Individual Cholesterol Variation in Response to a Margarine- or Butter-Based Diet: A Study in Families

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Cholesterol-lowering diets have been recommended for the population at large to reduce the incidence of coronary heart disease. Changes in the mean lipid and lipoprotein levels can be reliably predicted from changes in population intake of dietary fatty acids and cholesterol. The projected benefits of dietary modification are substantial and are directly linked to the magnitude of cholesterol level reduction.

Although populational responses to diet can be reliably predicted, it is impossible to predict how much cholesterol lowering a given individual will achieve as a result of dietary modification. Individual responses follow a peaked distribution around the mean population response. Theoretically, two thirds of individuals fall within 1 SD of the mean response, with some individuals having little or no cholesterol-lowering response to diet.

Predicting who will and will not respond to diet modification would allow the clinician to target aggressive cholesterol-lowering dietary therapy for those patients who are most responsive to diet. It also would allow the clinician to differentiate between nonresponders who are noncompliant from nonresponders who do not have the biological potential to respond to diet modification.

This study was designed to evaluate whether familial differences explain why individuals respond differently to cholesterol-lowering diets. The prevalence of individuals who do not respond to diet has been estimated at 17% of institutionalized men on a controlled diet and 15% to 20% of free-

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Context The effectiveness of dietary modification in reducing low-density lipoprotein cholesterol (LDL-C) levels can be reliably predicted for populations, but not for individuals.

Objective To determine whether individual variation in cholesterol response to dietary modification is a familial trait.

Design Two-period, outpatient crossover trial conducted from September 1997 to September 1999.

Setting and Participants Fifty-six families from the Dallas–Ft Worth, Tex, area with 2 biological parents and at least 2 children aged 5 years or older volunteered; 46 families (n=92 adults and n=134 children) completed the study.

Intervention All families followed two 5-week dietary regimens that included individualized daily dietary prescriptions and emphasized a low–saturated fat diet supplemented with specially manufactured baked goods and spreadable fat. One regimen used butter only and the other used margarine only.

Main Outcome Measure Mean LDL-C levels during the last 2 weeks of each dietary period.

Results Margarine intake compared with butter intake lowered LDL-C levels 11% in adults (95% confidence interval [CI], −13% to −9%) and 9% in children (95% CI, −12% to −6%) (P<.001 for both adults and children). The distribution of individual responses was peaked around the mean response. For adults and children together, family membership accounted for 19% of variability in response (P=.007). In children, family membership accounted for 40% of variability in response of percent change in LDL-C levels (P=.002). Body mass index and change in cholesterol ester (CE) 18:2/18:1 ratio accounted for 26% of variation, leaving 26% still attributable to family membership. In all participants, BMI predicted response—heavier individuals had higher LDL-C levels, less excursion in CE fatty acids, and less LDL-C response to dietary change.

Conclusions Our results suggest that individual variation in response to a cholesterol-lowering diet is a familial trait. Body weight is an important modifiable factor that influences response.

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living men, women, and children on counseled diets. Although associations between specific genotypes and dietary responsiveness among unrelated individuals have been reported, no factor has been found to be consistently associated with response, and no single factor has explained more than 10% of the individual variation observed.

**METHODS**

The study protocol was approved by the institutional review board at the University of Texas Southwestern Medical Center and the Human Subjects Review Committee at the Veterans Health Administration North Texas Center, Dallas.

**Subjects**

Families from the Dallas–Ft Worth metropolitan area were recruited during their attendance at various museums, health fairs, and church events over 2 years (September 1997 to September 1999). Families were selected by 2 criteria only: interest in participation and having an intact family with 2 biological parents and 2 or more biologically related children aged 5 years and older. During a follow-up telephone contact, a home visit was scheduled where the study was described, and the age, height, weight, physical activity, and dietary preferences for all family members were recorded. If all family members remained interested, a date was set to draw ad libitum fasting blood samples and study initiation. Fifty-six families agreed to participate, and 46 families completed the entire diet study. Reasons for dropout included difficulty following dietary protocol restrictions (5 families), refusal of a child to have blood drawn after the study was initiated (2 families), and change in health status of parent (3 families). Of the 46 families, 39 were white, 3 African American, 2 Hispanic American, 1 American Indian, and 1 Asian American. Baseline characteristics of the 46 families are detailed in Table 1; the characteristics of the 10 families who dropped out were similar to those who completed the trial. All children completing the trial received a $50 payment. All family members completing a 3-day diet record received 1 movie pass (value $4) for each of the 4 requested records.

**Dietary Design**

The study was a 2-period, crossover, outpatient diet counseling study designed to compare the isocaloric substitution of butter for margarine as the major dietary fat intake. Each dietary period was 5 weeks in duration. Since commercial tub margarine is 60% or less fat by weight and butter is 80% fat by weight, a single batch of 80% fat by weight margarine was produced for this study (courtesy of Unilever, Baltimore, Md). This allowed for a 1-to-1 substitution of the fats for use as a spread as well as in cooking and baking. The margarine contained 38.7% cis-polyunsaturated fatty acids and 7.5% trans-fatty acids. The butter contained 50.6% saturated fatty acids, of which 8.6% was stearic acid.

Specially formulated products were produced by a local bakery for use in the study. Participants/assessors could not be blinded to the type of fat because of the inherent differences in study products. Families were counseled to continue a low–saturated fat diet during their meals that did not contain study food choices. We expected an inability to adhere to the protocol for 3 meals each week, with a projected test fat intake of 21% of calories. Families were counseled to continue a low–saturated fat diet during their meals that did not contain study products. A portable food scale was provided and household cups and bowls were used to instruct families on how to estimate portion size.

The daily prescription was based on an intake of 25% of energy from test fat. Subjects were instructed to follow the plan as much as possible and to choose low-fat foods for their nonstudy food choices. We expected an inability to adhere to the protocol for 3 meals each week, with a projected test fat intake of 21% of calories. Families were counseled to continue a low–saturated fat diet during their meals that did not contain study products. A portable food scale was provided and household cups and bowls were used to instruct families on how to estimate portion size.

**Dietary Evaluation**

Compliance to diet was assessed by 3 measures:

**Product Inventory for Family.** During each weekly visit, sufficient study products were delivered to families by investigators to meet 100% adherence

| Table 1. Baseline Characteristics of Adults and Children From 46 Participating Families* |
|---------------------------------|-----------------|------------------|
| **Characteristics**        | **Adults** | **Children** |
| Age, y†                     | 41 (4)     | 12 (4)        |
| Sex                         |            |                |
| Males, No. (%)              | 46 (50)    | 71 (53)       |
| Females, No. (%)            | 46 (50)    | 73 (47)       |
| BMI, kg/m²‡                 | 28.8 (6.5) | 19.3 (4.3)    |
| Total cholesterol, mg/dL†   | 184 (27)   | 152 (25)      |
| Triglycerides, mg/dL‡       | 122 (74)   | 74 (41)       |
| HDL-C, mg/dL†               | 121 (27)   | 96 (22)       |
| ApoE, No. (%)§              |            |                |
| ApoE 4/4                    | 1 (1)      | 1 (0.7)       |
| ApoE 4/3                    | 27 (29)    | 36 (27)       |
| ApoE 3/3                    | 49 (53)    | 77 (57)       |
| ApoE 3/2                    | 12 (13)    | 13 (10)       |
| ApoE 4/2                    | 3 (3)      | 5 (4)         |
| ApoE 2/2                    | 0 (0)      | 2 (1)         |

*BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and ApoE, apolipoprotein E.
†Values are expressed as mean (SD). To convert mg/dL to mmol/L, multiply by 0.0259.
‡To convert mg/dL to mmol/L, multiply by 0.0113.
§Percentages may not equal 100 because of rounding.
to the daily dietary prescription. During the delivery, an inventory of un consumed food products was recorded. Allowing for 3 meals per week without study foods, 85% of the delivered food was expected to be consumed.

Daily Check Sheets. All family members were provided personalized daily check sheets to mark off how much of each study product they consumed each day. Sheets were collected during the weekly visit and recorded, and the grams of test fat consumed were calculated. Adherence was estimated as gram intake reported to be consumed divided by gram intake for 100% adherence. As with family inventory, the goal intake was 85%.

Three-Day Diet Records. During the third and fourth week of each diet period, each subject was asked to complete a 3-day diet record of total diet consumed during the weekend day and 2 weekdays. Records were analyzed using Nutritionist IV (San Bruno, Calif), and the gram intake of test fat was calculated. Goal intake of test fat was 21% of total energy.

**Laboratory Evaluation**

Subjects had blood drawn prior to initiation of the study (ad libitum) and twice during the last 2 weeks of each dietary period. Blood samples were drawn 4 to 7 days apart to minimize the influence of biological variation on mean response. All blood samples were obtained after having subjects fast for 10 hours; all blood samples were stored using numeric identification code that could be decoded only by the investigators.

Lipoprotein Analysis. Lipid and lipoprotein analyses were performed on each blood sample. Plasma was separated, and plasma concentrations of total cholesterol (Roche, Indianapolis, Ind) and triglycerides (Sigma Diagnostics, St Louis, Mo) were measured using an enzymatic procedure. High-density lipoprotein cholesterol (HDL-C) level was measured as the remaining cholesterol in whole plasma after precipitating apolipoprotein B-containing lipoproteins with 6.59 mmol/L of phosphotungstic acid (Dade International, Miami, Fla). To reduce phlebotomy requirements, the LDL-C level was calculated using the Friedewald equation. If a subject had a fasting triglyceride levels greater than 4.52 mmol/L (400 mg/dL), the LDL-C levels were determined by direct assay (Sigma Diagnostics).

**Dietary Response.** Response to diet was defined as the difference in mean LDL-C level of the margarine intake period minus the mean LDL-C level of the butter intake period.

**Cholesterol Ester and Triglyceride Fatty Acids.** Plasma triglyceride and cholesterol ester (CE) fatty acids levels were determined in the last blood draw of each diet period by extracting lipids from plasma and separating lipid classes by thin-layer chromatography. Genotypes for Apolipoprotein E (ApoE) and 7α-Hydroxylase. DNA was extracted from the white blood cell pellet with DNA-zol Reagent (GIBCO-BRL, Grand Island, NY). 7α-Hydroxylase DNA was amplified with 1 pmol/µL of each primer AP2 (5'-TGGTAGGTTAATTATTAATAGATG-3') and AE I and was electrophoresed. Apolipoprotein E DNA was amplified by PCR in a DNA thermal cycler using oligonucleotide primers F4 (5'-ACAGATTGCCCAAGCTCTTGAC-3') and F6 (5'-TAAAGCTTGACCGGCTGTCACA-3').

**Reproducibility of Response**

To evaluate the reproducibility of individual dietary response, each of the first 20 families that completed the study were asked at the time of their sign-out interview to consider repeating the entire diet study. Two families agreed (n = 4 adults and n = 8 children). The first family began the second dietary trial 5 months later and received the study foods in the same diet order as their original study. The second family repeated the study 3 months later, receiving the opposite diet order. Body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) measurements prior to each study were fairly comparable except in 2 members of the first family who gained 9 kg (20 lb) during the interval between their dietary trials.

**Statistical Methods**

The primary analysis was dietary response, which by definition could be determined only in those families who completed the trial. To avoid underestimating SEs because of correlations between family members, generalized estimating equations (GEEs) were used to compare the 2 diets and construct confidence intervals (CIs) to adjust for the lack of independence within families. Triacylglycerides levels were log transformed because of skewness; both untransformed and transformed data gave similar results so only untransformed data are reported. Also, GEE was used to assess the reproducibility among the 2 families who agreed to repeat the study. Mixed linear models were used to assess covariates and variance components. In these models, family membership was included as a random effect. Bakery run or diet order did not contribute to observed variance. Individual level covariates considered for the model were either clinically relevant or significantly associated with dietary response by univariate analysis. These covariates included age, BMI, ad libitum LDL levels, ApoE genotype, and change in serum fatty acid CE levels. Because of significant interrelationships among these covariates, all possible interactions between these covariates also were considered. Apolipoprotein E genotype was evaluated by combining several genotypes into 3 categories: ApoE 2,2 plus 2,3; ApoE 3,3 plus 2,4; and ApoE 3,4 plus 4,4. Comparison of these 3 categories was made using 2 dummy variables in the models. Variance components were used to estimate family intraclass correlation. Separate regressions also were estimated for adults and children. One extreme outlier, a child with a dietary response of −109 mg/dL.
(-2.8 mmol/L), was not included in regression models.

Statistical analysis was performed using SAS version 8.0 (SAS Institute, Cary, NC). Because of the multiple testing, a P < .01 was assigned as significant.

RESULTS

Dietary Adherence

By all measures, compliance to the dietary protocol was excellent. According to food inventory, families consumed a mean (SD) of 88% (12%) and 83% (16%) of test fat delivered during the margarine or butter intake periods, respectively. Daily check sheets showed consistently lower mean (SD) intakes of 75% (18%) and 77% (17%), respectively. The consistently lower intakes of test fat recorded on daily check sheets may reflect some days in which subjects consumed test fat but did not record their consumption.

The mean intake of macronutrients recorded on the 3-day food records is listed in Table 2. The goal of test fat intake of 21% of energy was achieved for the margarine intake period but was significantly lower for the butter intake period (18% of calories, P < .01). The lower intake of test fat in the butter intake period was accounted for by an unexpected preference for the margarine bread compared with the butter croissants. The 3% less energy from test fat during the butter intake period was offset by small increases in calories from protein (P < .01) and saturated fat (P < .01) from other sources (eg, whole milk and ice cream). Dietary cholesterol was significantly higher (P < .01) for the butter intake period. The overall dietary goal—to achieve a clinically significant difference in intake of cholesterol-raising fatty acids for the 2 diets—was achieved.

Mean Lipoprotein Response to Diet

Consistent with the reported intake, there was no change in body weight between the 2 diet periods (Table 3). Margarine intake produced significantly lower total LDL-C levels than butter intake (P < .001). Adults were more responsive than children on the basis of levels (0.41 mmol/L [16 mg/dL] vs 0.28 mmol/L [11 mg/dL], P = .03) but not when considered as percent reduction of LDL-C levels (11%; 95% CI, -13% to -9% mg/dL vs 9%, 95% CI, -12% to -6%; P = .17).

No significant differences in HDL-C levels were seen in adults (P = .83) and children (P = .80). A trend for an increase in triglycerides during the butter intake period was seen in adults (P = .03) but not in children (P = .45). Changes in CE fatty acids mirrored changes in dietary intake, with significant increases in CE 18:2 content and decreases in CE 16:0 content in the margarine intake period compared with the butter intake period (P < .005). The primary change in CE content was a substitution for the CE 18:1 content by CE 18:2 content during the margarine intake period, which expressed as a ratio fell from percent (SD) of 5.7% (0.9%) in the margarine intake period to 4.9% (0.8%) in the butter intake period (P < .001).

Dietary Responsiveness

Dietary responsiveness was defined as the mean margarine LDL-C level minus the mean butter LDL-C level. This...
value was expressed as either an absolute value (mmol/L [mg/dL]) or percentage change from the LDL-C value achieved in the margarine intake period.

**Individual Variation in Dietary Responsiveness.** The frequency distribution of individual responses to diet shows that 81% of subjects had lower LDL-C levels in the margarine intake period compared with the butter intake period, and 76% had a 3% or greater reduction in LDL levels (Figure).

**Reproducibility of Individual Variation in Dietary Responsiveness.** Two families (family 1 and family 2) repeated the diet study and 2 members of family 1 gained 9 kg (20 lb) between dietary challenges. Mean LDL-C levels and the ratio of CE 18:2/18:1 content obtained in the initial butter or margarine intake period were compared with those values obtained in the repeat period. The mean difference in change in LDL-C levels between the 2 trials was 0.01 mmol/L (0.5 mg/dL) ($P = .78; 95\% CI, −0.08 mmol/L (−3.3 mg/dL) to 0.11 mmol/L (4.4 mg/dL)). Results were fairly reproducible with low responders in the initial period having low response in the repeat period and vice versa; those subjects who gained weight were less responsive in the second dietary challenge, but their overall response remained in the same rank order.

**Familiality Evaluation Using Intraclass Correlation**

Self-reported paternity/maternity status was verified with ApoE and 7 α-hydroxylase genotypes expected/observed in the children compared with their parents. Estimates for proportion of variance explained by family membership were made using mixed linear models. Considering adults and children in the same model, family membership accounted for 19% of variability in percent change in LDL-C levels ($P = .007$). When children were considered separately (Table 4), 40% of the variability in percent change in LDL-C levels was explained by family membership ($P = .002$).

**Predictors of Responsiveness to Diet**

No significant correlations were observed between variations in compliance (estimated by family inventory, daily check sheet, and food record) and variation in response to diet. No significant correlations were found between dietary responsiveness and changes in body weight, diet order, age, 7 α-hydroxylase genotype, or sex. Significant associations were found between dietary responsiveness and BMI, ad libitum LDL-C levels, ApoE genotype, CE 18:2 content, CE 18:1 content, and changes in CE 18:2/18:1 ratio. These variables, in turn, were significantly intercorrelated, making it difficult to quantify how much each factor influenced response. Separate prediction models for adults (not genetically related) and children (2-9 per family genetically related) were as follows: Among children, family membership explained 42% of the variation in percent change in LDL-C levels ($P = .002$) (Table 4). Significant covariates of response were BMI and change in CE ratio, explaining 26% of variation and leaving 26% still attributable to family membership. The importance of BMI was even more striking considering the relative leanness of the children compared with the adults. Among adults, family membership accounted for 0% of variation in percent change LDL-C levels; BMI, ApoE genotype, and a BMI × ApoE interaction accounted for 14% of the variation observed.

The interrelationship between ad libitum LDL-C levels (a significant predictor in children) and ApoE genotype (a significant predictor in adults), the relationship between ApoE genotype, ad libitum LDL-C levels, and percentage change in LDL-C levels were further evaluated. The ApoE genotype was significantly associated with ad libitum LDL-C levels when comparing either ApoE 2,2 plus 3,2 vs 4,4 plus 4,3 or ApoE 3,3 plus 2,4 vs 4,4 plus 4,3 (both $P = .002$). However, ApoE genotype accounted for only 4% of the variation in ad libitum LDL-C levels. Although ApoE genotype contributed

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**Figure.** Frequency of Percent Change in Low-Density Lipoprotein Cholesterol Levels in Adults and Children
more than ad libitum LDL-C levels to dietary response in adults, in children the model including ad libitum LDL-C levels accounted for 7% additional variance than the model including ApoE genotype (data not shown).

Since BMI was the only factor consistently appearing in all models, the relationship between BMI and response was examined further. Compliance to diet was not associated with BMI, and differences in compliance were not seen across categories of BMI (data not shown). Surprisingly, the change in CE ratio paralleled the change in LDL-C levels; obese persons had approximately half the response in LDL-C levels and CE ratio than leaner persons (mean [SD] change in LDL-C levels and change in CE 18:2/18:1 ratio for BMI<21, −13 [17] and 0.85 [0.82], and for BMI ≥30, −9 [17] and 0.42 [0.75]).

**COMMENT**

The substitution of margarine for butter creates 3 simultaneous changes in dietary intake that, in turn, alter total cholesterol and LDL-C levels. Two changes—reductions in saturated fatty acids and dietary cholesterol intake—lower LDL-C levels. A third change—increases in trans-fatty acid intake—raises LDL-C levels and also may lower HDL-C levels. Increases in trans-fatty acid intake could potentially mitigate the benefits of a margarine-based diet. In our study, a low trans margarine-based diet achieved 11% lower LDL-C levels than a butter-based diet, without differences in HDL-C levels. Our findings agree with those from metabolic diet studies evaluating greater and lesser percentages of energy from butter vs margarine, confirming the long-standing advice to the public at large to choose a tub margarine over butter.

Translating the public benefits of dietary modification to a given individual are difficult because of individual variation in response to dietary change. As previously reported, we found the distribution of dietary response to peak around the mean: 19% of individuals had either no change or a paradoxical increase in LDL-C levels in the margarine intake period compared with the butter intake period. The differences in responsiveness to diet could be attributable to genetic factors. In our study, we tested this hypothesis by evaluating how individual family members responded to both a cholesterol-lowering and cholesterol-raising diet. Family dietary responsiveness data allowed for an estimation of the contribution of family membership (shared genes plus shared environment) on responsiveness. A margarine vs butter comparison was chosen since these 2 types of fats lend themselves to simple substitution in both baking and spreads, and previous studies suggested that the response to dietary cholesterol and saturated fat appear congruent.

Ideally, a study of dietary responsiveness would be conducted under

### Table 4. Predictive Models Evaluating the Contribution of Family Membership to the Variability in Dietary Responsiveness With or Without Inclusion of Significant Covariates

<table>
<thead>
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<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P Value</th>
<th>Coefficient</th>
<th>SE</th>
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<th>Coefficient</th>
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<td>&lt;.001</td>
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<td>.01</td>
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<td>&lt;.001</td>
<td>−16.93</td>
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<tr>
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<td>0.045</td>
<td>.001</td>
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<td>(\ldots)</td>
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<td>0.19</td>
<td>0.36</td>
<td>.60</td>
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</table>

Total variation explained by model covariates, % 26 (P=.003) 26 (P=.002) 0

Remaining variation explained by family membership, % 24 (P=.02) 26 (P=.02) 0

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*LDL-C indicates low-density lipoprotein cholesterol; BMI, body mass index; CE, cholesterol ester; and ApoE, apolipoprotein E. To convert mg/dL to mmol/L of LDL-C, multiply by 0.0259. Ellipses indicate that this factor was not a significant contributor to the model.

†Regression estimates are computed with random coefficient models to account for correlation among family members; ApoE 2 includes subjects with 2,2 and 3,2; ApoE 3 includes subjects with 3,3 and 4,2; ApoE 4 includes subjects with 3,4 and 4,4 genotypes.

§Five children with missing covariate data and the outlier were excluded from regression models.
more strict metabolic control to ensure standard intake of fats. For the number of subjects in our study, a metabolic diet study would have been unwieldy and costly. Using resources available, we taught families how to measure portion sizes at home and provided detailed low-fat dietary prescriptions for each family member. This base diet was supplemented with baked goods and spreadable fats that were provided to the families. Subjects were given an explicit daily and weekly goal for consumption of test fat and test fat products, and this goal and their progress was reviewed during a weekly home visit. Compliance was excellent, and the lipid lowering that was achieved matched that of the predicted data derived from other metabolic diet studies.

The primary literature linking genetic factors with dietary responsiveness in humans are reports from studies in unrelated individuals in which the genetic analysis occurred after the dietary trial was completed. One study in which subjects were preselected based on their genotype, the Apo A-IV allele was associated with variation in response to dietary cholesterol. Our study approached the issue of variability in dietary responsiveness from a different angle: we evaluated dietary responsiveness in families who shared genetic background.

ApoE and 7 α-hydroxylase are excellent candidate genes for dietary responsiveness, since both influence LDL-C levels, and dietary responsiveness is known to be influenced by baseline LDL-C levels. We did not find a significant association between 7 α-hydroxylase genotype and dietary responsiveness, but we did observe a small effect for ApoE genotype on the dietary response in adults but not in children. Our failure to confirm an association between ApoE genotype and responsiveness in children may be because of inadequate power or age differences in the expression of ApoE, since not all studies in children have found an ApoE influence on ad libitum LDL-C cholesterol levels. Similar to studies finding an association between ApoE genotype and response, only 5% to 10% of variance could be attributed to ApoE variation.

The observation that obese persons are less responsive to diet modification adds to a growing literature linking body weight to lipids and to dietary response. The linear and positive relationship between body weight and LDL-C levels is present in younger persons but appears blunted by age. In familial hypercholesterolemia, body fat is a significant predictor of ad libitum LDL-C levels. Thus, it should not be surprising that body weight, like ApoE genotype, is an excellent candidate factor for predicting responsiveness. Several studies have observed that obese women compared with lean women are less responsive to a cholesterol-lowering diet. One study found no difference in response between obese and nonobese men, but another observed that nonobese, overweight men achieved only half of the LDL-C level reduction by diet achieved by lean men. Our findings confirm and extend the notion that body weight predicts dietary responsiveness in children as well as adults and for body weight differences even among those who are lean. Excess body weight has no age or sex bias—people who are overweight achieve less of a cholesterol reduction by diet than people who are lean.

We measured CE fatty acids as a biological marker of adherence. In our study, the 18:2 content of the margarine diet was far greater than that of the butter diet. The expected increase in the CE content of 18:2 was observed, confirming adherence. Besides a marker of adherence, we did not anticipate the contribution that other factors make in determining CE content. The CE fatty acid content varies within a relatively narrow range, does not predict serum cholesterol levels, and may be subject to genetic regulation. In a study of 69 twin pairs and their brothers, monozygotic twins had smaller differences in CE fatty acid content compared with dizygotic twins and brothers. Body weight can alter CE fatty acid content. In the Atherosclerosis Risk in Communities study, even after stratifying for dietary intakes, the CE saturated fatty acid levels were higher and the CE content 18:2 was lower in overweight men and women than lean men and women. When all subjects are stratified by categories of BMI, clear differences in the change in CE fatty acid levels by diet were observed. Although a relative increase in CE 18:2 content in the margarine intake period was seen in every category of BMI, obese and overweight persons had less excursion in the CE fatty acid levels during dietary modification than more lean persons. The strong interrelationships between dietary responsiveness, CE ratio, and BMI raise the hypothesis that the influence of dietary fatty acids on serum cholesterol levels is tempered by the pool of endogenous fatty acids held in adipose tissue. If relatively fixed concentrations of fatty acids in adipose tissue mix with dietary fatty acids and compete for hepatic uptake, even on a low saturated fatty acid diet an obese person’s liver is exposed to more saturated fatty acid flux than a lean person’s liver. One can only speculate whether differences in fatty acid flux can explain the observations that obese persons are less responsive to diet and have higher cholesterol levels than lean persons.

The unimodal distribution of dietary responses observed in our study are consistent with our failure to identify a single genetic factor that accounts for variation in dietary response. By studying families, we could determine that 40% of the variability in response to a cholesterol-lowering diet is due to shared traits, whether these are heritable or habitual. Furthermore, our study underscores the nearly universal response to a cholesterol-lowering diet in both children and adults. This finding confirms the long standing recommendation promoting a cholesterol-lowering diet for the population at large.
RESPONSE TO A MARGARINE-OR BUTTER-BASED DIET

Author Contributions: Dr Denke designed and executed this investigation; Ms Adams-Huet performed all statistical analysis in all phases of the investigation; Ms Nguyen performed phlebotomy, delivered food, divided samples, and performed the assays for lipids and lipoproteins; Drs Chen, Katan, and Ernst performed all assay interpretation; Mr Pajk was responsible for funding the study; Mr Sengupta assisted with the design of the study, its execution, interpretation, analysis, and writing of the manuscript, or approved the version of the manuscript submitted for publication.

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