There was no significant weight change with the other interventions. Fasting triacylglycerols (−0·2 (SEM 0·07) mM; $P=0·04$), cholesterol and C-reactive protein (CRP) levels (0·8 (SEM 0·2) mg/l; $P=0·04$) fell with the substitution intervention, but not with the other interventions. Insulin-like growth factor-1 increased with both substitution and reduction ($P=0·02$). There was no significant change in fasting insulin or glucose with any intervention. The substitution model of dietary intervention is effective even over a relatively short interval of time in reducing fasting total cholesterol, triacylglycerols and CRP. Although the group size for the present study was small and involved females only, it has significant implications for population intervention strategies.

Dietary interventions: Substitution model: Cardiovascular risk factors: Lipids: C-reactive protein

CVD is a major cause of death worldwide. In the last five decades a great deal of effort has been put into understanding the factors (metabolic, inherited, and lifestyle) that predispose individuals to CVD. High fat intakes have been linked to CHD and obesity for more than 50 years.

Ancel Keys established the cholesterol hypothesis (Fidanza *et al.* 1970; Grande *et al.* 1970; Keys, 1975). From this the concept of risk factors for CHD evolved. In the last decade numerous prospective studies have been published identifying hypercholesterolaemia as a major risk factor in predicting coronary events (Anonymous, 1994; Shepherd *et al.* 1995, Downs *et al.* 1998; Sever *et al.* 2003).

There are numerous ways to reduce fat intake (Lawton *et al.* 1998), but these have often been expensive or too complicated and intensive for widespread public health efforts (Greene & Rossi, 1998). In essence, there are two key methods in which fat intake may be manipulated to successfully reduce levels in the diet. The first is the 'substitution model', whereby the substitution of high-fat foods is made with reduced-fat products wherever possible. This method has been reported to be easily adopted and highly acceptable (Marckmann *et al.* 1994). The second strategy is the reduction of high-fat foods by choosing food types that are intrinsically low in fat, which can be described as the 'reduction model' (Hill *et al.* 1998). Although this method is a popular strategy used to reduce fat in the diet, long-term compliance with such diets is difficult for a variety of reasons; for example it is likely to reduce the palatability of the diet (Walker *et al.* 1996). In broader terms, the perceived health benefits of a lower fat intake have promoted a proliferation on the market of reduced-fat products.

Abbreviations: CRP, C-reactive protein; DINE, dietary instrument for nutrition education; HOMA, homeostasis model assessment; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; RCT, randomised controlled trial.

* **Corresponding author:** Dr Adrian Heald, fax +44 161 787 5989, email aheald@fs1.ho.man.ac.uk

In the present study of women identified as high fat consumers, we aimed to compare the efficacy of dietary intervention strategies to reduce fat in modifying established cardiovascular risk factors. These factors included insulin like growth factor (IGF)-1 which has recently been shown to be implicated in the pathogenesis of impaired glucose homeostasis and CVD (Heald *et al.* 2001; Sandhu *et al.* 2002) and the acute-phase reactant C-reactive protein (CRP), which is an independent risk factor shown to be strongly predictive of future cardiovascular events (Ridker *et al.* 2000, 2003). Furthermore we explored the impact of these interventions on anthropometric parameters.

Methods

Subjects

Volunteers were recruited from women who responded to posters displayed in the Leeds General Infirmary and University of Leeds campus, UK. Of the 207 volunteers who initially expressed an interest to enrol in the study, only 132 subjects were eligible (64 %). The remaining subjects were excluded as they were either not classified as high fat consumers according to the dietary instrument for nutrition education (DINE) questionnaire (*n* 64; 31 %) or had a history of eating disorders (*n* 6; 3 %) or had been pregnant within the previous 6 months (*n* 5; 2 %).

Of the 132 subjects who fulfilled the criteria, eighty-six provided written consent (65 %). Of the eighty-six eligible volunteers, five withdrew before completing any baseline data and one subject was excluded at visit 1 because her BMI was 18·1 kg/m^2, classified as underweight. Therefore, eighty subjects who enrolled on to the study attended visit 1 and were given the relevant intervention.

All individuals were aged 18 years or more and had a desire to change their diet. Stage of readiness to change their diet was assessed by using a 'stage of change' questionnaire (DiClemente & Prochaska, 1998). Based on a series of questions, the subjects were classified into one of the following stages:

(1) pre-contemplation, i.e. the subject was not eating a low-fat diet and had no intention to reduce their fat intake within the next 6 months;
(2) contemplation, i.e. the subject was not eating a low-fat diet but wanted to reduce their fat intake within the next 6 months;
(3) preparation, i.e. the subject was not eating a low-fat diet but has tried to reduce their fat intake and is prepared to continue trying over the next 6 months;
(4) action, i.e. the subject had been eating a low-fat diet for less than 6 months;
(5) maintenance, i.e. the subject had been eating a low-fat diet for more than 6 months.

The study was approved by Leeds Health Authority and the United Leeds Teaching Hospitals Research Ethics Committee.

The subjects who consented to participate were randomly allocated into one of the four intervention groups.

Substitution. The aim in this group was to substitute high-fat foods with reduced-fat alternatives.

The group was provided with detailed instructions regarding the replacement of traditional full-fat items with reduced-fat alternatives but to stay on their usual diet. Wherever possible they were not specifically instructed to purchase any particular food items that were not already part of their habitual diet. They were not asked to modify portion size of the food consumed. They were also asked to replace red meats with chicken or fish and to buy lean cuts of meat, where possible.

Reduction. This group was asked to cut down on high-fat foods and increase foods that are intrinsically low in fat and/or serve smaller portion sizes of high-fat foods. At each meal their aim was to decrease the portion size of foods high in fat and increase fibre-rich foods such as bread, pasta, rice, cereals and potatoes, without adding fat.

Combination. The aim in this group was to substitute high-fat foods with reduced-fat alternatives and also to cut down on fatty foods and increase fibre-rich food such as bread, pasta, rice, cereals and potatoes and/or serve smaller portion sizes of fatty foods.

Control. This group was asked to continue with their normal diet and no change was advocated for the period of the study.

No other additional recommendations were made regarding modification of other risk-relevant behaviours. Specifically, participants were specifically asked not to make any alterations in their day-to-day physical activity or exercise regimen.

Study method and procedure

Dietary instrument for nutrition education. The DINE was used to assess dietary fat intake (Roe *et al.* 1994). It was designed so that foods with a similar nutrient content and dietary use were grouped together. Scores were assigned to the food groups proportionally to the fat content of a standard portion size (Crawley, 1988). The scores were weighted by the frequency of consumption using four categories, ranging from 'less than once a week' to 'six or more times a week'. The DINE provides a quick assessment of an individual's diet by adding the scores relevant to the frequency of consumption of the groups of foods to give a total fat score. A total score is calculated and the respondents can be classified as low, medium or high fat consumers. However for randomised controlled trials (RCT), it is essential that the DINE is effective in predicting high fat consumers. To this end, Jackson *et al.* (2002) investigated the suitability of the DINE cut-off points for high fat consumers (Jackson *et al.* 2002). This involved comparing the DINE method to data from the UK Women's Cohort Study, which used a 217-item food-frequency questionnaire to classify subjects into equal tertiles, based on their reported absolute fat intake (Calvert *et al.* 1996). By selecting a new cut-off point of 25, the agreement between the DINE and the UK Women's Cohort Study classification was improved. Therefore, subjects who scored 25 or more using the DINE questionnaire were classified as high fat consumers. It was on the basis of this that the cut-off point of 25 for DINE score was used in the present study.

Our subjects completed a pre- and post-intervention DINE questionnaire to assess the changes in fat scores and hence fat consumption over the 3 months.

Food diary records. To assess dietary intake, each subject completed 4 d food and drink weighed diaries on three occasions; at the start of the study (baseline intakes), after 1 month and post-intervention (after 3 months). All food diaries were reviewed with the subject at the sessions to ensure clarity and completeness and to minimise the degree of under-reporting. This method of dietary assessment involved each subject recording (either weighing or recording in household measures) all foods and drinks consumed over a period of 4 d. It has been reported that using dietary diaries in a study with highly motivated subjects can be a very reliable and valid method of assessing dietary intake (De Castro, 1994). However, there are limitations of this method. There is the possibility of the subjects altering their eating behaviour, the diaries require a high degree of cooperation from subjects, continued motivation is required to complete the diaries accurately, and the diaries are time-consuming for researchers and therefore expensive to use. Additional problems are incurred with accurately recording food intake when meals are consumed outside the home. In addition, it has been estimated that 12 d of weighed food records are required in order to correctly classify subjects' fat intake, and for the precision to be within 10 % (Bingham, 1987). However, expecting volunteers to complete 12 d diaries is unrealistic and 4 d diaries are considered to provide a reasonable compromise between precision and practicality.

Participants were asked to complete the food diaries on 3 weekdays and 1 weekend day at baseline and at the 3-month follow-up.

Analysis of all diet records was performed using the McCance & Widdowson food tables (Holland *et al.* 1991) in the form of an in-house dietary package (Diet and Nutrition Tool for Evaluation; DANTE).

Body-weight data. Body weight was measured before the start of the study and at the end of the intervention. Participants were weighed fasted, in light clothes and without shoes or socks. Body-weight change was calculated for each subject to assess any impact of the intervention. The mean weight change for each group was compared with the other three groups to assess any differential effects. Subjects were weighed on a digital balance (AE MSP 200; Adams Equipment Inc., Danbury, CT, USA) accurate to 0·1 kg. Height (m) was measured at the baseline visit only.

Body-fat data. Percentage of body fat was measured before the start of the intervention and at the end of the intervention. Percentage body fat was calculated using the bioimpedance technique with a tetrapolar bioimpedance analyser BIA 2000-M body composition analyser (Data Input Co., Frankfurt, Germany). This provides highly advanced composition analysis for diagnostics and treatment. Measurement is based on the principle of bioelectrical impedance analysis. It utilises state-of-the-art technology, segmental bioelectrical impedance analysis and multi-frequency bioelectrical impedance analysis (Dittmar, 2003). All measurements were performed under strictly standardised conditions by one of the co-authors (C. G.) to avoid inter-observer and interdevice variability. All were fasted and had abstained from strenuous exercise for at least 24 h. Reliability of duplicate bioimpedance measurements as determined by technical error of measurement was high ($<0{\cdot}05$). Duplicate measurements were obtained at baseline and at the 3-month follow-up.

Changes in percentage body fat were calculated for each subject to assess any impact of the intervention. The mean change in percentage body fat for each group was compared to assess any differential effects of the different dietary interventions.

Laboratory methods. Fasting blood samples were collected from each subject before the start and at the end of the intervention. These samples were separated by centrifugation, frozen immediately and stored at -40°C. They were analysed for lipid profile, glucose, CRP, intact insulin, IGF-1 and IGF binding protein (IGFBP)-1.

Lipid profile and glucose were measured on Integra 700, an automated analyser used for all the routine biochemistry at Hope Hospital, Salford, UK. Within- and between-assay CV were $<2{\cdot}5$ % for the measurement of total cholesterol, HDL-cholesterol and triacylglycerols and <2 % for the measurement of glucose.

CRP was measured on Immulite by immunometric assay by a high-sensitivity CRP kit supplied by Diagnostic Products Corporation (Los Angeles, CA, USA). It has an analytical sensitivity of 0·1 mg/l and a functional sensitivity of $<0{\cdot}2$ mg/l. The antibody is highly specific for CRP. The method is linear and has good precision with CV of 5–10 %.

Insulin was measured by the immunometric method on Immulite with the kit supplied by Diagnostic Products Corporation (Los Angeles, CA, USA). The method has analytical sensitivity of 2 μIU/l (13·9 pmol/l). The inter- and intra-assay CV was <5 %. The antibody was highly specific with no cross-reactivity detectable. Insulin sensitivity was calculated by the homeostasis model assessment (HOMA)-sensitivity (S) formula (Matthews *et al.* 1985).

Baseline IGF-1 was measured by ELISA using the Diagnostic Products Corporation (Los Angeles, CA, USA) Immulite Autoanalyser. The limit of sensitivity of the assay is 20 ng/ml; within- and between-assay CV is <8 %. Fasting circulating IGFBP-1 concentration at baseline was determined by a previously reported antibody-based assay (Westwood *et al.* 1994) with a detection limit of 3 μg/l and within- and between-assay CV of <8 %.

Both biochemical and anthropometric data were analysed for the change in relation to dietary intervention and at both visits for the control group.

Statistics

Statistical analyses were carried out using the statistical package SPSS for Windows (release 10; SPSS Inc., Chicago, IL, USA). Non-normally distributed variables were logarithmically transformed before analysis by intervention group. Comparison of the differences between visits by intervention group was carried out by one-way ANOVA across all intervention groups and by paired *t* tests for comparison of the difference between visits for each individual intervention *v.* the control group. For univariate correlations

between continuous variables, Spearman correlations were used.

Results

Demographic data

The demographic data were similar in the four dietary intervention groups as shown in Table 1. There were no significant differences between any of the groups in age or ethnicity, baseline weight, BMI, smoking status or measured metabolic parameters.

Stage of change scores

There was no significant difference found between the groups in the stages of change questionnaire. Self-reported stage of change score was approximately 3 in each intervention group. This indicates that the subjects classified themselves in the preparation phase; they believed they were not eating a low-fat diet but had tried to reduce their fat intake and were prepared to continue trying over the next 6 months.

Weight and percentage body-fat changes

In Table 2 we have shown *P* values for comparison of difference between visits 1 and 2 for the ANOVA across all intervention groups (P^a) and for the comparison of difference between visits 1 and 2 for each intervention *v.* the control group (P^b).

For the substitution group there was a significant reduction in weight (mean −1·4 (95 % CI −2·4, −0·2) kg; $P=0·03$ for comparison of change with the control group). However, there was no significant weight change with the other interventions: reduction (−0·4 (95 % CI −1·3, 0·4) kg; NS for comparison of change with the control group); combination (0 (95 % CI −1·5, 1·5) kg; NS for

Table 1. Age and anthropometric and metabolic data at baseline
(Arithmetic mean values and 95 % confidence intervals)

	Substitution group		Reduction group		Combination group		Control		
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	*FP*
Age (years)	39·1	37·2, 44	44·5	37·2, 52	43·8	49·7, 38	45	38·7, 52·3	0·9 NS
BMI (kg/m^2)	30·4	27·3, 33·5	30·0	27·1, 32·9	32·0	28·8, 35·1	27·2	23·5, 31·0	2·1 NS
Body fat (%)	35·0	30·1, 39·1	35·3	31·5, 39·2	36·6	33·1, 40·1	31·8	28·1, 35·5	1·6 NS
White European (*n*)	19		19		18		18		NS
Other ethnic group* (*n*)	3		1		1		2		NS
DINE score	42·6	37·2, 48·1	35·4	32·2, 38·6	42·6	35·7, 49·5	35·4	30·2, 40·6	NS
SOC score	3·1	2·8, 3·3	2·8	2·6, 3·0	3·1	2·8, 3·4	3·0	2·9, 3·1	NS
Cholesterol (mM)	4·9	4·4, 5·3	5·2	4·8, 5·6	4·9	4·4, 5·4	5·2	4·6, 5·82	0·6 NS
Triacylglycerol (mM)	1·4	1·0, 1·7	1·3	1·0, 1·6	1·4	1·0, 1·7	1·0	0·8, 1·2	2·1 NS
LDL-cholesterol (mM)	2·9	2·5, 3·3	3·2	2·8, 3·6	3·0	2·5, 3·4	3·2	2·8, 3·7	0·7 NS
CRP (mg/l)	4·1	2·2, 6·0	2·7	1·4, 4·0	3·5	2·1, 4·8	3·3	0·4, 6·0	0·4 NS
Glucose (mM)	4·9	4·6, 5·3	5·4	4·7, 6·1	5·0	4·3, 5·6	4·8	4·4, 5·3	0·9 NS
Insulin (pmol/l)	87·1	62·2, 112·0	64·6	41·0, 88·2	90·7	67·1, 114·2	68·1	58·5, 67·8	1·1 NS
IGF-1	173·3	145·7, 201	171·2	129·4, 213	190·5	147, 234·1	195·4	153·4, 237·3	0·4 NS
IGFBP-1	28·5	15, 42·1	30·4	16·4, 44·3	27·1	9·2, 45	28·0	21·7, 34·4	0·04 NS

DINE, dietary instrument for nutrition education; SOC, stage of change; CRP, C-reactive protein; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.
* Other ethnic group refers to South Asian, African Caribbean or African ethnic origin.

Table 2. Baseline and post-intervention measurements and change between baseline and post-intervention measurements (post-intervention−baseline)*
(Mean values and 95 % confidence intervals)

	Baseline (*n* 80)		Post-intervention (*n* 69)		Mean change (*n* 69)			
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	P^a†	P^b‡
Weight (kg)								
Substitution	82·7	75·2, 88·9	81·3	70·6, 84·2	−1·4	−2·4, −0·2	0·14	0·03
Reduction	82·7	75·5, 89·8	82·3	74·7, 89·8	−0·4	−1·3, 0·4		0·28
Combination	88·0	79·2, 96·8	87·9	76·8, 97·2	0·0	−1·5, 1·5		0·85
Control	72·6	62·7, 82·5	72·8	60·8, 84·1	0·2	−0·7, 1·0		
Body fat (%)								
Substitution	35·9	32·1, 39·8	34·6	29·2, 36·6	−1·3	−2·0, −0·5	0·01	0·06
Reduction	35·4	31·7, 39·1	35·7	32·9, 39·7	0·3	−0·9, 1·5		0·12
Combination	37·4	34·1, 40·8	38·1	34·1, 42·4	0·7	−0·4, 1·8		0·03
Control	31·8	28·1, 35·5	31·0	26·4, 34·9	−0·8	−1·5, 0·0		

* For details of subjects and procedures, see Table 1 and p. 810.
† Overall test comparing differences between visits 1 and 2 by intervention group (one-way ANOVA).
‡ Comparing differences between visits 1 and 2 for each intervention group *v.* the control group (*t* test).

comparison of change with the control group); control (0·2 (95 % CI −0·7, 1·0) kg; NS for comparison of change with the control group).

A similar effect was seen for percentage body fat, with the substitution group having a significant reduction in percentage body fat (−1·3 (95 % CI −2·0, −0·5) %; $P=0·01$ for comparison of change with all other groups). No significant change was seen in the other two intervention groups: reduction group (0·3 (95 % CI −0·9, 1·5) %); combination group (0·7 (95 % CI −0·4, 1·8) %); control group (−0·8 (95 % CI −1·5, 0·1) %). There was a trend for the substitution intervention to cause a reduction in percentage body fat when compared with the control group ($P=0·06$).

Fat intake

There was no difference in total fat or saturated fat intake at baseline between the groups (data not shown). There was an overall significant difference between the groups and change in DINE score after 3 months ($P<0·01$). The substitution group showed the greatest change with a decrease in the mean DINE score of 24 (95 % CI 17, 31) ($P<0·01$). The other groups also showed a significant decrease in DINE score: reduction group (13 (95 % CI 8, 17); $P<0·01$); combination group (20 (95 % CI 12, 27); $P<0·01$); control group (4 (95 % CI 0, 7); $P=0·03$).

Biochemical data

Fasting triacylglycerols (change of −0·2 (SEM 0·07) mmol/l; $P=0·04$) fell with the substitution intervention as did CRP levels (0·8 (SEM 0·2) mg/l; $P=0·04$ (−24·3 (SEM 8) %) (Fig. 1), but not with the other interventions. There was a trend for fasting cholesterol to fall with substitution (−0·3 (SEM 0·08) mmol/l; $P=0·06$) but not with the other interventions (Fig 1 (b)). No significant change in HDL-cholesterol was seen with any intervention.

Circulating IGF-1 rose significantly with the substitution (31 (SEM 17) ng/ml) and reduction interventions (19 (SEM 10) ng/ml) ($P=0·02$) (Fig. 2). No change was found with IGFBP-1. There was no significant change in fasting insulin, fasting glucose or HOMA-S with any intervention between visits 1 and 2.

Correlations between measured metabolic and anthropometric variables

IGF-1 levels were inversely associated with serum triacylglycerols, cholesterol and CRP concentrations and also with fasting glucose levels. IGF-1 correlated negatively with BMI and percentage body fat. A lower level of fasting IGFBP-1 was associated with higher CRP, fasting glucose and percentage body fat. As previously reported, IGFBP-1 correlated negatively with BMI and insulin (Table 3).

There was a strong positive relationship between CRP and fasting glucose, insulin, BMI and percentage body fat. CRP was not associated significantly with cholesterol or triacylglycerols levels. Reduction in weight positively correlated with reduction in triacylglycerols (Spearman's ρ 0·27; $P=0·03$) and cholesterol level (ρ 0·27; $P=0·03$) (Figs. 3 (a) and (b)).

Discussion

In the present study we have determined that the substitution model of dietary intervention is effective even over a relatively short interval of time in reducing weight, percentage body fat and fat consumption (as measured by the DINE questionnaire), together with fasting serum concentrations of triacylglycerols and CRP with a consequent improvement in cardiovascular profile.

The reduction seen in CRP is of a similar order to that seen in a recent study in which male dyslipidaemic subjects were given 15 ml linseed oil (rich in α-linoleic acid and with a high *n*-3:*n*-6 fatty acid ratio) per d and a reduction of 38 % in CRP was achieved (Rallidis *et al.* 2003). The recently published study of Kaaks *et al.* (2003) in forty-nine women showed no change in circulating IGF-1 and an increase in IGFBP-1. However, they used a reduction

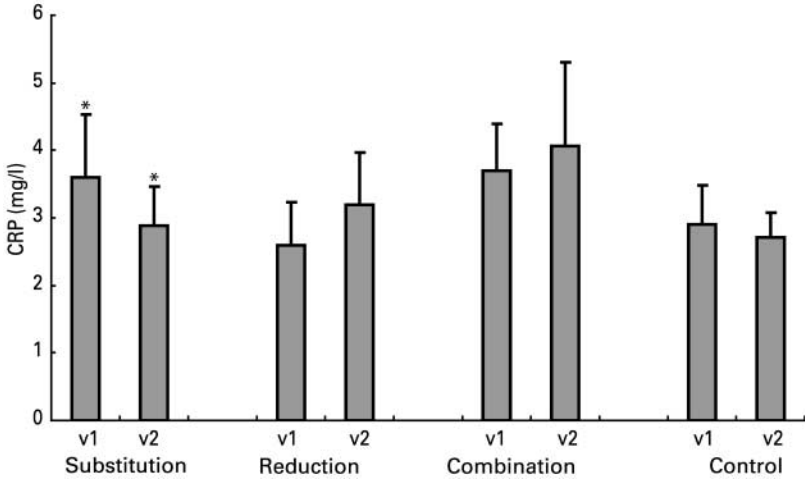

Fig. 1. Serum C-reactive protein (CRP) concentration at visit 1 (v1) and visit 2 (v2) for each intervention group. Values are means, with standard errors of the mean represented by vertical bars. *Mean values were significantly different ($P=0·04$).

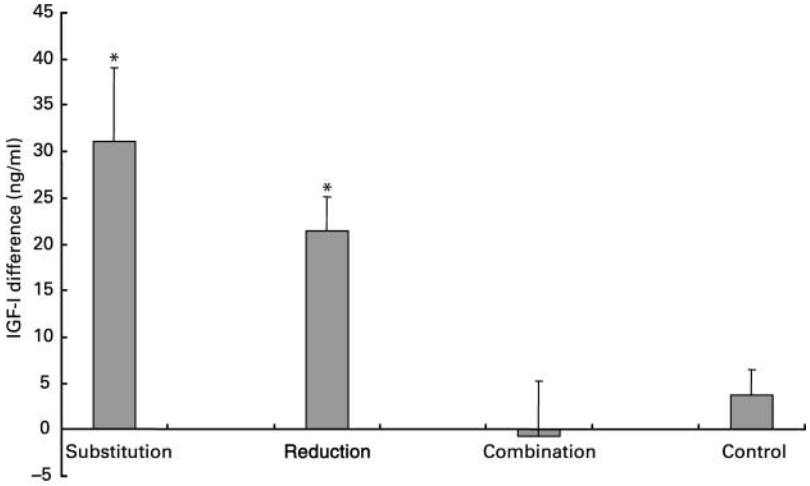

Fig. 2. Percentage change in circulating insulin-like growth factor (IGF)-1 from visit 1 to visit 2 (as a percentage of visit 1 circulating concentration) plotted for each intervention group. Values are means, with standard errors of the mean represented by vertical bars. *Mean value was significantly different from that at baseline ($P=0{\cdot}01$).

rather than a substitution model of dietary intervention, involving reductions in the intake of total fat and refined carbohydrates and an increase in the dietary ratio of *n*-3:*n*-6 plus saturated fatty acids.

Despite continuing recommendations to reduce fat intake and several national bodies highlighting the health risks, the UK population average intake of dietary fat still remains high. It is clear that the present strategies for modifying population fat intake are not as successful as public health nutritionists would desire. Thus there is a need for further interventions to promote successful dietary change (Department of Health, 1999). A number of systematic reviews have been carried out on the effects of advice concerning low-fat diets (Pirozzo *et al.* 2003) and the effects of a reduction or modification in dietary fat intake on CVD (Hooper *et al.* 2001). Reducing fat intake is a specific lifestyle change and need not necessarily be associated with weight reduction *per se*. In a recent meta-analysis of low-fat diets, Astrup *et al.* (2000) concluded that dietary fat restriction prevented weight gain in participants of normal weight and produced weight loss in overweight participants. The systematic review by Pirozzo *et al.* (2003) assessed the effects of advice about low-fat diets as a means of achieving sustained weight loss. This review focused primarily on participants who were overweight or clinically obese and were dieting for the purposes of weight reduction. They concluded that in overweight or obese individuals who are dieting for the purpose of weight reduction, low-fat diets are as efficacious as other weight-reducing diets for achieving sustained weight loss but not more so. Hooper *et al.* (2001) stated that there is a small but potentially important reduction in cardiovascular risk with the reduction or modification of dietary fat intake, seen particularly in trials of longer duration.

The use of low-fat foods has been reported to be easily adopted and highly acceptable, and to be one of the most effective approaches to reduce fat intake (Keenan *et al.* 1996). The present study confirmed for the first time using an RCT that in this British population the substitution model was most effective. A combination of strategies has also been considered likely to offer the best chance of successfully reducing levels of fat in the diet. However, in the present study this was not the case. Perhaps, this model may have proved difficult to comply with due to the greater complexity of the messages regarding dietary change. The absence of a significant difference

Table 3. Associations between measured metabolic and anthropometric variables†
(Spearman correlations)

	Triacylglycerol	Cholesterol	CRP	Glucose	Insulin	IGF-1	IGFBP-1	BMI	Percentage body fat
Triacylglycerol	1·00	0·435**	0·204	0·159	0·445**	−0·367**	−0·157	0·300**	0·214
Cholesterol		1·00	−0·038	0·129	0·068	−0·341**	0·000	0·064	0·069
CRP			1·00	0·241**	0·339*	−0·251*	−0·285*	0·605*	0·614**
Glucose				1·00	0·355**	−0·311**	−0·322**	0·373**	0·371**
Insulin					1·00	−0·189	−0·580**	0·655**	0·555**
IGF-1						1·00	0·014	−0·278*	−0·346**
IGFBP-1							1·00	−0·607**	−0·537**
BMI								1·00	0·927**
Percentage body fat									1·00

CRP, C-reactive protein; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.
*$P<0{\cdot}05$, **$P<0{\cdot}01$.
† For details of subjects and procedures, see Table 1 and p. 810.

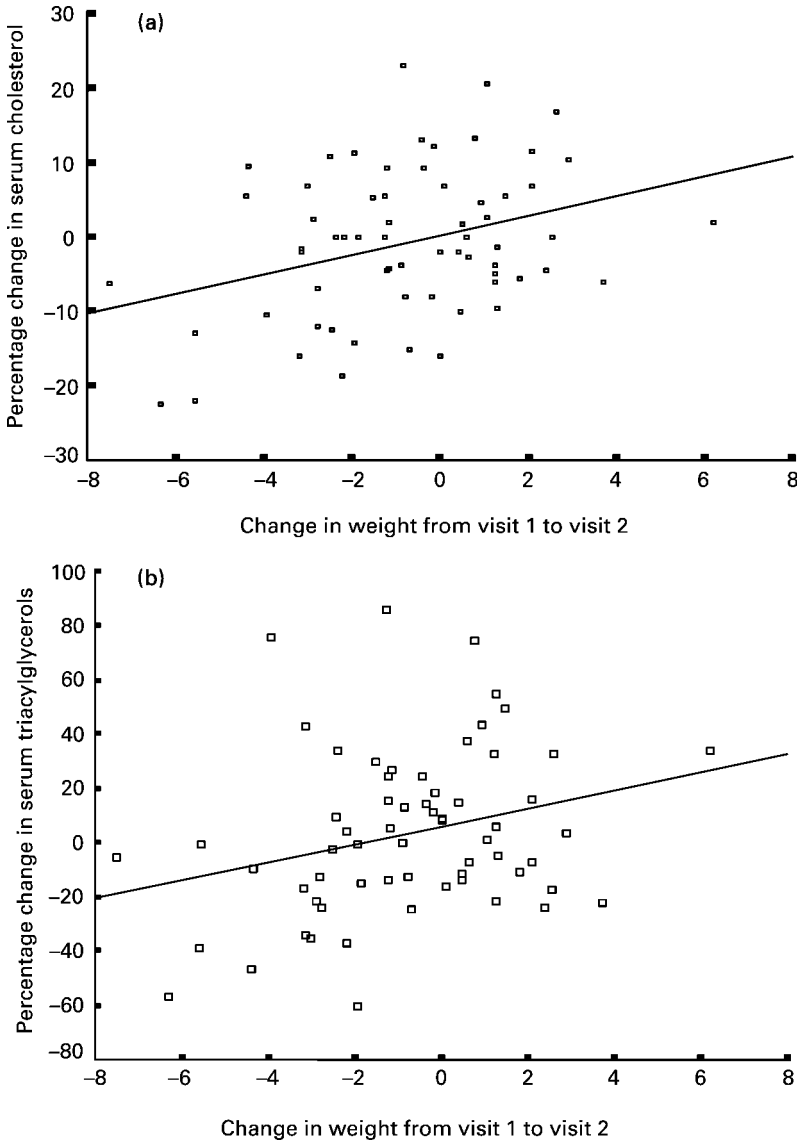

Fig. 3. (a) Scatterplot of change in weight *v.* percentage change in fasting serum cholesterol (r^2 0·11). (b) Scatterplot of change in weight *v.* percentage change in fasting serum triacylglycerols (r^2 0·09).

between the change in percentage body fat for the substitution intervention *v.* the control group is in our view a type 2 error related to sample size. The control group subjects were not given any specific advice about alteration in diet or activity levels. There was no change in intake of total fat or saturated fat in the control group during the study (data not shown).

As scientific evidence mounts for recommendations of a low-fat diet, there is a pressing need for more effective and less costly dietary change interventions. Little is known about how dietary interventions modify fat intake in the free-living population. This is because most of the previous studies that have observed a reduction in fat intake have focused on experimental manipulation of fat intakes in the laboratory setting, have been carried out over short periods of time and have used intensive and repeated group education, which can be extremely time-consuming (Gorbach *et al.* 1990). However, in the present study we have shown that such modifications reduce the intake of fat in free-living populations within the UK.

A reduction of fat is likely to reduce the palatability of the diet, which has been found to be an important barrier to adopting such diets (Lloyd *et al.* 1995). Our finding that the reduction and combination models did not result in any significant change in lipid or CRP levels suggests that compliance with these interventions was poorer than with the substitution model. The combination model may have proved difficult to comply with due to the greater complexity of the messages regarding dietary change. The reduction model, where high-fat foods are omitted from the diet and replaced by other food groups such as fruit and vegetables or bread and potatoes, is a popular strategy promoted in much of the available dietary literature on reducing fat intake (Kristal *et al.* 1992). The evidence presented here strongly supports the adoption of the substitution model because of its greater efficacy.

Although not all individuals who consume a high-fat diet are fat (Cooling & Blundell, 2000), it may be that dietary fat is a particular risk factor for obesity in a susceptible sub-population or phenotype (Astrup *et al.* 1994). In the present study, the utilisation of the DINE questionnaire to identify high fat consumers combined with the effectiveness of the substitution dietary intervention model in reducing CRP and increasing IGF-1 levels is particularly important. This is because of the close association of high CRP with obesity (Festa *et al.* 2001) and low circulating IGF-1 with the subsequent development of impaired glucose handling (Sandhu *et al.* 2002).

In these participants, baseline lipid levels were significantly below those at which intervention would conventionally be deemed necessary (Wood *et al.* 1998), although they did reflect average population values and, even so, significant changes were observed. This would suggest that the substitution model has potential utility for improving fasting lipids in individuals with a dyslipidaemic profile according to accepted definitions.

The positive cross-sectional associations between CRP and fasting glucose, fasting insulin, BMI, and percentage body fat are in accordance with results from the Insulin Resistance and Atherosclerosis Study where strong associations were found between CRP and measures of body fat (BMI, waist circumference), insulin resistance and fasting insulin (Festa *et al.* 2000). We have recently shown that IGF-1 and CRP independently contribute to variation in insulin sensitivity (Heald *et al.* 2003*a*) with low IGF-1 levels being associated with elevated circulating CRP. The negative correlations here between IGF-1 and CRP and between IGF-1 and other markers of cardiovascular risk concur with this and also with the finding that a low circulating IGF-1 is associated with the increased risk of diabetes and myocardial infarction (Vaessen *et al.* 2001). Although lower circulating IGFBP-1 levels are well known to be associated with a more adverse cardiovascular risk profile (Janssen *et al.* 1998), the very strong relationship between low IGFBP-1 and percentage body fat found in the present study is further evidence for a profound impact of increasing adiposity on IGFBP-1 production, an association that was independent of circulating insulin levels.

The significant increase in IGF-1 with both the substitution and reduction of dietary saturated fat is intriguing in the view of the potential long-term benefits of increased circulating IGF-1 on insulin sensitivity and cardiovascular risk (Heald *et al.* 2001, 2003*a*), although we did not see any measurable changes in HOMA-S in the present short-term study. IGF-1 production by hepatocytes is known to be up regulated by insulin at the level of hepatic gene transcription (Phillips *et al.* 1991; Pao *et al.* 1992). One possible mechanism for the increase in circulating IGF-1 seen in the present study may be a reduction in hepatic portal non-esterified fatty acid concentration which in turn results in improved insulin sensitivity at the liver (Cruickshank *et al.* 2001) and so improved responsiveness of hepatocytes to hepatic portal insulin.

Health promotion strategies have been devised to encourage a reduction in fat consumption by the population. Much of the research in dietary intervention has focused on the experimental manipulation of fat intakes in the laboratory setting and over short periods of time (Caputo & Mattes, 1992; Foltin *et al.* 1992*a*,*b*; Blundell *et al.* 1993). There remain important issues concerning longer-term adherence to dietary intervention strategies, which are relevant when the results of structured studies are generalised to the population at large (White *et al.* 1992). It is also pertinent to explore motivations behind changes in fat consumption at an individual level and the impact that dietary intervention has from a psychological perspective. This is the first RCT to explore the effectiveness of the two main methods of reducing fat in the diet; substitution with reduced-fat products or reduction of total fat.

Although the present study was a small-scale RCT, RCT are the best way of measuring the efficacy of intervention because of their ability to minimise bias and avoid false conclusions. A second strength of the study was the multiple measures of dietary change. The random assignment of subjects to different intervention groups was a good way of achieving a balance between the groups for the known and unknown factors that influence outcome (Stephenson & Imrie, 1998). The inclusion of a control group greatly aided the interpretation of the results. The limitations of the present RCT include feasibility and relevance to the real world, which are factors in most study designs. It was not feasible to examine the maintenance of changes beyond 3 months within the present study and it is not necessarily generalisable to the general population as the participants were high fat consumers at baseline assessed by the DINE questionnaire, were highly motivated and had an interest in health to inspire them to volunteer for research studies.

In conclusion, the efficacy of the substitution intervention in reducing body weight, total fat and energy consumption, fasting cholesterol and triacylglycerols and CRP in the study is important in that this model could potentially be applied to a larger population sample. Furthermore, the previously described relationships between IGF and IGFBP levels and macronutrient intake (Hellenius *et al.* 1995; Heald *et al.* 2003*b*) suggest that IGF bioavailability may be modifiable by dietary intervention. Thus the present findings have important preventative and therapeutic implications for managing disease risk within the population in the future.

Acknowledgements

Funding sources were the Department of Nutrition and Nuffield Institute for Health, University of Leeds and the Department of Diabetes and Endocrinology, Salford Royal Hospitals NHS Trust. There were no conflicts of interest.

References

Anonymous (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383–1389.

Astrup A, Buemann B, Western P, Toubro S, Raben A & Christensen NJ (1994) Obesity as an adaptation to a high-fat diet: evidence from a cross-sectional study. *Am J Clin Nutr* **59**, 350–355.

Astrup A, Grunwald GK, Melanson EL, Saris WH & Hill JO

(2000) The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. *Int J Obes Relat Metab Dis* **24**, 1545–1552.
Bingham SA (1987) The dietary assessment of individuals; methods, accuracy, new techniques and recommendations. *Nutr Abstr Rev* **57**A 705–742.
Blundell JE, Burley VJ, Cotton JR & Lawton CL (1993) Dietary fat and the control of energy intake: evaluating the effects of fat on meal size and post-meal satiety. *Am J Clin Nutr* **57**, Suppl. 5, 772S–777S, 777S–778S.
Calvert C, Cade JE, Woodhouse A, Barrett J & UKWCS Steering Group (1996) Food frequency questionnaire (FFQ) interpretation and analysis: issues for the UK Women's Cohort Study. *Proc Nutr Soc* **56**, 17A.
Caputo FA & Mattes RD (1992) Human dietary responses to covert manipulations of energy, fat, and carbohydrate in a midday meal. *Am J Clin Nutr* **56**, 36–43.
Cooling J & Blundell JE (2000) Lean male high- and low-fat phenotypes – different routes for achieving energy balance. *Int J Obesity* **24**, 1561–1566.
Crawley H (1988) *Food Portion Sizes*. London: H.M. Stationery Office.
Cruickshank JK, Heald AH, Anderson S, *et al.* (2001) Epidemiology of the insulin-like growth factor system in three ethnic groups. *Am J Epidemiol* **154**, 504–513.
De Castro JM (1994) Methodology, correlation analysis, and interpretation of diet diary records of the food and fluid intake of free-living humans. *Appetite* **23**, 179–192.
Department of Health (1999) *Saving Lives: Our Healthier Nation*. London: The Stationery Office.
DiClemente CC & Prochaska JO (1998) Toward a comprehensive, transtheoretical model of change: stages of change and addictive behaviors. In *Treating Addictive Behaviors*, 2nd ed. pp. 3–24 [WR Miller and N Heather, editors]. New York: Plenum Press.
Dittmar M (2003) Reliability and variability of bioimpedance measures in normal adults: effects of age, gender, and body mass. *Am J Phys Anthropol* **122**, 361–370.
Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W & Gotto AM Jr (1998) Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* **279**, 1615–1622.
Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP & Haffner SM (2000) Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* **102**, 42–47.
Festa A, D'Agostino R Jr, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP & Haffner SM (2001) The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord* **25**, 1407–1415.
Fidanza F, Puddu V, Imbimbo AB, Menotti A & Keys A (1970) Coronary heart disease in seven countries. VII. Five-year experience in rural Italy. *Circulation* **41**, Suppl. 4, I63–I75.
Foltin RW, Rolls BJ, Moran TH, Kelly TH, McNelis AL & Fischman MW (1992*a*) Caloric, but not macronutrient, compensation by humans for required-eating occasions with meals and snack varying in fat and carbohydrate. *Am J Clin Nutr* **55**, 331–342.
Foltin RW, Rolls BJ, Moran TH, Kelly TH, McNelis AL & Fischman MW (1992*b*) Caloric, but not macronutrient, compensation by humans for required-eating. Erratum. *Am J Clin Nutr* **56**, 954.
Gorbach SL, Morrill-LaBrode A, Woods MN, *et al.* (1990) Changes in food patterns during a low-fat dietary intervention in women. *J Am Diet Assoc* **90**, 802–809.
Grande F, Anderson JT & Keys A (1970) Comparison of effects of palmitic and stearic acids in the diet on serum cholesterol in man. *Am J Clin Nutr* **23**, 1184–1193.
Greene GW & Rossi SR (1998) Stages of change for reducing dietary fat intake over 18 months. *J Am Diet Assoc* **98**, 529–534.
Heald AH, Anderson SG, Ivison F, Laing I, Gibson JM & Cruickshank JK (2003*a*) C-reactive protein and the insulin-like growth factor (IGF)-system in relation to risk of cardiovascular disease in different ethnic groups. *Atherosclerosis* **170**, 79–86.
Heald AH, Cade JE, Cruickshank JK, Anderson S, White A & Gibson JM (2003*b*) The influence of dietary intake on the insulin-like growth factor (IGF) system across three ethnic groups: a population-based study. *Public Health Nutr* **6**, 175–181.
Heald AH, Cruickshank JK, Riste LK, *et al.* (2001) Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations. *Diabetologia* **44**, 333–339.
Hellenius ML, Brismar KE, Berglund BH & de Faire U (1995) Effects on glucose tolerance, insulin secretion, insulin-like growth factor 1 and its binding protein, IGFBP-1, in a randomized controlled diet and exercise study in healthy, middle-aged men. *J Intern Med* **238**, 121–130.
Hill JO, Seagle HM, Johnson SL, Smith S, Reed GW, Tran ZV, Cooper D, Stone M & Peters JC (1998) Effects of 14 d of covert substitution of olestra for conventional fat on spontaneous food intake. *Am J Clin Nutr* **67**, 1178–1185.
Holland B, Welch AA, Unwin ID, Buss DH, Paul AA & Southgate DAT (1991) *McCance and Widdowson's The Composition of Foods*, 5th ed. Cambridge and London: Royal Society of Chemistry and Ministry of Agriculture, Fisheries and Food.
Hooper L, Summerbell CD, Higgins JP, Thompson RL, Capps NE, Smith GD, Riemersma RA & Ebrahim S (2001) Dietary fat intake and prevention of cardiovascular disease. *BMJ* **322**, 757–763.
Jackson SL, Golding C, Greenwood DC, Cade JE & Hirst SE (2002) Development of a new cut-off point to distinguish between high-fat and medium-fat consumers using the Dietary Instrument for Nutrition Education questionnaire. *Proc Nutr Soc* **61**, 138A.
Janssen JAMJL, Stolk RP, Pols HAP, Grobbee DE & Lamberts SWJ (1998) Serum total IGF-I, free IGF-I and IGFBP-1 levels in an elderly population. *Arterioscler Thromb Vasc Biol* **18**, 277–282.
Kaaks R, Bellati C, Venturelli E, Rinaldi S, Secreto G, Biessy C, Pala V, Sieri S & Berrino F (2003) Effects of dietary intervention on IGF-I and IGF-binding proteins, and related alterations in sex steroid metabolism: the Diet and Androgens (DIANA) Randomised Trial. *Eur J Clin Nutr* **57**, 1079–1088.
Keenan DP, Achterberg C, Kris-Etherton PM, AbuSabha R & Von Eye A (1996) Use of qualitative and quantitative methods to define behavioral fat-reduction strategies and their relationship to dietary fat reduction in the patterns of dietary change study. *J Am Diet Assoc* **96**, 1245–1250, 1253.
Keys A (1975) Coronary heart disease – the global picture. *Atherosclerosis* **22**, 149–192.
Kristal AR, White E, Shattuck AL, Curry S, Anderson GL, Fowler A & Urban N (1992) Long-term maintenance of a low-fat diet: durability of fat-related dietary habits in the Women's Health Trial. *J Am Diet Assoc* **92**, 553–559.
Lawton CL, Delargy HJ, Smith FC, Hamilton V & Blundell JE (1998) A medium-term intervention study on the impact of high- and low-fat snacks varying in sweetness and fat content: large shifts in daily fat intake but good compensation for daily energy intake. *Br J Nutr* **80**, 49–61.
Lloyd HM, Paisley CM & Mela DJ (1995) Barriers to the adoption of reduced-fat diets in a UK population. *J Am Diet Assoc* **95**, 316–322.

Marckmann P, Sandstrom B & Jespersen J (1994) Low-fat, high-fiber diet favorably affects several independent risk markers of ischemic heart disease: observations on blood lipids, coagulation, and fibrinolysis from a trial of middle-aged Danes. *Am J Clin Nutr* **59**, 935–939.

Matthews DR, Hosker JB, Rudenski AS, Naylor BA, Treacher DF & Turner RC (1985) Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419.

Pao CI, Farmer PK, Begovic S, Goldstein S, Wu GJ & Phillips LS (1992) Expression of hepatic insulin-like growth factor-I and insulin-like growth factor binding protein-1 genes is transcriptionally regulated in streptozotocin-diabetic rats. *Mol Endocrinol* **6**, 969–977.

Phillips LS, Goldstein S & Pao CI (1991) Nutrition and somatomedin. XXVI. Molecular regulation of IGF-I by insulin in cultured rat hepatocytes. *Diabetes* **40**, 1525–1530.

Pirozzo S, Summerbell C, Cameron C & Glasziou P (2003) Should we recommend low fat diets for obesity? *Obes Rev* **4**, 83–90.

Rallidis LS, Paschos G, Liakos GK, Velissaridou AH, Anastasiadis G & Zampelas A (2003) Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. *Atherosclerosis* **167**, 237–242.

Ridker PM, Buring JE, Cook NR & Nader Rifai N (2003) C-Reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* **107**, 391–397.

Ridker PM, Hennekens H, Buring JE & Rifai N (2000) C-reactive protein and other markers of inflammation in prediction of cardiovascular disease in women. *Circulation* **342**, 836–843.

Roe L, Strong C, Whiteside C, Neil A & Mant D (1994) Dietary intervention in primary care: validity of the DINE method for diet assessment. *Fam Pract* **11**, 375–381.

Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB & Wareham NJ (2002) Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. *Lancet* **359**, 1740–1745.

Sever PS, Dahlof B, Poulter NR, *et al.* (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* **361**, 1149–1158.

Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH & Packard CJ (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* **333**, 1301–1307.

Stephenson J & Imrie J (1998) Why do we need randomised controlled trials to assess behavioural interventions? *BMJ* **316**, 611–613.

Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA & van Duijn CM (2001) A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. *Diabetes* **50**, 637–642.

Walker KZ, O'Dea K, Johnson L, Sinclair AJ, Piers LS, Nicholson GC & Muir JG (1996) Body fat distribution and non-insulin-dependent diabetes: comparison of a fiber-rich, high-carbohydrate, low-fat (23 %) diet and a 35 % fat diet high in monounsaturated fat. *Am J Clin Nutr* **63**, 254–260.

Westwood M, Gibson JM, Davies AJ, Young RJ & White A (1994) The phosphorylation pattern of insulin-like growth factor binding protein-1 in normal plasma is different from that in amniotic fluid and changes during pregnancy. *J Clin Endocrinol Metab* **79**, 1735–1741.

White E, Shattuck AL, Kristal AR, Urban N, Prentice RL, Henderson MM, Insull W Jr, Moskowitz M, Goldman S & Woods MN (1992) Maintenance of a low-fat diet: follow-up of the Women's Health Trial. *Cancer Epidemiol Biomarkers Prev* **1**, 315–323.

Wood DA, Durrington P, McInnes G, Poulter N, Rees A & Wray R (1998) Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* **80**, S1–S29.