

# Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial.

Citation for published version (APA):

Gogebakan, O., Kohl, A., Osterhoff, M. A., van Baak, M. A., Jebb, S. A., Papadaki, A., Martinez, J. A., Handjieva Darlenska, T., Hlavaty, P., Weickert, M. O., Holst, C., Saris, W. H., Astrup, A., & Pfeiffer, A. F. (2011). Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. *Circulation*, *124*(25), 2829-2838. <https://doi.org/10.1161/CIRCULATIONAHA.111.033274>

## Document status and date:

Published: 20/12/2011

## DOI:

[10.1161/CIRCULATIONAHA.111.033274](https://doi.org/10.1161/CIRCULATIONAHA.111.033274)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Effects of Weight Loss and Long-Term Weight Maintenance With Diets Varying in Protein and Glycemic Index on Cardiovascular Risk Factors

### The Diet, Obesity, and Genes (DiOGenes) Study: A Randomized, Controlled Trial

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**Background**—We sought to separately examine the effects of either weight loss or diets varying in protein content and glycemic index without further changes in body weight on cardiovascular risk factors within the Diet, Obesity, and Genes study (DiOGenes).

**Methods and Results**—DiOGenes is a pan-European controlled dietary intervention study in 932 overweight adults who first lost body weight on an 8-week low-calorie diet and were then randomized to 1 of 5 ad libitum diets for 26 weeks. The diets were either high or low protein or high or low glycemic index in 4 combinations or control. Weight loss (−11.23 kg; 95% confidence interval, −11.54 to −10.92;  $P<0.001$ ) reduced high-sensitivity C-reactive protein (−1.15 mg/L; 95% confidence interval, −1.30 to −0.41;  $P<0.001$ ), low- and high-density lipoprotein cholesterol, triglycerides, and blood pressure. During the 26-week weight maintenance period in the intention-to-treat analysis, the further decrease of high-sensitivity C-reactive protein blood levels was −0.46 mg/L greater (95% confidence interval, −0.79 to −0.13) in the groups assigned to low-glycemic-index diets than in those on high-glycemic-index diets ( $P<0.001$ ). Groups on low-protein diets achieved a −0.25 mg/L greater reduction in high-sensitivity C-reactive protein (95% confidence interval, −0.59 to −0.17) than those on high-protein diets ( $P<0.001$ ), whereas lipid profiles and blood pressure were not differently affected.

**Conclusions**—This large-scale intervention study clearly separates weight loss from dietary composition-related effects. Low-glycemic-index carbohydrates and, to a lesser extent, low-protein intake may specifically reduce low-grade inflammation and associated comorbidities in overweight/obese adults.

**Clinical Trial Registration**—<http://www.clinicaltrials.gov>. Unique identifier: NCT00390637. (*Circulation*. 2011;124:2829-2838.)

**Key Words:** cardiovascular diseases ■ cardiovascular risk factors ■ C-reactive protein ■ diet ■ inflammation

Dietary composition significantly influences cardiovascular risk factors and outcomes under ad libitum (free access to food/diets and type of nutrients) conditions, as reported in several observational and intervention

studies.<sup>1-4</sup> Although the role of different types of fat has been addressed in numerous studies, the roles of carbohydrate quality and of protein intake are less well established.

Received March 21, 2011; accepted September 29, 2011.

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.033274/-DC1>.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.033274

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**Clinical Perspective on p 2838**

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Although a high glycemic index is related to postprandial hyperglycemia and a greater release of insulin, which may lead to an unfavorable impact on other cardiovascular risk factors,<sup>5</sup> a lower glycemic index was correlated with favorable effects on blood lipids, particularly low-density lipoprotein cholesterol and triglycerides and a lower level of high-sensitivity C-reactive protein (hsCRP) as a marker of low-grade inflammation.<sup>6–8</sup> hsCRP was shown to correlate with the risk of cardiovascular events and type 2 diabetes mellitus in prospective studies.<sup>9,10</sup>

Dietary protein improves postprandial satiety,<sup>11</sup> and higher intakes may be associated with improved weight maintenance.<sup>12</sup> There is an ongoing controversy about the effects of dietary protein on glucose metabolism. Several studies showed that dietary protein, apart from saturated fatty acids, which may accompany animal protein in meat and cheese, itself seems to cause insulin resistance in both cross-sectional<sup>13</sup> and experimental studies.<sup>14–16</sup> Other studies showed that an increased protein content of up to 30% of energy intake has beneficial effects on postprandial and fasting plasma glucose concentrations, particularly in insulin-resistant subjects.<sup>17,18</sup> Favorable effects of high-protein intake on blood pressure and blood lipids were described in subjects with elevated cardiovascular risk factors,<sup>1</sup> but effects on inflammatory markers were not investigated in large human studies.

The role of the glycemic index and protein intake on cardiovascular risk markers in healthy but overweight and obese subjects under non-energy-restricted conditions has not been investigated in a large cohort. The design of the Diet, Obesity, and Genes study (DiOgenes), a multicenter, pan-European study, imposed an initial weight loss period of at least 8% of body weight in overweight and obese subjects followed by a 26-week dietary intervention period serving as a weight maintenance phase. Four different diets were compared with either high or low glycemic index or protein content, and an additional healthy diet according to national guidelines served as a background control. Table 1 shows the targeted macronutrient composition of the diets. The participants were provided with commercially available food, recipes, cooking and behavioral advice, and a point-based teaching system to achieve the targeted macronutrient compositions.<sup>19</sup> The primary hypothesis of the study was that one of these diets may be more beneficial for weight maintenance after the initial weight loss period than the others. As recently published, the participants in the low-glycemic-index/high-protein group were able to maintain their weight most successfully during the 26-week diet intervention phase.<sup>20</sup>

Weight loss is known to be associated with substantial improvements in blood lipids and inflammatory biomarkers.<sup>21</sup> Our DiOgenes study design clearly separates effects from weight loss from those due to different dietary intakes in the weight maintenance period. Therefore, the aim of the present study was to investigate whether improvements in hsCRP, triglycerides, total cholesterol, high-density lipopro-

tein cholesterol, and low-density lipoprotein cholesterol as well as blood pressure after the initial weight loss period can be maintained or even further improved with diets differing in protein content and glycemic index and whether these diets elicit additional weight loss-independent effects.

## Methods

### Participants

The study protocol was approved by the local ethical committees of each center, and all subjects provided written informed consent. Volunteer families from 8 European countries (Netherlands, Denmark, United Kingdom, Greece, Spain, Germany, Bulgaria, and the Czech Republic) were enrolled from November 2005 to April 2007 by various recruitment strategies. Families (2-parent or single-parent) who were generally healthy with at least 1 parent overweight (body mass index  $\geq 27$  kg/m<sup>2</sup>) and aged <65 years and with at least 1 child aged between 5 and 18 years were eligible for the study. Exclusion criteria for adults were body mass index >45 kg/m<sup>2</sup>, liver or kidney diseases, cardiovascular diseases, diabetes mellitus (type 1 or type 2), special diets/eating disorders, systemic infections/chronic diseases, cancer within the last 10 years, weight change >3 kg within the previous 3 months, and other clinical disorders or use of prescription medication that might interfere with the outcome of the study. A detailed description of inclusion and exclusion criteria has been published.<sup>19</sup>

### Study Design

After the first clinical investigation day (pre-low-calorie diet) with baseline measurements, eligible adults followed an 8-week low-calorie diet (Modifast, Nutrition et Santé, France) consisting of 800 kcal/d. In addition, 200 g of vegetables per day was allowed. Weight loss, compliance, and adverse events were checked at regular intervals during the low-calorie diet. Adults who achieved a weight loss of  $\geq 8\%$  after 8 weeks underwent the second clinical investigation day (post-low-calorie diet), and the respective family was randomized to 1 of 5 ad libitum diets differing in protein content and glycemic index: (1) low protein, low glycemic index; (2) low protein, high glycemic index; (3) high protein, low glycemic index; (4) high protein, high glycemic index; and (5) control diet according to accepted national dietary guidelines. Because we sought to specifically investigate the effects of low- versus high-glycemic-index diets as well as low- versus high-protein diets, the control diet served as a background healthy diet only. At the 8 participating study centers (Maastricht, Copenhagen, Cambridge, Heraklion, Potsdam, Pamplona, Sofia, and Prague), the participating families received dietary instruction for a 26-week period. Subjects were invited to the clinical investigation days after at least 10-hour overnight fasts and were asked to eat normally the day before the respective clinical investigation day (no alcohol consumption or exercise). A detailed description of the study design has been published.<sup>19,20,22</sup>

### Dietary Intervention

Subjects were advised to maintain their achieved weight during the intervention. All subjects had to complete a 3-day dietary record at weeks 4 and 26 of the dietary intervention period and were given careful, intensive, and regular dietary and behavioral guidance in regard to both the macronutrient composition and the glycemic index of their diets. The targeted macronutrient compositions are shown in Table 1. To obtain the correct protein/carbohydrate ratios and glycemic indexes, a point-based system was developed.<sup>19</sup> The control diet is according to the guidelines of the respective national associations for nutrition. During the whole intervention period (including the low-calorie diet), the average amount of plant protein from total protein intake was 36%, with very small changes over time: 37% at screening, 36% at week 4, and 36% at week 26 of the dietary intervention. The urinary nitrogen excretion was measured to control for adherence to the targeted protein intake. The study was ad libitum concerning the individual choice of food from

**Table 1. Targeted Composition of Nutritional Intake in the 5 Diet Groups During the 26-Week Diet Intervention Phase**

Component	Low Protein		High Protein		Control (Healthy) Diet
	Low Glycemic Index	High Glycemic Index	Low Glycemic Index	High Glycemic Index	
Protein		10–15		23–28	12–15
Carbohydrate		57–62		45–50	55–63
Difference in glycemic index*		15 points		15 points	
Fat			23–28		25–30

Values, except points, are percentages of total energy intake.

\*The difference in glycemic index in points is the targeted difference between the low-glycemic-index and the high-glycemic-index diet groups.

food lists/recommendations but was carefully controlled concerning the macronutrient composition of the respective diets and adherence to the dietary protocol. Detailed information on the strategy to manipulate ad libitum macronutrient intake and glycemic index has been published.<sup>22</sup>

### Anthropometric Measurements, Blood Pressure, and Blood Parameters

Detailed descriptions of measurement of anthropometric parameters, blood pressure, and blood parameters are given in Methods in the online-only Data Supplement and a recent report of the Diogenes consortium.<sup>19</sup>

### Statistical Analysis

Detailed information on the statistical analysis is given in Methods and Table II in the online-only Data Supplement.

In brief, results are presented as mean  $\pm$  SD. Statistical significance was defined as  $P < 0.05$ . Statistical significance of changes in hsCRP, lipid profile parameters, and blood pressure was tested by applying 2-tailed Student *t* tests for unpaired samples. In the case of hsCRP, the matching of the diet groups during the low-calorie diet phase was tested by ANOVA without adjustment.

For hsCRP, triglycerides, and total, high-density lipoprotein, and low-density lipoprotein cholesterol concentrations as well as blood pressure, intention-to-treat analyses were performed including data from all 773 participants who underwent randomization by fitting linear mixed models, taking into account missing values from participants who dropped out and missing records.

For a sensitivity analysis on hsCRP data, records from all 773 randomized participants were included. For missing data from participants who withdrew during the dietary intervention, the baseline data at the time of randomization were carried forward. The same model as in the intention-to-treat analysis was calculated.

A completion analysis was performed including all 487 participants with data available at randomization and at the end of the intervention. Dietary effects on hsCRP during intervention were calculated by ANCOVA.

In the case of hsCRP, in which the diet term was significant for the predicted model (intention-to-treat, sensitivity, and completion analyses), significance between the main effects (glycemic index and protein) was tested by applying 2-tailed Student *t* tests for unpaired samples on the already adjusted model predictors.

The statistical analysis was performed with the use of IBM SPSS Statistics version 18.0 (IBM, Somers, NY).

## Results

### Study Progress

A total of 1209 adults (mean age, 41 years; body mass index, 34 kg/m<sup>2</sup>) were screened. The participant flow through the study is presented in Figure 1. Of 773 adults who were randomized to the 5 different diets, 546 completed the study (71%). Details about dropouts are shown in Results in the online-only Data Supplement. The characteristics of the

participants of the 5 dietary groups were not significantly different either at randomization or during the low-calorie diet phase (Table I in the online-only Data Supplement). Detailed information about dietary intake is given in the online-only Data Supplement.

### Weight Change

Detailed data on the influence of the different diets on weight maintenance have been published.<sup>20</sup> In brief, the participants showed a substantial and significant reduction in body weight during the low-calorie diet phase of the study ( $-11.23$  kg; 95% confidence interval [CI],  $-11.54$  to  $-10.92$ ;  $P < 0.001$ ). Only the low-protein, high-glycemic-index diet was associated with a subsequent weight regain (1.67 kg; 95% CI, 0.48–2.87;  $P < 0.05$ ), whereas in an intention-to-treat analysis, the weight regain was 0.93 kg less in high-protein versus low-protein diet groups (95% CI, 0.31–1.55;  $P = 0.003$ ) and 0.95 kg less in low-glycemic-index versus high-glycemic-index groups (95% CI, 0.33–1.57;  $P = 0.003$ ).

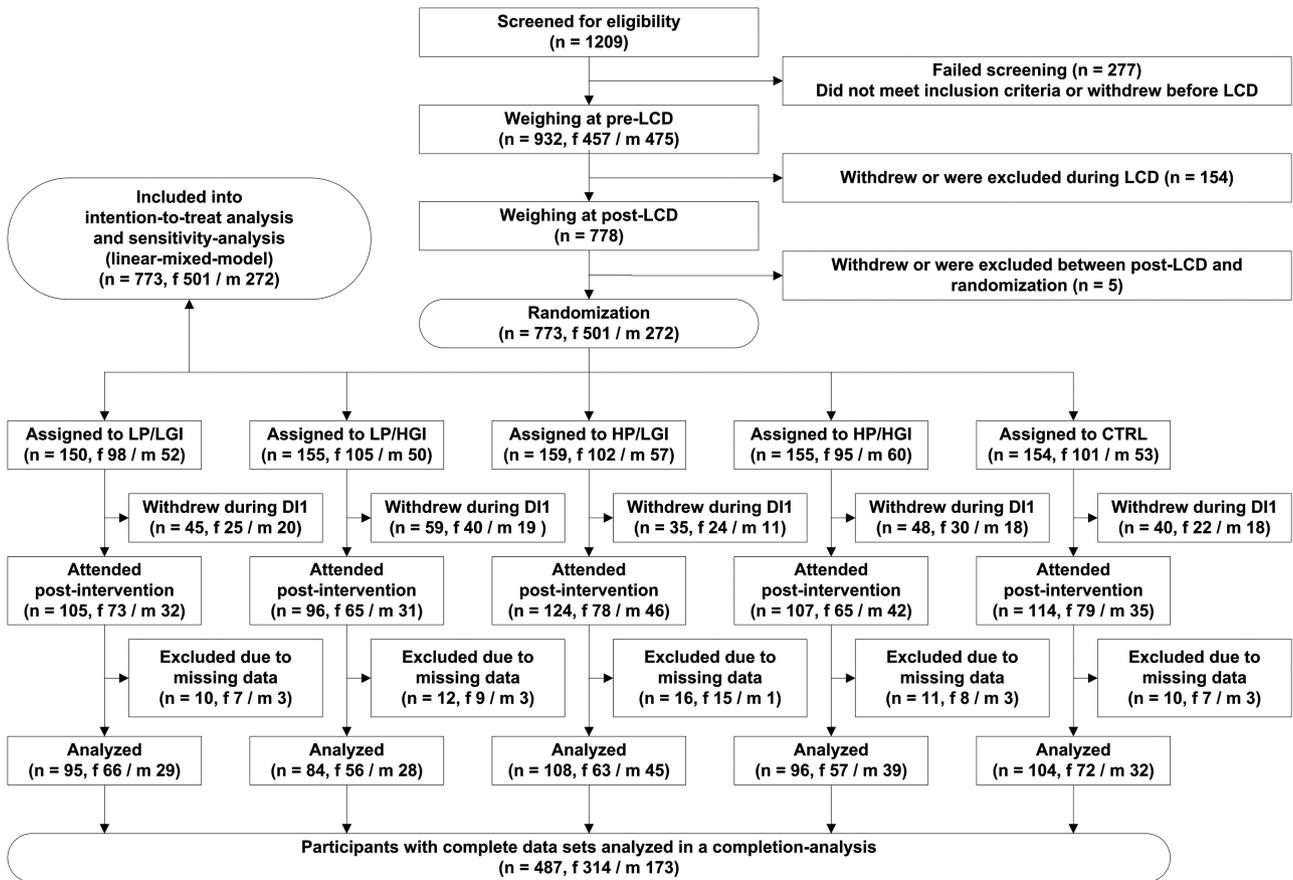
### Blood Parameters

#### High-Sensitivity C-Reactive Protein

Before the low-calorie diet phase, hsCRP (mg/L) was slightly increased compared with routine reference clinical values in all diet groups (ie, hsCRP  $> 3$  mg/L; Table I in the online-only Data Supplement). The hsCRP values decreased significantly in all groups during the low-calorie diet period (low-protein, low-glycemic-index group,  $-1.41 \pm 5.55$ ; low-protein, high-glycemic-index group,  $-0.87 \pm 3.55$ ; high-protein, low-glycemic-index group,  $-1.29 \pm 2.84$ ; high-protein, high-glycemic-index group,  $-1.23 \pm 2.90$ ; control,  $-0.92 \pm 1.76$ ; unadjusted  $P < 0.001$  each; Table I in the online-only Data Supplement) but did not differ significantly between diets, demonstrating that the groups were well matched (unadjusted  $P = 0.703$ ; Table I in the online-only Data Supplement). The subsequent 26-week randomized intervention period led to a further decrease in hsCRP, which appeared to be different in the distinct diet groups (Figure 2 and Table 2).

#### Intention-to-Treat Analysis

A linear mixed model was fitted. During the dietary intervention, the decrease in hsCRP of participants in the low-glycemic-index groups was  $-0.46$  mg/L (95% CI,  $-0.79$  to  $-0.13$ ) greater than in the high-glycemic-index groups ( $P < 0.001$ ) and was  $-0.25$  mg/L (95% CI,  $-0.59$  to  $-0.17$ ) greater in the low-protein groups than in the high-protein groups ( $P < 0.001$ ). There was no significant

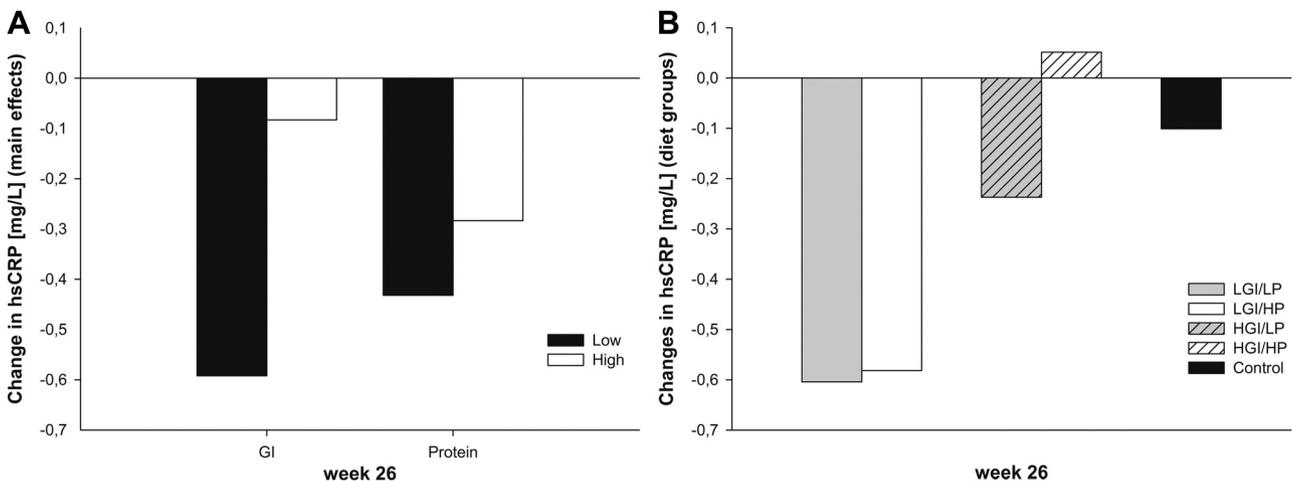


**Figure 1.** Organizational chart of participant flow through the study. Participants entering subsequent stages of the study as well as dropouts are indicated in total and separated by gender. LCD indicates low-calorie diet; f/m, female/male; HP, high protein; LP, low protein; HGI, high glycemic index; LGI, low glycemic index; CTRL, control, and DI1, diet intervention.

interaction between the low-glycemic-index and the low-protein groups (Table 3). A summary of all fitted models is shown in Table II in the online-only Data Supplement.

The low-glycemic-index groups were more likely to achieve an additional reduction of hsCRP concentration of

>15% of the value at randomization than the high-glycemic-index groups (odds ratio, 1.57; 95% CI, 1.13–2.17;  $P=0.007$ ). By contrast, achieving an additional decrease in hsCRP >15% by varying the protein content of the diet was unlikely (low protein: odds, 1.05; 95% CI, 0.79–1.39; high



**Figure 2. A.** Changes of high-sensitivity C-reactive protein (hsCRP) between post-low-calorie diet (week 0) and postintervention (week 26). The values were normalized to post-low-calorie diet. For absolute values, see Tables I and II in the online-only Data Supplement. **B.** Changes of hsCRP between post-low-calorie diet (week 0) and postintervention (week 26) for the combined low-glycemic-index (LGI) diets (HP/LGI and LP/LGI) vs high-glycemic-index (HGI) diets (HP/HGI and LP/HGI) and for the combined high-protein (HP) (HP/HGI and HP/LGI) vs the low-protein (LP) diets (LP/LGI and LP/HGI).

**Table 2. Blood Parameters and Anthropometric Measurements and Unadjusted Changes Between Randomization and Week 26 of the Diet Intervention Period**

Variable	Low Protein				High Protein				Control	
	Low Glycemic Index		High Glycemic Index		Low Glycemic Index		High Glycemic Index		No. of Participants	Change From Randomization to Week 26
	No. of Participants	Change From Randomization to Week 26	No. of Participants	Change From Randomization to Week 26	No. of Participants	Change From Randomization to Week 26	No. of Participants	Change From Randomization to Week 26		
<b>Blood parameters</b>										
hsCRP, mg/L	95	-0.60±2.84*	84	-0.24±2.40	108	-0.58±1.81*	96	0.05±2.26	104	-0.10±2.01
Cholesterol, mmol/L	95	0.70±0.72*	84	0.79±0.87*	107	0.80±0.75*	95	0.64±0.66*	103	0.75±0.71*
High-density lipoprotein, mmol/L	95	0.23±0.21*	84	0.23±0.26*	107	0.21±0.24*	96	0.20±0.21*	104	0.19±0.21*
Low-density lipoprotein, mmol/L	93	0.40±0.53*	83	0.52±0.74*	108	0.50±0.63*	95	0.37±0.60*	104	0.47±0.61*
Triglycerides, mmol/L	93	0.13±0.53*	82	0.13±0.52*	107	0.19±0.51*	94	0.14±0.38*	102	0.19±0.41*
Systolic blood pressure, mm Hg	92	4.47±12.81*	80	5.12±10.67*	105	4.24±14.27*	93	2.72±13.39	101	4.50±12.90*
Diastolic blood pressure, mm Hg	92	1.01±7.89	80	3.55±7.68*	105	1.94±8.01*	93	0.96±7.99	102	3.49±8.02*
Fasting insulin, mU/L	81	0.79±8.28	69	3.17±9.30*	82	1.56±3.49*	80	1.32±5.23*	85	1.30±3.70
Insulin 120-min OGTT, mU/L	85	-7.73±31.38*	77	-4.31±32.91	104	-3.02±28.74	90	-7.62±32.01*	98	-3.40±30.36*
Fasting glucose, mmol/L	92	0.11±0.58	83	0.24±0.46*	103	0.10±0.60	94	0.08±0.71	103	0.14±0.44*
Glucose 120-min OGTT, mmol/L	85	-1.28±1.84*	79	-0.93±1.75*	102	-1.01±1.73*	88	-1.06±1.79*	98	-0.89±1.65*
<b>Anthropometric measures</b>										
Body weight, kg	95	0.27±5.01	84	1.45±5.34*	108	-0.38±6.28	96	0.36±5.41	104	0.55±4.46
Fat-free mass, kg	79	0.80±3.73	67	0.75±5.87	91	0.05±4.41	78	1.79±5.82*	86	1.58±3.83*
Fat mass, kg	79	-0.92±5.54	67	-0.40±4.96	91	-1.00±5.65	78	-0.20±7.52	86	-1.14±4.73*
Waist circumference, cm	93	0.09±7.07	81	0.89±6.84	104	0.49±6.82	95	-0.07±7.09	103	-0.67±6.45
Hip circumference, cm	93	-0.64±6.54	81	-0.15±6.45	104	-0.46±5.90	95	-0.47±6.23	103	-0.59±5.36
Sagittal diameter, cm	91	0.07±1.60	80	0.15±2.14	102	-0.12±1.98	91	-0.10±2.42	100	0.20±2.35

Values shown are mean±SD. Participants were included in this analysis if they had completed the diet intervention period and had complete records for high-sensitivity C-reactive protein (hsCRP) at the beginning (randomization) and the end of the diet intervention period. OGTT indicates oral glucose tolerance test.

\*Significant changes (Student *t* test for paired samples, *P*<0.05).

protein: odds, 0.87; 95% CI, 0.66–1.15; odds ratio, 1.20; 95% CI, 0.87–1.66; *P*=0.267) (Table 3).

**Sensitivity Analysis**

In the sensitivity analysis, the decrease in hsCRP was -0.33 mg/L (95% CI, -0.65 to -0.02) greater in the low-glycemic-index versus the high-glycemic-index groups (*P*<0.001) and, as well, was -0.13 mg/L (95% CI, -0.45 to 0.19) greater in the low-protein versus the high-protein groups (*P*=0.001) and was therefore similar to that in the intention-to-treat analysis (Table 3).

**Completion Analysis**

In the completion analysis, only participants randomized to the low-glycemic-index diet groups had significantly reduced hsCRP concentrations after the 26-week intervention period (low glycemic index/low protein: -0.59 mg/L; 95% CI, -1.04 to -0.15; low glycemic index/high protein: -0.43; 95% CI, -0.89 to 0.03) (Table 2). ANCOVA confirmed the significantly different influences on hsCRP among the diets (*P*<0.001). The isolated effect on lowering hsCRP was more pronounced in the low-glycemic-index groups compared with the high-glycemic-index groups than in the low-protein

groups compared with the high-protein groups (low glycemic index versus high glycemic index: -0.51 mg/L; 95% CI, -0.98 to -0.04; *P*<0.001; low protein versus high protein: -0.15 mg/L; 95% CI, -0.62 to 0.32; *P*=0.037) (Table 3).

**Lipid Profile**

Triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol decreased significantly in all groups after the low-calorie diet period (*P*<0.001; Figures 3 and 4 and Table I in the online-only Data Supplement) and increased again significantly during the 26-week dietary intervention period (*P*<0.001; Table 2 and Figures 3 and 4). Triglycerides tended to remain lower than at baseline (Figure 3A and Table 2). High-density lipoprotein cholesterol also decreased substantially during the low-calorie diet but then increased to significantly higher levels than before the low-calorie diet in all dietary groups (*P*<0.001) (Figure 4A and Table 2). Despite lower body weight at the end of the intervention, total cholesterol and low-density lipoprotein cholesterol returned to the baseline level after the intervention (Figures 3B and 4B and Table 2). The total cholesterol/high-density lipoprotein cholesterol ratio decreased significantly during the low-calorie diet period

**Table 3. Lowering of hsCRP and Odds Ratios for Achievement of Additional Loss of >15% of hsCRP at Randomization During the 26-Week Diet Intervention Period\***

Variable	Change in hsCRP, mg/L, (95% CI)			P	Comparison of Glycemic-Index Groups, mg/L (95% CI)			P	Comparison of Protein Groups, mg/L (95% CI)			P	Control Change in hsCRP, mg/L (95% CI)
	Low Glycemic Index	High Glycemic Index	Odds (95% CI)		Low Glycemic Index	High Glycemic Index	Odds Ratio for Low Glycemic Index vs High Glycemic Index (95% CI)		Low Protein	High Protein	Low Protein-High Protein		
<b>hsCRP decrease</b>													
Intention-to-treat analysis	-0.64 (-0.88 to -0.41)	-0.18 (-0.41 to 0.05)		<0.001	-0.46 (-0.79 to -0.13)			-0.29 (-0.49 to -0.09)		-0.25 (-0.59 to -0.17)		<0.001	-0.16 (-0.45 to 0.12)
Sensitivity analysis	-0.41 (-0.63 to -0.18)	-0.07 (-0.29 to 0.15)		<0.001	-0.33 (-0.65 to -0.02)			-0.18 (-0.37 to 0.02)		-0.13 (-0.45 to 0.19)		0.001	-0.07 (-0.35 to 0.21)
Completion analysis	-0.59 (-0.92 to -0.27)	-0.08 (-0.42 to 0.26)		<0.001	-0.51 (-0.98 to -0.04)			-0.28 (-0.57 to 0.00)		-0.15 (-0.62 to 0.32)		0.037	-0.10 (-0.49 to 0.29)
<b>Achievement of additional loss of &gt;15% of hsCRP at randomization</b>													
Intention-to-treat analysis	1.21 (0.91 to 1.61)	0.77 (0.58 to 1.03)		0.007	1.57 (1.13 to 2.17)			0.87 (0.66 to 1.15)		1.20 (0.87 to 1.66)		0.267	0.77 (0.51 to 1.15)
Sensitivity analysis	0.60 (0.45 to 0.79)	0.39 (0.29 to 0.53)		0.019	1.52 (1.07 to 2.15)			0.51 (0.38 to 0.68)		0.91 (0.64 to 1.27)		0.593	0.54 (0.36 to 0.82)
Completion analysis	1.13 (0.81 to 1.59)	0.82 (0.57 to 1.17)		0.109	1.39 (0.93 to 2.06)			0.96 (0.69 to 1.35)		1.03 (0.69 to 1.54)		0.891	0.96 (0.60 to 1.54)

hsCRP indicates high-sensitivity C-reactive protein; CI, confidence interval.

\*All 773 participants who passed the randomization were included into the intention-to-treat analysis and the sensitivity analysis. For the sensitivity analysis, we assumed that the hsCRP of participants who dropped out of the diet intervention period remained on the level at randomization. The completion analysis included 487 participants who had complete records for hsCRP at randomization and the end of the diet intervention period.

but showed no significant change during the 26-week dietary intervention (data not shown). Furthermore, changes during the dietary intervention showed no differences between groups in regard to the lipid profile. Similar to the analysis of hsCRP, we fitted a linear mixed model for triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, which showed no significant diet term ( $P>0.7$  for all parameters). A summary of all fitted models is shown in Table II in the online-only Data Supplement.

### Blood Pressure

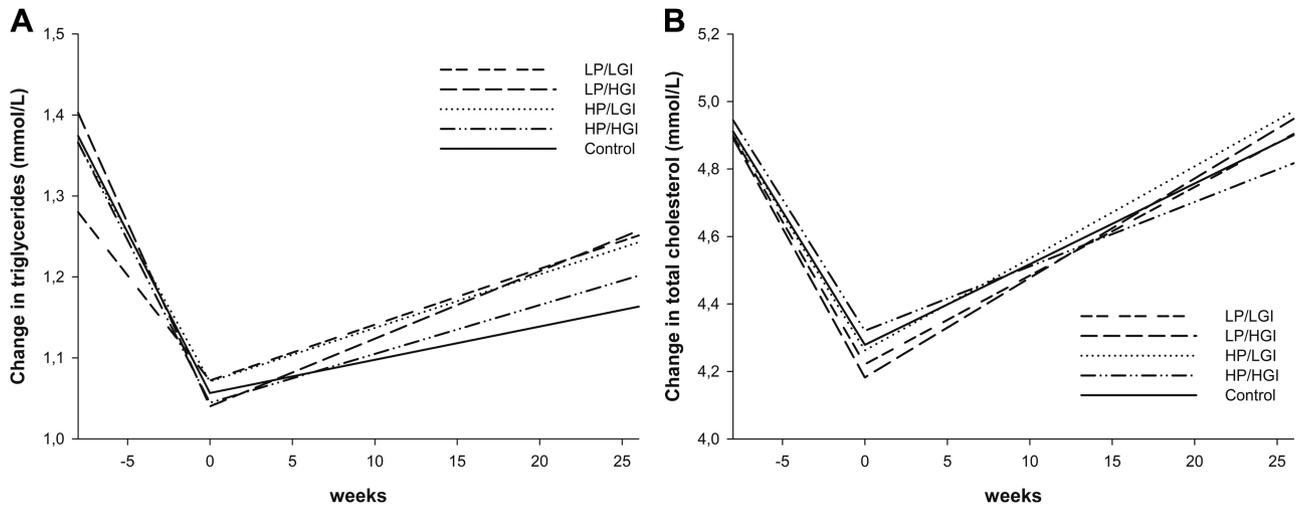
Both systolic and diastolic blood pressure decreased significantly during the low-calorie diet period and increased again in all dietary groups during the 26-week intervention period (Figure 5, Table 2, and Table I in the online-only Data Supplement).

Although there was no obvious difference between groups in increase of systolic blood pressure during the 26-week intervention period, the diastolic blood pressure tended to increase less in the low-protein, low-glycemic-index group compared with the low-protein/high-glycemic-index group ( $1.01 \pm 7.89$  versus  $3.55 \pm 7.68$  mm Hg). Again, a linear mixed model failed to reach significance level for the diet term for both systolic blood pressure ( $P=0.556$ ) and diastolic blood pressure ( $P=0.098$ ). A summary of all fitted models is shown in Table II in the online-only Data Supplement.

### Discussion

This dietary intervention study compared the subsequent effects of low or high glycemic index and protein content diets on cardiovascular risk factors in healthy overweight adults, after a substantial weight loss exceeding 8% of body weight. The energy-restricted period resulted in an expected and marked improvement of blood lipids, blood pressure, and hsCRP as a marker for inflammation.<sup>23</sup> Caloric restriction is known to be a strong activator of protective metabolic pathways, thereby leading to lower blood pressure, improved blood lipids, and reduced inflammatory markers, including hsCRP.<sup>24–28</sup> However, little is known about the effects of subsequent non-energy-restricted diets varying in protein content and glycemic index on these end points. Previous studies comparing different diets under ad libitum conditions were small and of short duration<sup>29,30</sup> or included patients with other comorbidities such as diabetes mellitus.<sup>8</sup> Moreover, the design of the DiOGenes study allowed a clear separation of the effects of caloric restriction from those of dietary composition.

The main outcome of this study was a significant further decrease of hsCRP after the initial weight loss, which was observed with the low-glycemic-index diets only and independent of protein content and small weight changes (Table 2 and Figure 1A). This might be related to expected reductions of postprandial glucose levels with low-glycemic-index diets, with glucose known to stimulate the expression of inflammatory genes by epigenetic mechanisms.<sup>27,31,32</sup> Furthermore, transient increases in glucose induce persistent changes in histone methylation patterns at promoters of inflammatory genes,<sup>31–34</sup> which is related to glucose-induced mitochondrial generation of oxygen radicals. Long-term increases in basal glucose concentrations are associated with both high fasting



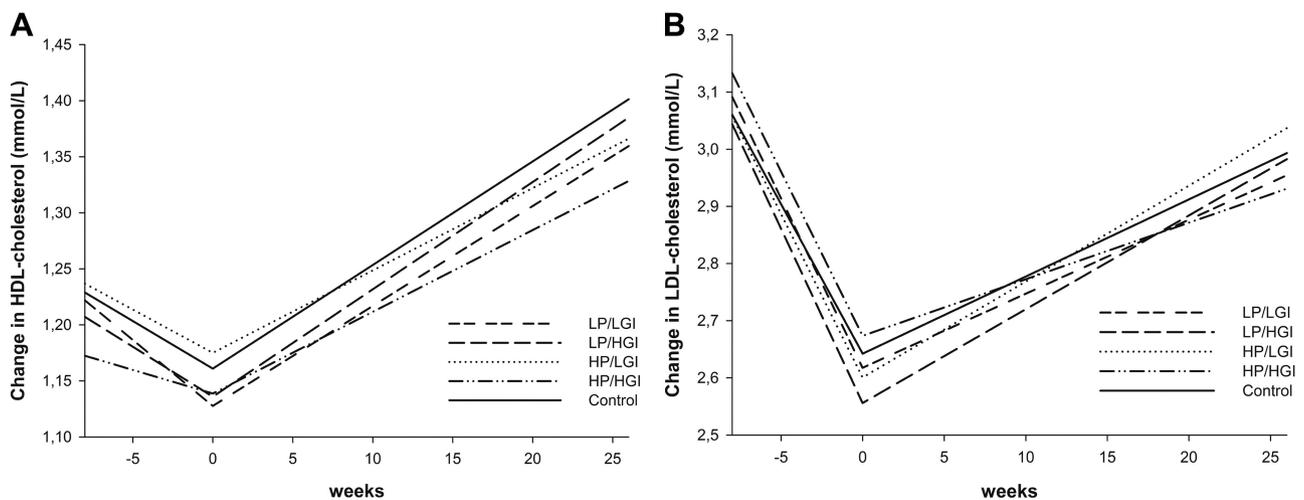
**Figure 3.** Changes of triglycerides (**A**) and total cholesterol (**B**) on the different diets between pre-low-calorie diet (week 8), post-low-calorie diet (week 0), and postintervention (week 26). LP indicates low protein; LGI, low glycemic index; HGI, high glycemic index; and HP, high protein.

insulin concentrations and insulin resistance, which is known to promote inflammatory processes and an increment of hsCRP.<sup>35</sup>

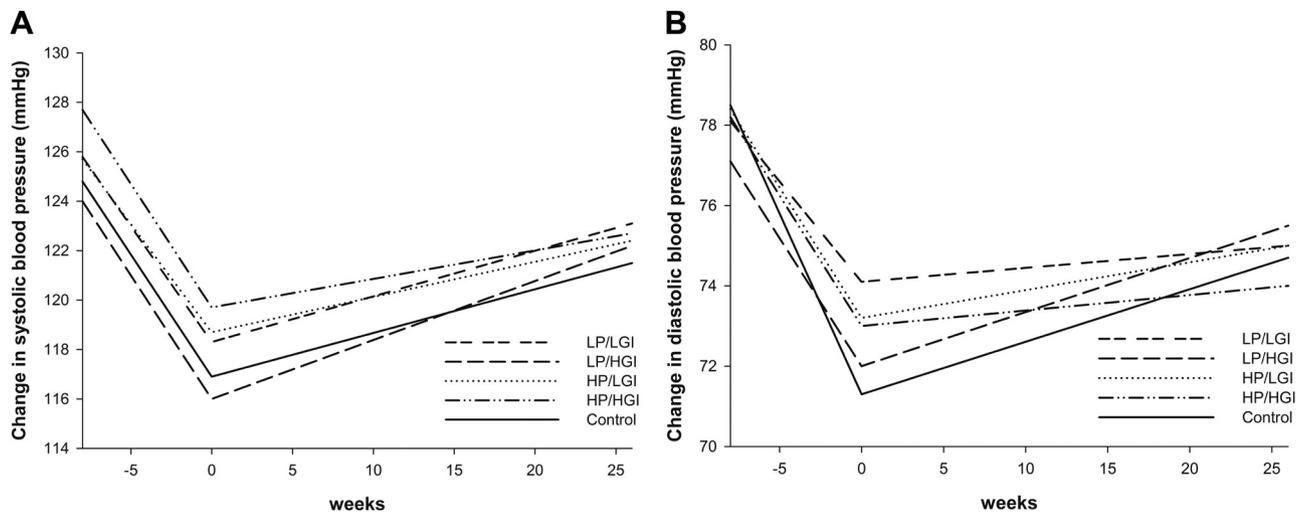
A low-glycemic-index diet was also associated with reduced levels of hsCRP in a prospective Canadian study in subjects with type 2 diabetes mellitus.<sup>8</sup> Moreover, a cross-sectional study in a Dutch population associated a low glycemic index with lower values of hsCRP.<sup>36</sup> Furthermore, in randomized controlled trials in overweight subjects, it was shown that diets based on low-glycemic-index carbohydrates produced better cardiovascular-related outcomes than conventional low-fat diets.<sup>37</sup> Otherwise, no significant effects on hsCRP and other cardiovascular risk factors were observed in shorter and smaller ad libitum studies combining low glycemic index and weight loss.<sup>38</sup>

The DiOGenes study goes beyond these observations: All diets supported the maintenance of reduced hsCRP concentrations as achieved by weight loss, with a background of a healthy, low-fat food pattern that was rich in vegetables and

fruits in all groups. However, a further decrease in hsCRP was associated with a low glycemic index and, to a lesser extent, a lower protein intake only. Thus, repeated increases in postprandial blood glucose related to high-glycemic-index food components appear to play an important role in modulating hsCRP. The observation that the dietary protein content influences hsCRP values has not been reported previously. The effect was small but significant in all analyses, showing the robustness of this result. The higher protein content appeared to interfere with a further decrease of hsCRP compared with the low-protein diet. Since we have also shown recently that a high-protein diet in comparison with an isoenergetic carbohydrate-rich diet high in cereal fibers unfavorably influences whole-body insulin sensitivity in overweight and obese participants,<sup>16</sup> evidence is accumulating that high-protein diets may have less favorable metabolic effects in comparison to high-fiber and/or low-glycemic-index diets,<sup>39</sup> despite their known beneficial effects on weight loss and blood lipids.



**Figure 4.** Changes of high-density lipoprotein (HDL) cholesterol (**A**) and low-density lipoprotein (LDL) cholesterol (**B**) on the different diets between pre-low-calorie diet (week 8), post-low-calorie diet (week 0), and postintervention (week 26). LP indicates low protein; LGI, low glycemic index; HGI, high glycemic index; and HP, high protein.



**Figure 5.** Changes of systolic (A) and diastolic (B) blood pressure on the different diets between pre–low-calorie diet (week 8), post–low-calorie diet (week 0), and postintervention (week 26). LP indicates low protein; LGI, low glycemic index; HGI, high glycemic index; and HP, high protein.

The initial low-calorie diets resulted in decreases of triglycerides, as expected.<sup>40–43</sup> The subsequent increase of triglycerides during the ad libitum food intake did not differ between the diets and remained below the initial levels. Thus, neither the glycemic index nor the protein content significantly influenced triglyceride levels under these conditions.

Changes in lipids were described in shorter-term studies that usually were associated with weight loss.<sup>21</sup> Remarkably, a 1-year study of diabetic patients treated with a low-glycemic-index diet similarly did not observe changes in triglyceride or cholesterol levels or hemoglobin A<sub>1c</sub>,<sup>8</sup> whereas cross-sectional studies typically observe an increase of triglycerides with higher glycemic index.<sup>44</sup> These associations thus appear to be related to the overall pattern of nutrition rather than the glycemic index only. However, improvements in blood lipids may also be expected because of the weight loss and the associated metabolic improvements of insulin resistance. Total and low-density lipoprotein cholesterol decreased markedly during the energy-restricted phase and then increased back to baseline levels and comparably in all dietary groups, which is in agreement with results from another long-term study in patients with type 2 diabetes mellitus.<sup>8</sup> By contrast, high-density lipoprotein cholesterol decreased slightly during the energy-restricted phase of the study but then increased comparably between groups and significantly during the diet phase to levels markedly above those before the low-calorie diet period at the start of the study, indicating an overall metabolic improvement due to weight loss and the healthy pattern of nutrition in all dietary groups. Cross-sectional studies reported higher levels of high-density lipoprotein cholesterol on low-glycemic-index diets, which again may be related to the general nutritional pattern rather than specifically to the low glycemic index.<sup>36,42,44,45</sup>

Systolic blood pressure decreased from normal values during weight loss but then increased to initial levels during the diet phases with no differences between diets. By contrast, diastolic blood pressure decreased during weight loss

but did not return to the initial levels on all diets. Differences between diets were subtle, and the changes were not associated with protein content but may have been moderately influenced by the glycemic index.

## Conclusions

In summary, our findings in this large and multinational cohort further confirm and substantially extend our knowledge regarding an overall benefit of a low-fat, low-glycemic-index food pattern. High-protein intake did not elicit relevant unfavorable effects on cardiovascular risk markers. However, a low-glycemic-index diet supported by a low-protein diet appears to further reduce hsCRP, and as such low-grade inflammation, even after a substantial reduction due to weight loss. These data therefore provide an important argument in favor of low-glycemic-index diets in obese healthy individuals.

## Acknowledgments

We wish to thank Andreas Wagner, Andrea Ziegenhorn, and Katrin Sprengel for technical assistance.

## Sources of Funding

The DiOGenes project is funded by a grant from the European Union Food Quality and Safety Priority of the Sixth Framework Program (contract No. FP6-2005-513946). DiOGenes is supported by the European Community (contract No. FOOD-CT-2005-513946) (<http://www.diogenes-eu.org>).

## Disclosures

The European Union commission that decided on funding of this study has had no role in designing the study or in analyzing and interpreting the data. The authors report no conflicts.

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### CLINICAL PERSPECTIVE

Food components are well known to affect cardiovascular risk, for which blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and the inflammatory marker C-reactive protein (CRP) are established biomarkers. In the present randomized, multicenter study, the separate effects of 11 kg weight loss achieved during an 8-week low-calorie diet as well as a subsequent 26-week intake of diets varying in protein and glycemic index on these biomarkers were studied. The choice of food was ad libitum but was strictly controlled by nutritional advice concerning the targeted fat and protein content as well as glycemic index. Expectedly, the initial weight loss significantly reduced systolic and diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and CRP. The subsequent consumption of different low-fat isocaloric diets resulted in moderate increases of blood lipids and blood pressure, which, however, were independent of the protein content and glycemic index of the diet. This clearly indicated that the beneficial effects on blood lipids and blood pressure were driven by the weight reduction itself but not by the dietary composition. In explicit contrast to the other biomarkers, consumption of low-glycemic-index diets led to a further decrease of CRP compared with high-glycemic-index diets. A low protein content enhanced the CRP-lowering effect, whereas a high protein content diminished it. Thus, the combination of low glycemic index and low protein intake appears to be most effective to reduce CRP, an established marker of low-grade inflammation and cardiovascular risk.