Long-Term Safety and Efficacy of a Cholesterol-Lowering Diet in Children With Elevated Low-Density Lipoprotein Cholesterol: Seven-Year Results of the Dietary Intervention Study in Children (DISC)

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ABSTRACT. *Objective.* **Diets reduced in fat and cholesterol are recommended for children over 2 years of age, yet long-term safety and efficacy are unknown. This study tests the long-term efficacy and safety of a cholesterol-lowering dietary intervention in children.**

Methods. **Six hundred sixty-three children 8 to 10 years of age with elevated low-density lipoprotein cholesterol (LDL-C) were randomized to a dietary intervention or usual care group, with a mean of 7.4 years' follow-up. The dietary behavioral intervention promoted adherence to a diet with 28% of energy from total fat, <8% from saturated fat, up to 9% from polyunsaturated fat, and <75 mg/1000 kcal cholesterol per day. Serum LDL-C, height, and serum ferritin were primary efficacy and safety outcomes.**

Results. **Reductions in dietary total fat, saturated fat, and cholesterol were greater in the intervention than in the usual care group throughout the intervention period. At 1 year, 3 years, and at the last visit, the intervention compared with the usual care group had 4.8 mg/dL (.13 mmol/L), 3.3 mg/dL (.09 mmol/L), and 2.0 mg/dL (.05 mmol/L) lower LDL-C, respectively. There were no differences at any data collection point in height or serum ferritin or any differences in an adverse direction in red blood cell folate, serum retinol and zinc, sexual maturation, or body mass index.**

Conclusion. **Dietary fat modification can be achieved and safely sustained in actively growing children with elevated LDL-C, and elevated LDL-C levels can be improved significantly up to 3 years. Changes in the usual care group's diet suggest that pediatric practices and societal and environmental forces are having positive public health effects on dietary behavior during adolescence.** ***Pediatrics* 2001;107:256–264; *children, fat intake, serum cholesterol, saturated fat.***

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ABBREVIATIONS. LDL-C, low-density lipoprotein cholesterol; DISC, Dietary Intervention Study in Children; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; CI, confidence interval.

Atherosclerosis begins in childhood,[1] and elevated serum levels of total and low-density lipoprotein cholesterol (LDL-C) are associated with fatty streaks and fibrous plaques in adolescents and young adults.[2,3] Reducing dietary saturated fat and cholesterol reduces blood total cholesterol and LDL-C,[4] so diets reduced in total fat, saturated fat, and cholesterol are recommended for healthy children 2 years of age and older, with greater reductions recommended for children with elevated blood cholesterol and a family history of premature coronary heart disease.[1,5]

Questions have been raised about the safety of diets reduced in total fat, including possible growth retardation, nutritional inadequacy, and adverse psychosocial effects,[6,7] and about the efficacy on blood lipids of diets reduced in saturated fat and cholesterol in children.[8] In 1987, the Dietary Intervention Study in Children (DISC), a multicenter, controlled, randomized trial, was initiated to address these efficacy and safety questions in children with elevated LDL-C.[9] As previously reported, after 3 years, the intervention group lowered their mean dietary intake of total and saturated fat and their serum LDL-C more than the usual care group.[10] At the time of their 3-year visit, participants were invited to continue until they reached age 18 to assess long-term effects of intervention on LDL-C and near-adult stature after completion of sexual maturation. The intervention group continued receiving dietary

counseling, although at a lower intensity than during the first 3 years. Herein we report the 7-year DISC results.

METHODS

Design

DISC was a randomized, controlled trial, with 6 participating clinical centers, a coordinating center, and a project office. The study was approved by the institutional review boards of all participating centers. The protocol was reviewed by an independent data and safety monitoring committee appointed by the study's sponsor, the National Heart, Lung, and Blood Institute.

DISC recruited 663 participants 8 to 10 years of age with elevated LDL-C whose parents or guardians gave informed consent. Children were randomly assigned to an intervention or usual care group and entered into the study over 2.5 years.

After DISC was extended to follow the children to age 18 years, intervention and annual measurement visits were continued. Participants were last assessed either at age 18 years (15.3%) or, because of funding constraints, at a closeout visit before age 18 years (84.7%). Some participants who initially declined to continue (n = 19; 3%) gave consent for a closeout visit, although those assigned to the intervention group had not received intervention during the interim. The age 18 years and closeout visits are combined in analyses and are termed last visit.

The primary efficacy and safety outcomes for the last visit were serum LDL-C, height, and serum ferritin. Secondary efficacy and safety outcomes were serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C ratio, triglycerides, red blood cell folate, serum retinol and zinc, and sexual maturation. Psychosocial information, not collected after 3 years, has been reported elsewhere.[10,11] The trial was designed for 90% power to detect a difference of 5.4 mg/dL (.14 mmol/L) in LDL-C and .8 cm in height and had 90% power to detect a difference of 3.5 mg/mL in serum ferritin.[9,10]

Participants

Prepubertal children aged 7.8 to 10.1 years for girls and 8.6 to 10.8 years for boys were recruited from schools, a health maintenance organization, and pediatric practices.[9,10] After prescreening for total cholesterol by nonfasting capillary blood, fasting venipuncture LDL-C measurements were obtained in 2 screening visits. Children were eligible if the average of the 2 LDL-C measurements was ≥80th (≥111.5 mg/dL for boys and ≥117.5 mg/dL for girls) and <98th (≤164.5 mg/dL for boys and girls) age- and sex-specific percentiles of the Lipid Research Clinics population.[12] The upper limit of LDL-C was chosen to select children for whom dietary intervention, rather than medications, can be recommended. Exclusions were medical conditions or medications that could affect growth or serum cholesterol, behavioral problems, or onset of pubertal maturation.

Intervention

The DISC dietary recommendations, similar to the National Cholesterol Education Program Step 2 diet,[1] were: 28% of energy from total fat, <8% from saturated fat, up to 9% from polyunsaturated fat, and <75 mg/1000 kcal of cholesterol per day, not to exceed 150 mg/day. Children were assessed for calorie needs, and nutrient adequacy was monitored throughout the study.

Intervention strategies were based on social learning theory[13] and social action theory,[14] which suggest that children learn behaviors through observation and imitation of models, such as parents, siblings, and other family members; peers; and celebrities. These strategies as used in DISC have been described elsewhere.[15,16] In the first 6 months, 6 weekly and then 5 biweekly group sessions were led by nutritionists and behaviorists, and 2 individual visits were held with the nutritionist. Over the second 6 months, 4 group and 2 individual sessions were held. During the second and third years, group and individual maintenance sessions were held 4 to 6 times per year, with monthly telephone contacts between group sessions.

By the fourth year of follow-up, individual visits, an important intervention strategy for the increasingly busy teenagers,[17] used an individualized approach based on motivational interviewing[18] and stage of change.[19] Two group events plus 2 individual visits were planned annually, with additional telephone contacts as appropriate. The individual visits evaluated personally established adherence goals and engaged the participant in problem solving, and the groups provided opportunities for modeling appropriate eating behavior in social situations.

Usual Care

At the trial's beginning, parents or guardians of children assigned to the usual care group were informed that their child's blood cholesterol level was high, and they were given educational publications on heart-healthy eating available to the public. Usual care children were examined annually for study-wide measurements.

Measurements

To minimize regression to the mean, 2 fasting venipunctures for serum lipids were taken 1 month apart at baseline and year 3. Single lipid measurements were obtained at 1 year, 5 years, and at the last visit. Serum triglycerides, total cholesterol, and HDL-C were analyzed as described previously,[9,10] and LDL-C was calculated.[20] Analyses were conducted at the Johns Hopkins Lipoprotein Analytical Laboratory, a participant in the Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute Lipid Standardization Program,[21] which used regular quality control procedures including use of reference pools and blinded duplicate samples.

Two measurements of height and one of weight were taken at baseline and annually. Body mass index (BMI) was calculated from weight and height (kg/m^2). Sexual maturation was assessed annually by Tanner staging[22] until Tanner stage 5 was reached. Maturation was not assessed at the last visit because most participants had reached stage 5. Until menarche, onset of menses was ascertained annually by questionnaire and calendars.

Dietary intakes were measured by a method previously validated[23] using 3 nonconsecutive 24-hour dietary recalls at baseline, years 1, 3, and 5, and the last visit. The first recall was conducted by interview at the clinic, and the 2 subsequent recalls were obtained by telephone within 2 weeks of the clinic visit. Nutrient analyses were performed by the Nutrition Coordinating Center (database version 20) at the University of Minnesota. Data from the 3 recalls were averaged to calculate mean nutrient intakes for each visit.

Red blood cell folate and serum ferritin, zinc, and retinol were measured at baseline, years 1 and 3, and at the last visit by the Nutritional Biochemistry Branch of the Centers for Disease Control and Prevention.[10,24]

All data collectors were centrally trained and certified and were blinded to treatment assignment. Quality control procedures included periodic centralized training, central monitoring of data, site visits to clinical centers, and 6% duplicate samples of dietary recalls, with appropriate feedback to measurement staff.

Clinical monitoring procedures were centralized to detect cases requiring physician referral for inadequate growth or nutrition, delayed sexual maturation, or abnormal blood chemistries, including levels of LDL-C >160 mg/dL. Additional safety monitoring procedures implemented for the intervention group included review of nutrient intakes and height and weight measurements obtained at intervention visits.

Data Analysis

To test whether missing outcome data at the last visit could have biased intervention/usual care comparisons, we compared participants with and without last visit data within each treatment group on baseline values of age, height, weight, BMI, percent of energy from total fat and saturated fat, serum ferritin, and LDL-C, and distributions of sex, household income, and parental education. χ^2 tests for categorical variables and analysis of variance for continuous variables were used to test for treatment-related missingness.

Analysis of primary and secondary outcomes at the last visit used analysis of covariance models[25] to test treatment differences, with sex, age at the last visit, and baseline value of the outcome variable as covariates. Interactions between treatment assignment and sex were tested and found to be nonsignificant for the primary outcomes. Analyses of outcomes at 1, 3, and 5 years were similar, except the covariates were sex and baseline level of the outcome

variable. Wilcoxon tests were used to test for differences in treatment groups for ordered categorical variables. P values, adjusted differences between groups, and 95% confidence intervals (CIs) for the differences were calculated. All analyses used SAS (Cary, NC)[26] or S-Plus.[27]

For the primary efficacy outcome, a 2-sided significance test at $\alpha = .05$ was used. For the primary safety outcomes, 1-sided tests of the alternative hypothesis of usual care superiority at $\alpha = .05$ were performed. One-sided tests were used because safety concerns would exist only if height or serum ferritin were less in the intervention group.

Analyses of the primary outcomes were performed according to intention-to-treat principles, with participants analyzed according to randomization assignment. The primary efficacy and safety analyses were performed using observed data, which is equivalent to imputing the missing participant's same group mean for missing values. Analyses were also performed using data imputed for missing values of the primary outcomes of LDL-C, ferritin, and height, by using treatment-specific multiple linear regression to predict values from the participant's projected age at the last visit (defined as the participant's age at the midpoint of the study closeout period), sex, and baseline value of the outcome variable.

Secondary analyses adjusting for income were performed because of the imbalance in income between intervention and usual care groups at baseline. Secondary analyses using the same approaches as for the primary analyses were also performed to examine differences in LDL-C, height, and ferritin in a subset of participants who attended all clinic visits (n = 461; 70%), an indicator of higher study adherence.

RESULTS

Baseline Characteristics

Baseline characteristics of the 663 participants (179 boys and 155 girls in the intervention group, 183 boys and 146 girls in the usual care group) have been reported.[9,10] Briefly, 86.5% of the study sample was white, 53.3% had parents with at least some college education, and 35.6% had household incomes ≥$50 000. There were no baseline differences between intervention and usual care groups in age, height, weight, BMI, or serum lipid levels. A higher proportion of the intervention group than the usual care group had household income <$20 000 (15.1% vs 5.9%; $P = .002$). There were no baseline differences in age, BMI, serum LDL-C, height, and serum ferritin between intervention and usual care groups for the subset who attended all clinic visits.

Follow-Up

Overall, 87.5% of participants attended the last visit. Comparing those who attended the last visit and those who did not, there were no differences in age, height, weight, BMI, total and saturated fat intake, serum LDL-C, or serum ferritin, and in distributions of sex, household income, and education. Missing the last visit was not related to treatment assignment.

Average length of follow-up at the last visit was 7.4 years for both intervention and usual care groups (median: 7.2; range: 6.5–9.3 years). Age distributions and mean age were not different between intervention and usual care groups at baseline or the last visit, but the age distribution was wider at the last visit than at baseline because of the 2.5-year recruitment period and the early closeout for those who had not reached age 18 years (Table 1).

Intervention attendance diminished over time, from an average of 96% at scheduled or makeup intervention group sessions in the first 6 months to 89% during year 3 and 72% during year 5. After year 5, in the last 3 years of intervention, the percentage of intervention children having 2 or more individual or group visits per year decreased from 55% to 42% to 37%, respectively. During these 3 years, on average 1.8, 1.4, and 1.3 intervention contacts per participant per year were achieved.

TABLE 1. Sample Size and Age Distribution at Baseline and Last Visit

	Intervention n = 334	Usual Care n = 329	Total n = 663
Baseline	%	%	%
Age distribution, y			
8	29.3	28.9	29.1
9	46.4	47.7	47.1
10	24.3	23.4	23.8
Mean age, y (SD)	9.5 (.74)	9.5 (.70)	9.5 (.72)
Last visit*	n = 295	n = 285	n = 580
Age distribution, y	%	%	%
14	0	1.1	.5
15	13.9	17.9	15.9
16	34.6	31.6	33.1
17	36.6	34.7	35.7
18	14.9	13.3	14.1
19	0	1.4	.7
Mean age, y (SD)	17.0 (.88)	17.0 (.93)	17.0 (.91)

* Percent of participants seen at final visit was 87.5% overall: 88.3% for intervention and 86.6% for usual care group.

Dietary Intake

Percent of energy intake from total fat and saturated fat in the intervention group decreased from mean baseline levels of 33.4% and 12.5%, respectively, to 28.5% and 9.8% at 1 year and remained low, averaging 28.5% and 10.2% at the last visit (Fig 1). Percent of energy intake from total fat and saturated fat began to decrease in the usual care group in the later years, from baseline levels of 34.0% and 12.7%, respectively, to 31.4% and 11.7% at 5 years and 30.6% and 11.3% at the last visit. Adjusted differences in total fat and saturated fat between the 2 groups were significant at all time points (intervention group lower, all $P < .001$), although the difference between the 2 groups narrowed at 5 years and the last visit. After an initial reduction from 118 to 90 mg/1000 kcal at 1 year, dietary cholesterol of the intervention group remained relatively low at 3 years (95 mg/1000 kcal) and 5 years (89 mg/1000 kcal), but increased at the last visit to 99 mg/1000 kcal. Cholesterol intake of the usual care group changed little over the first 3 years from baseline levels of 114 mg/1000 kcal but decreased to 104 and 103 mg/1000 kcal at 5 years and the last visit, respectively (Fig 1). Adjusted differences in dietary cholesterol intake between intervention and usual care groups were significant at 1, 3, and 5 years (all $P < .0001$), but not at the last visit.

Energy intake was 98 and 148 kcal/day (411 and 619 kJ/day) lower in the intervention than usual care group at 1 ($P = .01$) and 3 years ($P < .001$), and not different at subsequent time points.

Primary Efficacy and Safety Outcomes

LDL-C decreased in the intervention and usual care groups from 130.6 mg/dL (3.38 mmol/L) and

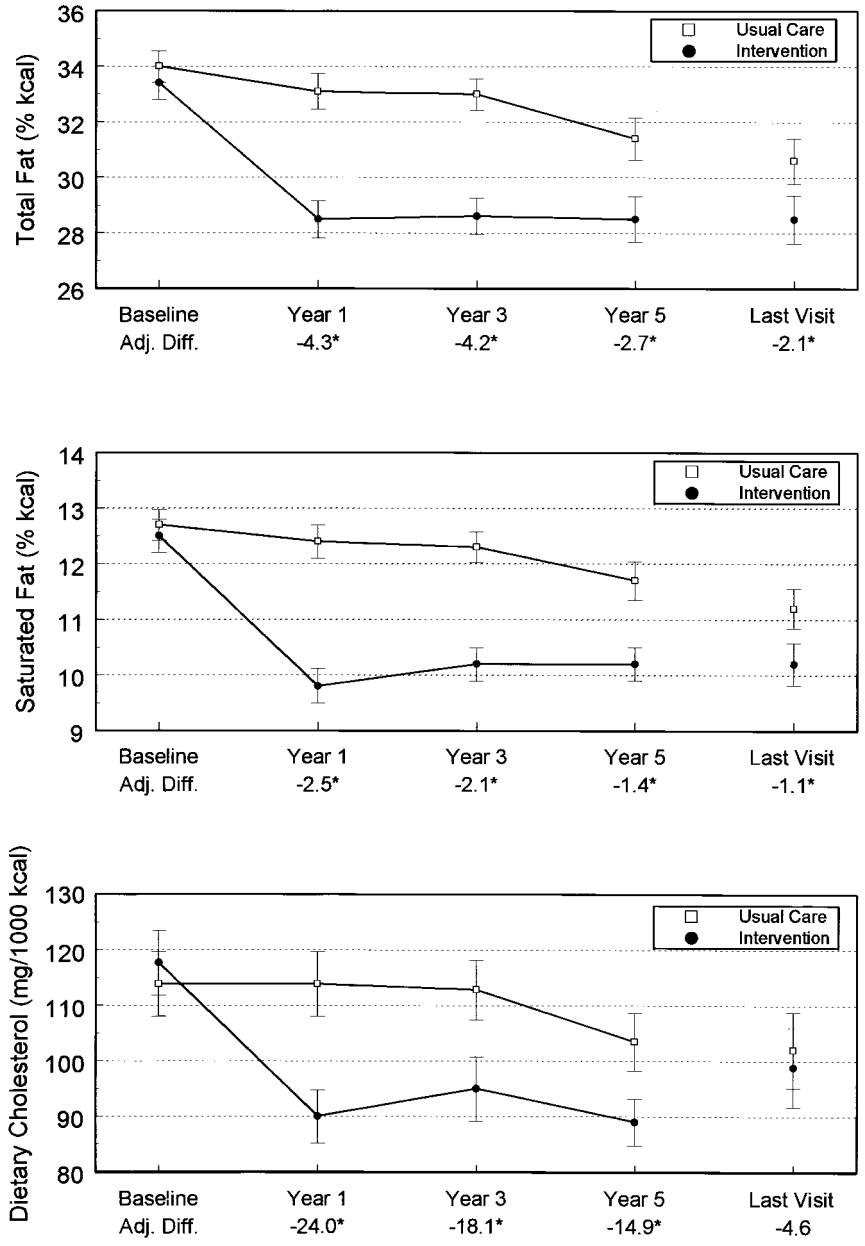

Fig 1. Total fat, saturated fat, and dietary cholesterol intakes (means and 95% CIs; *$P < .001$). Differences adjusted for baseline values of outcome variable, sex, and age at last visit (for last visit only).

130.6 mg/dL (3.38 mmol/L) to 109.8 mg/dL (2.84 mmol/L) and 112.2 mg/dL (2.90 mmol/L) at 5 years, respectively. LDL-C increased at the last visit to 114.1 mg/dL (2.95 mmol/L) and 115.9 mg/dL (3.00 mmol/L) in the intervention and usual care groups (Fig 2). Mean adjusted differences between the 2 groups were significant at 1 and 3 years ($P < .001$ and $P < .02$, respectively), but not at 5 years ($P = .11$) or at the last visit ($P = .25$). Results were virtually the same after imputation for missing values (data not shown).

The intervention and usual care groups grew to similar heights, with no significant differences at any time point (Table 2). In both groups, serum ferritin decreased during the first 3 years and increased at the last visit, with no significant differences at any time point (Table 2). Results for height and serum ferritin were similar after imputation (data not shown).

Secondary Efficacy and Safety Outcomes

Total serum cholesterol followed a similar pattern as LDL-C and was significantly lower in the intervention than the usual care group at 1 and 3 years, but not at 5 years or the last visit (Table 3). There were no differences between the 2 groups at any time point in HDL-C (except at 1 year), LDL-C/HDL-C ratio (data not shown), or triglycerides. Except at 1 year, there were no differences in BMI between the 2 groups (Table 3).

There were no differences between intervention and usual care groups in nutritional biochemical measures at 1 and 3 years[10] or at the last visit (data not shown), except for serum retinol, which was higher in the intervention group by .4 μg/dL (.04 μmol/L) at 3 years ($P = .04$) and by 2.4 μg/dL (.07 μmol/L) at the last visit ($P = .02$). There were no differences in weight or sexual maturation by Tanner

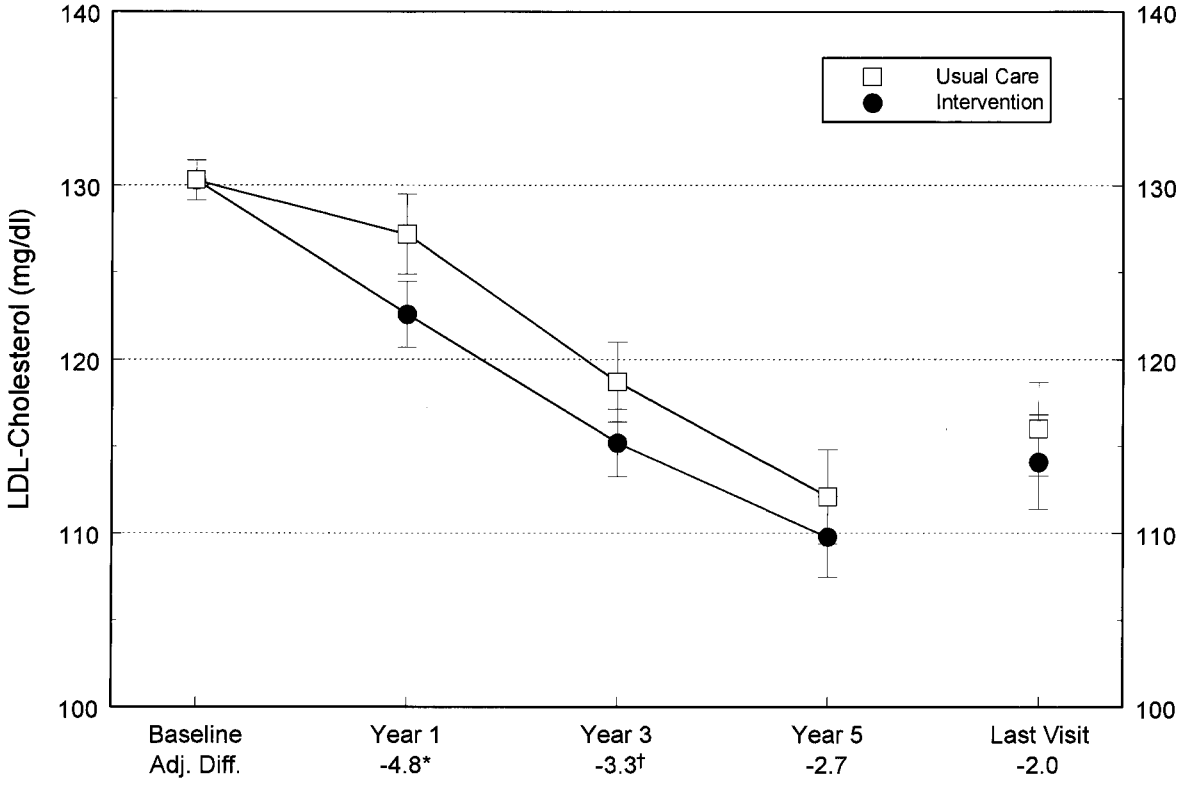

Fig 2. Primary efficacy outcome: serum LDL-C (means and 95% CIs; *$P < .001$; †$P < .05$). Differences adjusted for baseline LDL-C level, sex, and age at last visit (for last visit only).

TABLE 2. Primary Efficacy and Safety Outcomes: Height and Serum Ferritin

	Intervention			Usual Care			Adjusted Difference*		*P* Value†
	n	Mean	(SD)	*n*	Mean	(SD)	Difference	(95% CI)	
Height (cm)									
Baseline	334	136.2	(6.8)	329	136.5	(7.0)	—	—	—
Year 1	313	143.1	(6.9)	307	143.1	(7.4)	.4	(0, 0.7)	.98
Year 2	303	149.2	(7.5)	299	149.2	(7.8)	.4	(0, 0.9)	.97
Year 3	318	156.2	(8.1)	306	156.2	(8.7)	.5	(−.1, 1.1)	.95
Year 4	278	162.8	(8.2)	261	162.4	(8.6)	.6	(−.1, 1.2)	.96
Year 5	276	167.3	(8.4)	264	167.4	(8.7)	.4	(−.2, 1.0)	.88
Year 6	251	170.0	(8.7)	237	169.7	(9.1)	.3	(−.4, 0.9)	.78
Last visit	294	170.8	(8.8)	283	171.4	(9.1)	−.3	(−1.0, 0.4)	.20
Serum ferritin (mg/mL)									
Baseline	322	36.3	(19.2)	321	38.7	(21.2)	—	—	—
Year 1	310	35.2	(21.4)	303	37.3	(18.6)	−.9	(−3.5, 1.7)	.25
Year 3	299	29.7	(17.7)	286	33.5	(22.8)	−2.1	(−4.9, .8)	.08
Last visit	287	40.1	(28.9)	270	43.8	(32.6)	−2.9	(−7.2, 1.4)	.10

SD indicates standard deviation.
* Adjusted for baseline value, sex, and age at last visit (for last visit only).
† One-sided test.

staging any time during the first 6 years of the trial (data not shown). The mean age of menarche, 12.8 years, was the same for girls in both groups; 90% of intervention and 91% of usual care girls attained menarche by the last visit. Similar to findings at 1 and 3 years, there were no differences at 5 years or at the last visit in mean intakes or in the proportion who met or exceeded two thirds of the recommended daily allowances of vitamins A, C, and B_6, calcium, iron, and zinc (data not shown).

Secondary Analyses

In analyses adjusting for income, at 5 years the difference in LDL-C was somewhat larger than in the primary analysis (−3.0 mg/dL vs −2.7 mg/dL [−.08 mmol/L vs −.07 mmol/L]; $P < .08$ vs $P = .11$), respectively, but at the last visit results were the same as in the primary analysis (−2.1 mg/dL [−.05 mmol/L]; $P = .24$).

In the subset of participants who attended all clinic visits ($n = 461$), at 5 years differences in total fat, saturated fat, and cholesterol intake, as well as serum LDL-C, were larger than for the entire study population: total fat −3.1% vs −2.7% of energy; saturated fat −1.5% vs −1.4% of energy; cholesterol −16.7 vs −14.9 mg/1000 kcal; and LDL-C −4.5 mg/dL vs −2.7 mg/dL (−.12 mmol/L vs −.07 mmol/L), with the LDL-C difference significant ($P < .02$). At the last

TABLE 3. Secondary Outcomes: Lipoproteins, Lipids, and BMI

	Intervention			Usual Care			Adjusted Difference*		*P* Value
	n	Mean	(SD)	*n*	Mean	(SD)	Difference	(95% CI)	
Total Cholesterol, mg/dL [mmol/L]									
Baseline	334	200.0 [5.17]	(14.6) [.38]	329	200.0 [5.17]	(14.6) [.38]	—	—	—
Year 1	315	191.4 [4.95]	(20.9) [.54]	303	197.4 [5.10]	(21.4) [.55]	−6.1 [−.16]	(−9.1, −3.2) [−.23, −.08]	<.001
Year 3	320	183.3 [4.74]	(21.5) [.56]	303	186.4 [4.82]	(22.3) [.58]	−3.3 [−.09]	(−6.4, −0.2) [−.17, −.00]	.04
Year 5	268	175.6 [4.54]	(22.4) [.58]	254	177.9 [4.60]	(25.7) [.67]	−2.6 [−.07]	(−6.3, 1.2) [−.16, .03]	.18
Last visit	283	179.4 [4.64]	(24.1) [.62]	265	180.1 [4.66]	(26.3) [.68]	−1.1 [−.03]	(−5.0, 2.8) [−.13, .07]	.59
HDL-C, mg/dL [mmol/L]									
Baseline	334	57.1 [1.48]	(10.7) [.28]	329	57.0 [1.47]	(11.0) [.29]	—	—	—
Year 1	315	55.5 [1.44]	(11.1) [.29]	303	56.8 [1.47]	(11.1) [.29]	−1.3 [−.03]	(−2.4, −.2) [−.06, .00]	.03
Year 3	320	52.7 [1.36]	(10.0) [.26]	303	52.6 [1.36]	(10.3) [.27]	−0.2 [.00]	(−1.2, 0.9) [−.03, .02]	.75
Year 5	268	50.5 [1.31]	(11.2) [.29]	254	51.1 [1.32]	(10.2) [.26]	−.8 [−.02]	(−2.2, .6) [−.06, .02]	.28
Last visit	283	49.8 [1.29]	(11.1) [.29]	265	49.3 [1.27]	(9.6) [.25]	.3 [.01]	(−1.0, 1.7) [−.03, .04]	.62
Triglycerides, mg/dL [mmol/L]									
Baseline	334	80.1 [.90]	(28.8) [.33]	329	80.9 [.91]	(28.0) [.32]	—	—	—
Year 1	315	86.2 [.97]	(38.7) [.44]	303	87.1 [.98]	(39.4) [.44]	−.5 [−.01]	(−5.8, 4.7) [−.07, .05]	.84
Year 3	320	99.5 [1.12]	(46.0) [.52]	303	98.9 [1.12]	(44.8) [.51]	1.5 [.02]	(−4.5, 7.5) [−.05, .08]	.62
Year 5	268	100.3 [1.13]	(58.3) [.66]	254	94.5 [1.07]	(46.8) [.53]	6.6 [.07]	(−1.8, 15.0) [−.02, 0.17]	.12
Last visit	283	100.5 [1.13]	(51.2) [.58]	265	97.0 [1.10]	(44.0) [.50]	3.4 [.04]	(−4.1, 10.9) [−.05, .12]	.3
Body mass index, kg/m^2									
Baseline	334	17.5	(2.3)	329	17.6	(2.4)	—	—	—
Year 1	313	18.2	(2.7)	307	18.5	(3.0)	−.2	(−.3, 0)	.03
Year 3	317	19.9	(3.3)	305	20.1	(3.4)	0	(−.3, .2)	.39
Year 5	276	21.7	(3.8)	265	21.7	(3.7)	.1	(−.3, .5)	.67
Last visit	293	22.9	(3.8)	283	23.0	(4.1)	−.1	(−.5, .4)	.39

SD indicates standard deviation.
* Adjusted for baseline value, sex, and age at last visit (for last visit only).

visit, the results in this subset were similar to the primary analysis results.

DISCUSSION

DISC is a long-term, randomized, controlled trial of a supervised lipid-lowering dietary intervention in children with elevated LDL-C, averaging 7½ years of intervention and observation. The intervention group reduced their self-reported mean total and saturated fat intakes at 1 year and generally maintained these lower levels, despite a decrease in intervention intensity over time. Intervention/usual care comparisons remained statistically significant for dietary total fat and saturated fat throughout the trial, although not for dietary cholesterol at the last visit.

Self-reported dietary intake data indicated that dietary adherence was well-maintained by the intervention group; however, differences between intervention and usual care groups in total fat, saturated fat, and cholesterol decreased over time, resulting in nonsignificant differences in LDL-C at 5 years and at the last visit. The narrowing and then eventual absence of a significant intervention effect on LDL-C may be attributable to several factors.

The narrowing of differences in dietary total fat and saturated fat occurred primarily because of dietary changes in the usual care group, which began at 5 years. These changes may reflect national trends of increasing heart-healthy eating habits and wider availability of low-fat foods.[28] Downward trends have been observed nationally in serum total cholesterol of 5 to 7 mg/dL in adolescents from the late 1960s to the early 1990s.[29] These secular trends may have been pronounced in the DISC usual care group because they were informed of their elevated blood cholesterol levels and their pediatricians may have intervened. Also, study volunteers tend to be more health conscious and to have higher socioeconomic levels than the general public. A smaller proportion of the DISC usual care than intervention group came from households with incomes <$20 000, and secondary analyses suggest that the lower income of the intervention group may have contributed to lower dietary adherence, because between-group differ-

ences in LDL-C widened at 5 years after adjusting for income. The intervention program in the latter years of the trial simply may not have been intensive enough to do better than the secular trend. Although based on sound behavioral theories,[13,14,18,19] of the 4 intervention visits scheduled during the last year, only 1.3 visits per intervention participant were actually achieved.

In both intervention and usual care groups, LDL-C declined during adolescence, when pubertal changes have a strong impact on blood lipids,[30,31] and rose at the last visit, consistent with the LDL-C rise in late adolescence or early adulthood reported by others.[32] In a previous report, DISC observed that sexual maturation had a stronger effect than diet on LDL-C.[31] The impact of pubertal changes could be so powerful that the additional impact of dietary change is more difficult to observe.

DISC results are based on the intention-to-treat analysis principle. At the last visit, attempts were made to measure all randomized children, regardless of whether they were active participants. Thus, the final LDL-C levels include the LDL-C values of some assigned intervention participants who did not have continuous exposure to the DISC intervention, thereby potentially diluting the overall intervention effect. Analyses examining the subset of children who attended all clinic visits (an indicator of higher study adherence) suggest that decreased adherence did play a role in narrowing the between-group difference in LDL-C. In this subset, differences in dietary fat were evident, and LDL-C was significantly lower in the intervention than usual care group at 5 years.

The DISC intervention focused on lowering total fat, saturated, fat, and cholesterol to reduce LDL-C. Although part of the intervention, polyunsaturated fat changed very little and did not contribute to LDL-C lowering. Other dietary and lifestyle factors that were not part of the DISC intervention but that promote a favorable lipid profile include maintaining a healthy body weight, increasing physical activity, and lowering trans fatty acids.[33]

Reporting bias in the intervention group could have occurred, particularly for dietary fat, as suggested by the lower reported energy intakes than the usual care group. It is likely, however, that true differences in total and saturated fat intake were achieved, because the dietary data were consistent with the serum lipid data: at all follow-up visits, lower saturated fat intakes were accompanied by lower LDL-C levels in the intervention than in the usual care group. As saturated fat differences between the 2 groups narrowed over time, differences in LDL-C also narrowed, becoming no longer significant, although always with the intervention group lower. In the subset of children who attended all clinic visits, there were greater between-group differences in saturated fat and cholesterol, and correspondingly greater LDL-C differences, than in the entire DISC study sample.

The magnitude of the net difference in LDL-C between intervention and usual care groups in DISC at 3 years (2.5%) is similar to other studies. School- and community-based studies of children, which have targeted several health behaviors including diet, physical activity, and smoking, have reported net reductions of 3% to 4% in total cholesterol over a 2- to 5-year follow-up,[34–36] although others have reported no effect on total cholesterol.[37] A 1-year clinic-based, randomized study of 261 children with elevated LDL-C, 4 to 10 years of age, reported a net reduction in LDL-C of <2%[38]—approximately half the 3.7% net reduction observed in DISC at 1 year. Another randomized study of 1062 seven-month-old infants reported a 6.6% net reduction in total cholesterol over 3 years.[39] Whether this magnitude of difference experienced early in life impacts future disease risk warrants further investigation and follow-up of these cohorts.

A salient finding from DISC is the safety of an intervention to promote a fat-reduced diet in actively growing children with elevated LDL-C, when they are instructed properly and followed at regular intervals. Consistent with the 3-year results, when no adverse effects were observed in the intervention group and when no growth or biochemical outcomes were adversely related to lower fat intake,[10,40] continued intervention resulted in no difference between intervention and usual care groups in growth, sexual maturation, or nutritional adequacy, including serum ferritin level, despite differences in self-reported dietary fat intake.

A limitation of the present study was that the differences in total fat intake at 5 years and the last visit were only half as large as those observed in the earlier years of the trial. However, the present study showed that reduced fat diets during peak growing years did not have long-term adverse effects on children's height, serum ferritin levels, or nutritional status years later as the children reached late adolescence. Furthermore, in the subset of children who attended all clinic visits, no adverse effects on height and serum ferritin were evident between the intervention and usual care children after 5 years of intervention, when significant dietary fat and LDL-C differences were present.

CONCLUSION

The DISC trial provides needed information on the long-term feasibility, efficacy, and safety of dietary intervention in rapidly growing children with elevated LDL-C. Results show that dietary fat modification can be achieved and safely sustained in pubertal children, with no adverse effects observed up to 7.4 years later. LDL-C levels can be improved: significantly over 3 years with intensive dietary intervention, although not significantly over 5 years with a lower-intensity maintenance intervention. Albeit nonsignificant at 5 years or the last visit, the net LDL-C differences observed between intervention and usual care groups over the entire course of the study indicate the potential for decreasing lifetime exposure to elevated LDL-C by dietary intervention. Also, changes in the usual care group's diet suggest that pediatric practices and societal and environmental forces are having positive public health effects on dietary behaviors during adolescence. A combina-

tion of individual counseling from pediatricians and other primary health care providers, along with community-based programs and public health campaigns, may work together to promote cardiovascular health in children.

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REFERENCES

1. Expert Panel on Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program report. *Pediatrics*. 1992;89: 525–584
2. Pathobiological Determinants of Atherosclerosis in Youth Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking: a preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *JAMA*. 1990;264:3018–3024
3. Berenson GS, Wattigney WA, Tracy RE, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). *Am J Cardiol*. 1992;70:851–858
4. National Research Council, Committee on Diet and Health. Fats and other lipids. In: *Diet and Health: Implications for Reducing Chronic Disease Risk*. Washington, DC: National Academy Press; 1989:159–258
5. US Department of Agriculture, Department of Health and Human Services. *Nutrition and Your Health: Dietary Guidelines for Americans*. 4th ed. Washington, DC: US Department of Agriculture/Department of Health and Human Services; 1995
6. Kaplan RM, Toshima MT. Does a reduced fat diet cause retardation in child growth? *Prev Med*. 1992;21:33–52
7. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *Br Med J*. 1990;301:309–314
8. Mauer AM. A pediatrician attends the National Institutes of Health Consensus Conference on Lowering Blood Cholesterol. *Pediatrics*. 1985; 76:125–126
9. DISC Collaborative Research Group. Dietary Intervention Study in Children (DISC) with elevated low-density-lipoprotein cholesterol: design and baseline characteristics. *Ann Epidemiol*. 1993;3:393–403
10. The Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol: the Dietary Intervention Study in Children (DISC). *JAMA*. 1995;273:1429–1435
11. Lavigne JV, Brown KM, Gidding S, et al. A cholesterol-lowering diet dose not produce adverse psychological effects in children: results from the Dietary Intervention Study in Children (DISC). *Health Psychol*. 1999; 18:604–613
12. Lipid Research Clinics. *Population Studies Data Book, I: The Prevalence Study*. Washington, DC: US Public Health Service; 1980
13. Bandura A. *Social Learning Theory*. Englewood Cliffs, NJ: Prentice Hall; 1977
14. Ewart C. Social action theory for public health psychology. *Am Psychol*. 1991;46:931–946
15. Stevens VJ, Obarzanek E, Franklin FA, et al. Dietary Intervention Study in Children (DISC): intervention design and participation. *J Nutr Educ*. 1995;27:133–140
16. Hartmuller VW, Snetselaar L, Van Horn L, et al. Creative approaches to cholesterol lowering used in the Dietary Intervention Study in Children. *Top Clin Nutr*. 1994;10:71–78
17. Berg-Smith SM, Stevens VJ, Brown KM, et al. A brief motivational intervention to improve dietary adherence in adolescents. *Health Educ Res*. 1999;14:399–410
18. Miller W, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behaviors*. New York, NY: Guilford Press; 1991
19. Prochaska JO, Velicer WF, Rossi JS, et al. Stages of change and decisional balance for twelve problem behaviors. *Health Psychol*. 1994;13:1–8
20. DeLong DM, DeLong ER, Wood PD, Lippel K, Rifkind BM. A comparison of methods for the estimation of plasma low- and very low-density lipoprotein cholesterol: the Lipid Research Clinics Prevalence Study. *JAMA*. 1986;256:2372–2377
21. Myers GL, Cooper GR, Winn CL, Smith SJ. The Centers for Disease Control-National Heart, Lung, and Blood Institute Lipid Standardization Program: an approach to accurate and precise lipid measurements. *Clin Lab Med*. 1989;9:105–135
22. Tanner JM. *Growth at Adolescence*. 3rd ed. Oxford, England: Blackwell Scientific; 1962
23. Van Horn L, Gernhofer N, Moag-Stahlberg A, et al. Dietary assessment in children using electronic methods: telephones and tape recorders. *J Am Diet Assoc*. 1990;90:412–416
24. Gunter EW, Lewis BG, Koncikowski SM. *Laboratory Methods Used for the Third National Health and Nutrition Examination Survey (1988–1994)*. Atlanta, GA: Centers for Disease Control and Prevention; 1995
25. Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression Analysis and Other Multivariate Methods*. 2nd ed. Boston, MA: PWS-Kent Publishing Co; 1988
26. SAS Institute Inc. *SAS/STAT User's Guide*. 4th ed. Cary, NC: SAS Institute Inc; 1989
27. MathSoft I. *S-Plus 4 Guide to Statistics*. Seattle, WA: MathSoft; 1997
28. Ernst ND, Sempos CT, Briefel RR, Clark MB. Consistency between US dietary fat intake and serum total cholesterol concentrations: the National Health and Nutrition Examination Surveys. *Am J Clin Nutr*. 1997;66:965S–972S
29. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among US children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. *Prev Med*. 1998;27:879–890
30. Tell GS, Mittelmark MB, Vellar OD. Cholesterol, high density lipoprotein cholesterol, and triglycerides during puberty: the Oslo Youth Study. *Am J Epidemiol*. 1985;122:750–761
31. Kwiterovich PO Jr, Barton BA, McMahon, et al. Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty: the Dietary Intervention Study in Children (DISC). *Circulation*. 1997;96:2526–2533
32. Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. *Am J Epidemiol*. 1981;113:157–170
33. Krauss RM, Deckelbaum RJ, Ernst N, et al. Dietary guidelines for healthy American adults: a statement for health professionals from the

Nutrition Committee, American Heart Association. *Circulation*. 1996;94: 1795–1800
34. Resnicow K, Cross D, Wynder E. The role of comprehensive school-based interventions: the results of four Know Your Body studies. *Ann N Y Acad Sci*. 1991;623:285–298
35. Tell GS, Vellar OD. Noncommunicable disease risk factor intervention in Norwegian adolescents: the Oslo Youth Study. In: Hetzel B, Berenson GS, eds. *Cardiovascular Risk Factors in Childhood: Epidemiology and Prevention*. New York, NY: Elsevier Science Publishers BV; 1987:203–217
36. Vartiainen E, Tossavainen K, Viri L, Niskanen E, Puska P. The North Karelia youth programs. *Ann N Y Acad Sci*. 1991;623:332–349
37. Luepker RV, Perry CL, McKinlay SM, et al. Outcomes of a field trial to improve children's dietary patterns and physical activity: the Child and Adolescent Trial for Cardiovascular Health (CATCH). *JAMA*. 1996;275: 768–776
38. Tershakovec AM, Shannon BM, Achterberg CL, et al. One-year follow-up of nutrition education for hypercholesterolemic children. *Am J Public Health*. 1998;88:258–261
39. Niinikoski H, Viikari J, Ronnemaa T, et al. Prospective randomized trial of low-saturated-fat, low-cholesterol diet during the first 3 years of life: the STRIP Baby Project. *Circulation*. 1996;94:1386–1393
40. Obarzanek E, Hunsberger SA, Van Horn L, et al. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). *Pediatrics*. 1997; 100:51–59

PROTECTING RESEARCH SUBJECTS

. . . In a report released in February 2000 by the Office of the Inspector General of the Department of Health and Human Services,[2]disturbing recruitment practices were brought to my attention . . . The report focused on studies funded by drug companies, which sponsor most clinical research. It noted that aggressive recruiting by researchers who have been offered money or other inducements might be contributing to the erosion of informed consent. As researchers are pressured to recruit subjects quickly in order to discover the next blockbuster drug, they may misrepresent the true nature of a trial, or they may simply appeal to their patients' trust. The report also described misleading promotions and advertisements. Researchers promised treatment for disease, when in fact they wanted to use patients in trials of drugs that were potentially both risky and ineffective. Neither for financial reasons nor under the guise of furthering science can we allow any erosion of informed consent. To use human subjects without their full knowledge and understanding, to place them at needless risk, is unconscionable . . . Institutional review boards (IRBs), the key element of the system to protect research subjects, are under increasing strain. In June 1998, the Office of Inspector General of the Department of Health and Human Services issued four investigative reports, which indicated that IRBs have excessive workloads and inadequate resources.[4–7] At a number of institutions, IRB oversight was inadequate, and on occasion, researchers were not providing the boards with sufficient information for them to evaluate clinical trials fully.

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REFERENCES

1. *Report on University Protections of Human Beings Who Are the Subjects of Research.* Washington, DC: Association of American Universities; 2000
2. *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research.* Washington, DC: Department of Health and Human Services; 2000
3. Henney JE. Remarks. Presented at the Association of American Medical Colleges Council of Teaching Hospitals Spring Meeting, Washington, DC, May 10–12, 2000
4. *Institutional Review Boards: Their Role in Reviewing Approved Research.* Washington, DC: Department of Health and Human Services; 1998
5. *Institutional Review Boards: Promising Approaches.* Washington, DC: Department of Health and Human Services; 1998
6. *Institutional Review Boards: The Emergence of Independent Boards.* Washington, DC: Department of Health and Human Services; 1998
7. *Institutional Review Boards: A Time for Reform.* Washington, DC: Department of Health and Human Services; 1998
8. *Protecting Human Research Subjects: Status of Recommendations.* Washington, DC: Department of Health and Human Services; 2000
9. Angell M. Is academic medicine for sale? *N Engl J Med.* 2000;342–1516-1518

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