Variability in Individual Serum Cholesterol Response to Change in Diet

David R. Jacobs, Jr., Joseph T. Anderson, Peter Hannan, Ancel Keys, and Henry Blackburn

Few systematic data are available on the range of individual blood lipid responsiveness to specific diet changes. Multiple, carefully standardized total serum cholesterol (TC) measurements were made in 58 men under a variety of controlled dietary conditions. Responsiveness was defined for each individual as the change in mean TC per unit change in Diet Score based on the Keys-Minnesota equation. Only 3% were potentially "nonresponders," and even these probably evidenced some response. Of the group, 64% responded within 30% of prediction. We classed 9% as hyporesponders, while in another 9% responsiveness exceeded 1.5 times expectation. We conclude that in metabolically normal individuals the variation in short-term response to dietary change is normally distributed but that nonresponse to diet change is rare. Because metabolic, intrinsic hyporesponsiveness of TC to change in diet composition is uncommon, assessment of the real effectiveness of a dietary regimen in an individual is best based on observed dietary changes. TC changes among individuals under treatment should be based on multiple determinations and interpreted with caution. (Arteriosclerosis 3:349-356, July/August 1983)

Keys, Anderson, and Grande1,2 experimentally established a quantitative relationship between the changes in dietary intake of fatty acids and cholesterol and the resulting serum cholesterol change. Hegsted and co-workers3 have produced a similar formula. The relationship between these dietary changes and serum cholesterol change is well-founded and predictable for groups.

However, in our experience with dietary counseling over the years in a research prevention clinic, the question has often arisen as to whether a given individual had atypical responsiveness, for example, when the participant's professed dietary changes were not reflected in serum cholesterol change. Some clinicians believe there are persons who are nonresponders to diet. Spritz4 opines that the use of diet in the treatment of hyperlipidemia should be closely monitored; if it is ineffective, drug treatment should be instituted. Other authors find variations in responsiveness in humans5-15 and in animals,16 17 both in response to dietary cholesterol and to dietary fats. Several observations of serum cholesterol are necessary to accurately know a person's level; without several observations, within-person, day-to-day serum cholesterol variation makes change or lack of change difficult to validate.18 19 Sometimes the absence of serum cholesterol change is falsely indicated when, in fact, the patient may have importantly changed his diet, and vice versa. In dietary counseling all this leads to confusion, lack of credibility, and poor motivation for change in eating patterns.

Several points need to be made about any study of intrinsic responsiveness and variability in blood lipid measurements. First, measurement of individual responsiveness of serum cholesterol change requires at least two observations per person. Second, an ample range of dietary conditions is desirable to improve accuracy of estimation. Third, careful standardization of blood cholesterol measurement is required and, even then, the large within-person variation tends to attenuate estimates. Fourth, each individual should be studied under several experimental conditions to examine the consistency of response. If it varies widely between experiments, responsiveness as an individual attribute has no meaning.

The present paper examines the issue of how individuals differ in serum cholesterol responsiveness to a change in dietary composition of fatty acids and...
cholesterol, and addresses three questions: 1) What is the average response in the population? 2) Are individuals' responses consistent between different diets and experiments? 3) What is the distribution of the observed individual responses, are there any zero responses, and what are the proportions of reasonably defined hypo- and hyperresponders?

**Methods**

**Subjects**

These unique observations are part of the original data from which was developed the Keys-Minnesota equation to predict serum cholesterol change from change in fatty acid and cholesterol composition of the diet. This has been summarized into a Diet Score, defined below. In groups of mentally retarded men living at the Faribault State School and Hospital from the fall of 1963 until the spring of 1966, controlled dietary manipulations were used to change serum cholesterol concentrations. The subjects ranged in age from the 30s to the 70s and were selected on the basis of good physical health and appetite. A total of 83 men participated in two or more diet experiments. To ensure precision in this study, all men who had fewer than 12 data points were excluded; 58 remained. The maximum number of data points for any subject was 45.

**Description of Experiments**

Six consecutive diet experiments are designated FB to FG; the experimental periods were from 3 to 10

<table>
<thead>
<tr>
<th>Table 1. Description of Diets in the Minnesota Experiments</th>
</tr>
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<tr>
<td><strong>Experiment, Date</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>FB</td>
</tr>
<tr>
<td>1/63-</td>
</tr>
<tr>
<td>6/65</td>
</tr>
<tr>
<td>FC</td>
</tr>
<tr>
<td>3/64</td>
</tr>
<tr>
<td>FD</td>
</tr>
<tr>
<td>5/64</td>
</tr>
<tr>
<td>FF</td>
</tr>
<tr>
<td>12/65</td>
</tr>
<tr>
<td>6/65</td>
</tr>
<tr>
<td>9/65</td>
</tr>
<tr>
<td>FG</td>
</tr>
<tr>
<td>7/66</td>
</tr>
<tr>
<td>9/66</td>
</tr>
<tr>
<td>12/65</td>
</tr>
<tr>
<td>7/66</td>
</tr>
</tbody>
</table>

*Chain length as specified.
†Primarily 18:1.
‡Containing 2.42 g. Trans monoenes.
§Containing 9.6 g. Trans dienes.
MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.
weeks. The diets were always fed in a criss-cross or Latin square design by dividing the subjects into matched groups and assigning a different order of dietary treatment to each group. Each diet consisted of a base diet and an experimental supplement which provided 28% of total calories.

In Experiment FB, the dietary changes were made by interchanging five different supplements having widely contrasting amounts of sugars, saturated and polyunsaturated fatty acids. In Experiment FC (unpublished) compared corn oil with the same oil selectively hydrogenated, as in the process of making margarine. In Experiments FD and FF, saturated fatty acids of 18-carbon and 16-carbon chain length were exchanged, thus showing that the 18-carbon fatty acids do not raise serum cholesterol. Experiment FG consisted of comparing flours and starches of corn, potatoes, rice, and wheat with each other. This unpublished study resulted in no significant serum cholesterol change except for a small elevation when dehydrated potatoes were fed.

The diet information is presented in Table 1. The value \( \Phi \) is the Diet Score defined by the expression:

\[
\Phi = 1.26 (2S - P) + 1.5 \times \left( \frac{1000 \times \text{CHOL}}{E} \right)^{25}
\]

where \( S \) is the saturated fatty acids of 12 to 16 carbon chain length, expressed as a percentage of total energy of the diet, \( P \) is the polyunsaturated fatty acids similarly expressed, CHOL is dietary cholesterol in milligrams per day, and \( E \) is the total energy of the diet in kilocalories per day. For example, the first line of Table 1 indicates that the Butter diet in Experiment FG provided 11.8% of calories from saturated fatty acids of chain length 12, 14 or 16, 1.8% of calories from polyunsaturated fatty acids, and had a \( \Phi \) value of 46.

The results are summarized in Table 2, which shows the number of men involved in each experimental diet, the total number of person-diet data points, the mean observed serum cholesterol, and the mean level after adjustment for the experiment.
Laboratory Methods and Reliability

Serum total cholesterol was determined by saponification of esterified cholesterol, extraction of cholesterol into petroleum ether, and development of color with a modified Liebermann-Burchard reagent. Samples of reference plasma were included to insure accuracy in each batch of determinations. The reference plasma was prepared by weighing a portion of freeze-dried human plasma and reconstituting it with a fixed volume of water. Each lot of dried human plasma was large enough to last about 2 years. It was well mixed and analyzed several times in batches that also included the previous reference plasma to make sure the assigned concentration was correct. Soon after the last of these experiments, when the Center for Disease Control (then called the National Communicable Disease Center) in Atlanta set up an interlaboratory comparison program for serum cholesterol determination, this method was consistently found to agree within 4 mg/dl with their modification of the method of Abell et al. The standard deviation for repeat analyses of the same serum on different days was consistently between 3 and 5 mg/dl. The implication is that this level of agreement was also present during the period of these studies.

Responsiveness

In the present report we have re-analyzed the data from which Tables 1 and 2 were derived, looking particularly at the relationship between serum cholesterol and the Diet Score within each person. For each individual, we obtain a least squares regression estimate B of responsiveness (defined in the Appendix) as the change in serum cholesterol in that individual for unit change in Diet Score.

Adjustment for Between-Experiment Cholesterol Differences

Our interest originally focused on the serum cholesterol change in response to isocaloric manipulation of dietary fat and cholesterol with all other dietary factors held constant within each experiment. There was no between-experiment control of other dietary factors that might modify serum cholesterol. An analysis of covariance of serum cholesterol over experiments showed statistically significant differences between experiments. Adjusted serum cholesterol values for each individual were used in the subsequent calculations.

Criteria for Atypical Responsiveness

First we defined a nonresponder as one for whom B equals zero. Second, an atypical response was defined as having B different from one. A hyporesponsive individual was defined as one for whom B was less than one; for him a change of 1 unit of Diet Score implied a change of less than 1 mg/dl in serum cholesterol. A hyperresponsive individual was defined as having B different from one. A change of 1 unit of Diet Score implied a change of greater than 1 mg/dl in serum cholesterol.

Results

Differences in Serum Cholesterol between Experiments

There were statistically significant differences in average serum cholesterol levels between experiments after fixing the Diet Score \( \Phi \) by regression analysis. The computed differences from experiment FG were +45, +31, +20, 0, and +7 mg/dl for Experiments FB, FC, FD, FE, and FF respectively. These differences were used to adjust serum cholesterol values to a common level, independent of the experiment. The adjusted mean values for each diet are given in the last column of Table 1.

We investigated the possibility that these experimental differences were seasonal effects. If so, the dates of the experiments, given in Table 1, should suggest similar levels for FB and FE, and for FC and FG. Since this is not the case, a seasonal effect does not explain the differences in serum cholesterol levels between experiments.

Responsiveness

The average responsiveness of these individuals is 1.03 (standard error 0.046). This value is to be compared to the average responsiveness of 1.00 for the larger population that served as the source of data for the Diet Score given in Equation 1. For each person for each experiment, a value was estimated for responsiveness. In only two (in the same man) of these 197 cases was a responsiveness value less than zero obtained. Thus with the exception of this man, everyone always responded; that is, had a decreased serum cholesterol for a decreased value of the Diet Score.

What is the within-person repeatability of serum cholesterol response to dietary manipulation? We examined consistency of response within each person, by comparing the estimate of responsiveness from each experiment in which he participated. Experiments FC and FG were not eligible for this analysis because of the limited range of Diet Scores used; for purely mathematical reasons such a limited range causes unstable slope estimates. After this exclusion, 48 men remained. We found consistent responsiveness in 40 of them. Usually the range of responsiveness estimates across experiments did not exceed 0.6 in these 40 men. The other eight men took part in FB and FD. They all were more responsive in FB than in FD, a pattern seen in 20 of the remaining 25 participants in these two experiments. These eight men always responded.

Table 3 presents the distribution of observed responsiveness. Five men (9%) had responsiveness less than 0.5. Another 64% had responsiveness be-
between 0.7 and 1.3, and 82% were between 0.5 and 1.5. Five men (9%) had responsiveness greater than or equal to 1.5.

Only two men are candidates for the label "nonresponder." These two men had 95% confidence intervals for their estimates of responsiveness of 0.09 ± 0.848 and 0.19 ± 0.318. Only two men are candidates for the label "nonresponder." These two men had 95% confidence intervals for their estimates of responsiveness of 0.09 ± 0.848 and 0.19 ± 0.318.

Three men are candidates for the label "hyporesponder." These men had 95% confidence intervals for their estimates of responsiveness which included neither 0 nor 1. Finally, five men are candidates for the label "hyperresponder." These men had lower 95% confidence limits for their estimates of responsiveness which exceeded 1.

### Table 3. Serum Cholesterol Response to Dietary Change: Frequency Distribution of $B$, the Estimate of Responsiveness of Serum Cholesterol to Dietary Change in 58 Men

<table>
<thead>
<tr>
<th>$B$</th>
<th>No.</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>5</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>0.5–0.59</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>0.6–0.69</td>
<td>3</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>0.7–0.79</td>
<td>4</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>0.8–0.89</td>
<td>5</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>0.9–0.99</td>
<td>5</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>1.0–1.09</td>
<td>9</td>
<td>15</td>
<td>57</td>
</tr>
<tr>
<td>1.10–1.19</td>
<td>7</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>1.20–1.29</td>
<td>5</td>
<td>9</td>
<td>78</td>
</tr>
<tr>
<td>1.30–1.39</td>
<td>5</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>1.40–1.49</td>
<td>5</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>≥1.50</td>
<td>5</td>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

By arbitrary definition of clinically important responses to diet, 9% of these men were "hyporesponders" (less than half of prediction) and 9% "hyperresponders" (more than 1.5 times prediction).

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### Table 4. Within-Person Standard Deviation, $S$, of Serum Cholesterol for Fixed Diet

<table>
<thead>
<tr>
<th>$S$ (mg/dl)</th>
<th>No.</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–9.9</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>10–14.9</td>
<td>18</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>15–19.9</td>
<td>19</td>
<td>32</td>
<td>70</td>
</tr>
<tr>
<td>20–24.9</td>
<td>9</td>
<td>16</td>
<td>86</td>
</tr>
<tr>
<td>25–29.9</td>
<td>6</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>30–34.9</td>
<td>1</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>35–39.9</td>
<td>0</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>≥40</td>
<td>1</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Minimum = 6.0 mg/dl; maximum = 44.9 mg/dl. Diet is fixed by adjusting for experimental diet score and for experiment.

---

### Day-to-Day Variability in Serum Cholesterol

From the within-person regressions, we obtained for each person the standard deviation of serum cholesterol as it varied during a given experiment. This statistic estimates the within-person standard deviation, adjusted for Diet Score and between-experiment serum cholesterol differences. It has a mean of 17.8 mg/dl, and a standard deviation of 6.9 mg/dl; its distribution is skewed, stretching from a minimum of 8.0 mg/dl to a maximum of 44.9 mg/dl (see Table 4).

Using Bartlett’s test (see Appendix), we conclude that there are statistically significant differences among individuals in the day-to-day variation in serum cholesterol level.

### Discussion

The three questions posed in the introduction have been answered. First, the average serum cholesterol responsiveness to changes in Diet Score was 1.03 in this study group, quite close to the 1.00 that we expected. Second, though there was much variation from person to person and even for the same person between occasions, individual diet responsiveness was consistent from experiment to experiment in most men. However, the lack of consistency of responsiveness estimates for the same person between experiments underscores the wide variation in serum cholesterol between occasions.

Third, there was a range of deviations from our predictions based on the best characterization of the serum cholesterol effects of diet change, i.e., the Diet Score. Of these men, 64% responded within 30% of prediction and 82%, within 50% of prediction. We do not consider deviations in responsiveness within 50% of prediction to be a source of confusion in the dietary management of hypercholesterolemia. We reason that if it were known that a person changed Diet Score by 30, and if his individual responsiveness were actually 0.5, the serum cholesterol change would still be 15 mg/dl, a change that we consider significant.

Only 9% had responsiveness less than 50% of prediction. Of these five men, only two might be labelled "nonresponder," but because both have positive estimates of responsiveness, chances are that these men are actually "hyporesponders." Three others we would label "hyporesponders." An additional five men (9%) might be labelled "hyperresponders."

Keys suggested that men having higher serum cholesterol levels have a greater response to diet. He proposed a modification to the Diet Score in which responsiveness is multiplied by a factor which depends on that person’s intrinsic serum cholesterol level. These two formulas may be compared in terms of the number of men each correctly describes. The analysis of Keys’ modification is complex. It has an inherent difficulty. An estimation of Keys’ respon-
siveness multiplier depends on a knowledge of the intrinsic serum cholesterol level. This level is not esti-

able directly in our data, but only through the esti-
mation of responsiveness itself. For these reasons, and because the unmodified Diet Score described more men accurately than the Keys’ modification, we have omitted these analyses.

This particular study has an advantage among studies of day-to-day variation in that the serum cholesterol levels were measured under well controlled, institutional diet-ward conditions. We have estimated the day-to-day variability for each person, holding the Diet Score constant. The average of this stan-

dard deviation was 17.8 mg/dl. The amount of within-

person variation differed between individuals. Given today’s improved research laboratory techniques, the within-person standard deviation of serum cho-

lesterol level is probably now somewhat lower than 18 mg/dl.

We addressed the issue of the highly significant individual and group differences found in serum cho-

lesterol level from one Minnesota experiment to the next. Statistical estimation indicates a maximum group difference of 45 mg/dl for the comparison of FB with FE or FG, unexplained by either the Diet Score or the season of the year. Both FB and FE were experiments centered around the winter months, although FG was centered around the spring months. Among environmental factors com-
mom to all participants in a particular experiment is the base diet provided, to which was added each experi-
mental supplement. The base diet was differ-
ent in each experiment. Thus, other dietary factors, as well as fatty acid composition and cholesterol, could explain the between-experiment serum cho-

lesterol differences.

Conclusions

We recognize that this analysis is not “the final solution” to the question of serum cholesterol re-
sponsiveness to dietary change. First, the groups were selected for apparent metabolic normality. At least there were no major or monogenic lipoprotein metabolic defects. Given high within-person vari-
ation, the study was also limited by relatively few observations for more than half the men. The study was also limited to 58 men and therefore lacked generalizability for age and gender. Data on lipoprotein fractions were not available. Nevertheless, the study utilized data not, to our knowledge, available else-
where and was unique methodologically in that serum cholesterol was measured in duplicate or trip-
licate on succeeding days after each of the 12- to 45-
day (or longer) dietary periods, and the diets were carefully prepared and scrupulously adhered to. Both Diet Score and serum cholesterol levels were thereby measured under conditions conducive to minimal variation.

We believe this study has important implications for counseling “metabolically normal” people in at-
tempts to lower serum cholesterol level by dietary change. Identification of specific patients or partici-
pants who differ in a clinically important way from the norm of diet responsiveness or variability is not prac-
tical; it requires many measurements.18 In light of our finding that most people respond as expected and, in our opinion, in a clinically important way to changes in diet composition (expressed as a Diet Score), it should be possible to judge the “success” of a di-
etary regimen on eating behavior or dietary adher-
ence alone. Measurements of serum cholesterol lev-
el are useful for establishing the general level of risk at the outset. However, during the period of dietary change, these levels should be interpreted with caution or not communicated to the participant. Because of the day-to-day variation, an individual might be led to believe that he is a “nonresponder” or a “hyperre-
ponder” when, in fact, he is responding as expect-
ed. The poor results sometimes seen in counseling about eating patterns may be attributable to confu-
sion and loss of motivation from the wide variations in observed serum cholesterol values that are con-
tradictory to the assessments of diet adherence. Of course, other possibilities have to be considered such as weight change, dietary factors other than fatty acids and cholesterol (vegetable protein, fiber, alcohol), and metabolic changes due to disease.

In sum, we find a normally distributed range of deviation of serum cholesterol response to diet as expressed in the Diet Score. A total of 64% of the men responded within 30% of prediction and 82%, within 50%. Although 3% were candidates for the label “nonresponders,” even these probably showed some response.

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Appendix

Definition

Within each Person i with multiple measurements referenced by j in Experiment k, define a regression equation of serum cholesterol (Cijk) on the Diet Score (Φjk):

$$E(C_{ijk}) = A_k + B_k \cdot \Phi_{jk} \quad (A1)$$

where E indicates the expectation; A_k, the intercept; and B_k, the slope of the relationship between serum cholesterol and Diet Score for the i-th person, estimated from his repeated observations in Experiment k. There is consistency over experiments when the slope within each experiment is the same. This is tested by an F-test (see below); when there is consistency, the average slope (weighted appropriately over the experiments) is calculated. This weighted average slope B is the estimator of responsiveness for Person i. As in parallel line bioassay, this use of adjusted values is tantamount to computing the estimated responsiveness for each person within each experiment, and then taking a weighted average across experiments.

Statistical Methodology

Precision of Estimates and Predictions

We are concerned with the precision of the estimate of the slope and of any predicted value of serum cholesterol for some given Diet Score. From the within-person regression there will be available the number of points (n), the mean and variance of the Diet Score, (Φ bar and VΦ), the correlation (R), the slope (B), and the residual standard deviation (S). The sum of squares of the Diet Scores (about the mean Diet Score), SSΦ, is necessary for calculating precision; it can be obtained from VΦ. Then the standard error of B (see p. 160 of reference 30) is given by

$$se_B = S/\sqrt{SS\Phi} \quad (A2)$$

and the standard error of prediction at a Φ value of Φ0 is given by (see p. 163 of reference 30)

$$sep = S/\sqrt{1/n + (Φ0 - Φ-bar)^2/SS\Phi} \quad (A3)$$


Note that in both standard errors, the wider the range of the Diet Scores, the larger will be $SS\Phi$ and the better the precision. In fact, $SS\Phi$ is the weighting factor used to compute the weighted average slope across experiments.

**F tests for Consistency over Experiments**

Suppose a person participates in four experiments. Within each experiment the regression equation (1) above yields an estimate of the slope $B_1$; five parameters are estimated, namely, four slopes and an intercept; (using cholesterol values adjusted for experiment there is a single intercept in the four regressions). If consistency over experiments is postulated, a single slope is estimated over all experiments so only two parameters are needed. The "analysis of variance test for deletion of variables" (see pp. 312–313 of reference 30) tests whether the mean sum of squares attributable to the extra three parameters is significantly greater than the error mean sum of squares when all five parameters are fitted. If the variance ratio $F$-statistic is significant, the extra parameters are necessary and a different slope in each experiment is required to describe the data, whereas, if not, the simpler model is adequate and the response (slope) is consistent over experiments.

**Bartlett's Test for Homogeneity of Variance**

Suppose there are $m$ estimates of variance $V_i$ ($i = 1..m$) with degrees of freedom $N_i$ ($i = 1..m$). Bartlett constructed a test that the $V_i$ are all estimates of a common variance of a parent normal distribution. If we represent the mean of the $V_i$ by $V$ and the sum of the $N_i$ by $N$, then we evaluate $M$ and $C$ by the equations:

$$M = N \cdot \ln(V) - \sum N_i \cdot \ln(V_i) \quad (A5)$$

and

$$C = 1 + \frac{\sum 1/N_i - 1/N}{(3(m-1))} \quad (A6)$$

The ratio $M/C$ is approximately distributed as chi-square with $m-1$ d.f. (See p. 214 of reference 30.)

**Reference**


Index Terms: serum cholesterol • dietary fat • dietary cholesterol • individual variation • responsiveness
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