Special Communication ▬▬▬▬▬▬▬▬

Estimating an Individual's True Cholesterol Level and Response to Intervention

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An individual's blood cholesterol measurement may differ from the true level because of short-term biological and technical measurement variability. Using data on the within-individual and population variance of serum cholesterol, we addressed the following clinical concerns: *Given a cholesterol measurement, what is the individual's likely true level?* The confidence interval for the true level is wide and asymmetrical around extreme measurements because of regression to the mean. Of particular concern is the misclassification of people with a screening measurement below 5.2 mmol/L who may be advised that their cholesterol level is "desirable" when their true level warrants further action. *To what extent does blood cholesterol change in response to an intervention?* In general, confidence intervals are too wide to allow decision making and patient feedback about an individual's cholesterol response to a dietary intervention, even with multiple measurements. If no change is observed in an individual's cholesterol value based on three measurements before and three after dietary intervention, the 80% confidence interval ranges from a true increase of 4% to a true decrease of 9%.

(*JAMA.* 1991;266:1678-1685)

CLINICIANS need to consider the effects of the substantial within-individual variability of blood cholesterol when making decisions about treatment even

when the cholesterol measurement is made under standardized conditions in the best laboratories. There are numerous published estimates of within-indi-

vidual variance,[1] and several reports deal with the need for repeated measurement.[1-4] However, this information has not been presented in a manner that helps the clinician make decisions based on the likely range of an individual's true cholesterol level or true response to intervention.

Apart from change in the true long-term level, there are two main sources of observed change or within-individual variability of blood cholesterol: technical (the collection and laboratory measurement methods) and biological (individual short-term variability). Considerable attention has been given to the variability due to collection and laboratory procedures.[5,6] The biological

component of within-individual variance in cholesterol values is less controllable, mostly not attributable to known sources, and a larger source of variation than the technical component. Cooper et al[1] report that the mean biological coefficient of variation (CV, ie, the ratio of within-individual SD to the mean) in 11 studies ranged from 3.1% to 9.1%, while the mean total (biological plus technical) CV ranged from 3.7% to 9.4%[1].

An individual's true cholesterol value can be estimated as the mean of a very large number of measurements. Measurements should be 1 to 8 weeks apart to capture short-term within-individual variability without allowing sufficient time for the true level to have changed.[7-9] Deciding how many measurements are needed to obtain an acceptable estimate of the true mean value has been the source of some controversy.[10] Cooper et al[1] have estimated that measuring a true total cholesterol value of an individual within a CV of 5% would require analysis of three separate specimens in triplicate or four samples in duplicate, assuming a biological within-individual CV of 6.5% and a laboratory CV of 5%.[1] However, regardless of the number of measurements, the clinician is still in the position of having an observed value and wishing to make inferences about that patient's true level. Making correct inferences requires understanding the phenomenon of regression to the mean.

Regression to the mean[11] can best be explained by an example: Let us consid-

er a threshold that is above the mean (average) value for a population. Suppose true levels for 100 people are in the region just below this threshold and true levels for 10 people are in the region just above this threshold, but 10% are incorrectly measured as being across the threshold from their true level. Thus, one would expect that 10 of those truly below but only one of those truly above the threshold will be measured as being on the other side of the threshold. Hence, the group *measured* as being above the threshold consists of 19 individuals, 10 of whom are truly below it. If the true cholesterol level of these individuals is established by a large number of remeasurements, they will, on average, be found to have lower values; that is, they will have regressed toward the mean. This phenomenon will also be evident even on a single remeasurement. The same argument applies to very low values for which the true level and repeated measurement will on average be higher than the initial measurement. A practical demonstration of this phenomenon is the study of Morrison et al,[12] who found in a pediatric sample that the mean difference in cholesterol level remeasured at least 6 weeks later was +0.26 mmol/L (+10.0 mg/dL) in those originally measured at 3.23 mmol/L (125 mg/dL) or lower and −0.27 mmol/L (−10.5 mg/dL) in those originally measured at 5.30 mmol/L (205 mg/dL) or greater. The greater the within-individual variation and the more extreme the measurement, the greater the regression to the mean.

Despite difficulties with measurement, decisions still need to be made about how to deal with blood cholesterol as an important cardiovascular risk factor. The report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults details guidelines for identification and treatment of high-risk individuals, suggesting that[7]:

Serum total cholesterol should be measured in all adults 20 years of age and over at least every five years. . . . Levels below 200 mg/dL [5.2 mmol/L] are classified as "desirable blood cholesterol," those 200 to 239 mg/dL [5.2 to 6.1 mmol/L] as "borderline-high blood cholesterol," and those 240 mg/dL [6.2 mmol/L] and above as "high blood cholesterol." [The Système International values were added by the authors of the present report. To convert cholesterol values in milligrams per deciliter to millimoles per liter, multiply by 0.02586. Throughout this report, we have rounded values in millimoles per liter to the first decimal place and those in milligrams per deciliter to the nearest 5.]

The NCEP Expert Panel suggests that people with screening cholesterol measurements of 5.2 mmol/L or greater should have a repeated determination, and the average of the two should be used to guide subsequent decisions. Individuals with high blood cholesterol measurements and individuals with borderline-high blood cholesterol measurements who have definite coronary heart disease or two other risk factors (including male gender) should undergo a full lipoprotein analysis to ensure that it is the low-density lipoprotein cholesterol component that is elevated. Every individual who is treated, therefore, should have a cholesterol value calculated as the mean of three measurements. A stepped treatment plan is then recommended, commencing with dietary advice and proceeding to drug therapy if there is an inadequate response. Response is to be monitored by measurement of blood total cholesterol, with less-frequent measurement of low-density lipoprotein cholesterol.

In applying the NCEP recommendations, it is inevitable that a proportion of those tested will be misclassified because of within-individual variability. In a computer simulation of the effects of within-individual variance on cholesterol screening, Byers[2] has reported that repeating the test and using the mean of the two test results for those found to have values of 5.2 mmol/L (200 mg/dL) or higher on the initial screen reduced the overall NCEP risk category misclassification from 16% to 11%.[2] Weissfield et al[3] have considered the effect of within-individual variability in their computer simulations on the likely low-density lipoprotein cholesterol reduction and costs associated with the NCEP recommendations.[3]

The clinician, however, is more concerned with decisions for a particular individual. Previous reports have examined the 95% confidence interval (CI) around true cholesterol levels, that is, the interval within which 95% of measurements will lie.[13] This is not very helpful for the practicing clinician who has one or more measurements, rather than the true value, on which to base a management decision. Rather than the CI of *measurements around a true cholesterol level*, the clinician needs the inverse of this: the CI of *true levels around the observed measurement(s)*. [A more appropriate but less familiar term would be the Bayesian "credible interval," which expresses the chance that the true value lies within that range.] The present report provides such information as an aid to answering clinical questions, such as: Is an individual's cholesterol level truly high? Has an individual responded to an intervention, such as dietary change?

METHODS

The problem described in the last paragraph suggests the use of Bayesian methods, which are detailed in the Appendix. We give a nonmathematical explanation here.

There are two sources of information, or "signals," that could be used to estimate an individual's true cholesterol level: a measurement of that individual and the population mean. Each of the signals has "noise," represented by variances. The best estimate of an individual's true cholesterol level can be shown to be a combination of these two signals, giving more weight to the signal with least noise, ie, weighting by the inverse of the variances. This weighted average provides an estimate of the regression to the mean for an individual. Using the mean of several measurements decreases the variance so that more weight is given to several measurements than to a single measurement. Use of the method requires assumptions of normality and constancy of variance that are reasonably fulfilled if log cholesterol values are used; this has been done throughout the present report.

Our calculations use three different population mean values: 5.2 mmol/L (200 mg/dL), 5.8 mmol/L (225 mg/dL), and 6.4 mmol/L (245 mg/dL). These are called groups A, B, and C, respectively. Because the 10-year age-specific mean cholesterol values for men under 35 years and women under 45 years of age are close to 5.2 mmol/L (Table), results for these age-sex groups are represented in the calculations as group A. Likewise, the mean cholesterol values for men from 35 through 74 years and women from 45 through 64 years are close to 5.8 mmol/L (Table), so results for these age-sex groups are represented in calculations as group B, whereas women age 65 years and older are represented in the calculations as group C. In this way, all age-sex groups can be represented by three sets of figures. The population variance has been estimated from published centiles of the National Centre for Health Statistics as 0.03347 on the log scale (Appendix).[14] The within-individual variance of 0.00589 was derived from reanalysis of the Lipid Research Clinics Prevalence data, in which repeated measurements were available for almost 5000 individuals.[15] This corresponds to a coefficient of variation of about 8% for cholesterol and 5% for log cholesterol. The values of population and individual variance are similar to those expected from other published studies.[1,15-18]

As discussed above, regression to the mean affects the interpretation of a par-

ticular cholesterol measurement. It is also important when one is judging change in an individual's cholesterol measurements in response to an intervention. The estimation of an individual's response to intervention uses the same concept outlined above. However, the "signals" are (1) the observed change in cholesterol value, corrected for regression to the mean, and (2) the mean population response to therapy. The example used for the latter is derived from a randomized trial showing a 13% mean decrease in serum cholesterol in response to dietary advice. The variance was estimated from the information that cholesterol values decreased in at least 90% of the population (Appendix).[19] Obviously, our results depend on these estimates, and different results may be obtained with interventions of different efficacy.

RESULTS
Screening Measurements

Estimating True Cholesterol Levels. — Figure 1 shows how the estimated true cholesterol level differs from an initial single measurement in populations with mean cholesterol values of 5.2 mmol/L (group A, young men and women) and 6.4 mmol/L (group C, women 55 years and older) (Table). Note that the estimated true level equals the measurement only at the mean value of the group. The further the measurement from the group mean, the more the estimated true level regresses toward the mean. For example, someone from group A with a single screening measurement of 9.0 mmol/L (350 mg/dL) would have an estimated true level of 8.3 mmol/L, ie, 0.7 mmol/L (25 mg/dL) lower than the measurement. Throughout this report we present 80% CIs as a reasonable basis for clinical decision making. The CI is large; for the same example, the upper limit corresponds roughly to the original measurement, and the lower limit is 7.6 mmol/L, ie, 1.4 mmol/L below the original measurement. For someone from group C, which has a higher population mean than group A, the same measurement of 9.0 mmol/L has an estimated true level of 8.6 mmol/L, with an 80% CI of 9.4 to 7.8 mmol/L.

Figure 2 shows results for the mean of three measurements. Results are shown for group B, corresponding roughly to all men 35 years and older and women 45 through 54 years old. With the added certainty of a value based on three measurements, there is less regression to the mean, and the CI of the estimated true level is smaller. For example, when a value of 9.0 mmol/L is obtained on a single measure-
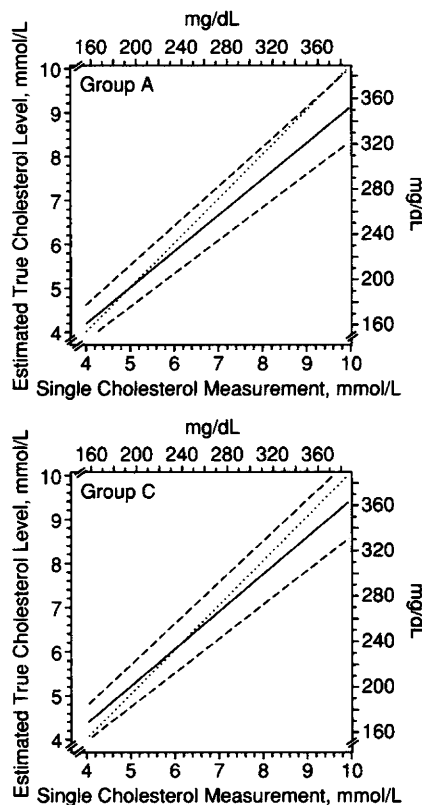

Fig 1.—Estimated true cholesterol level from one measurement for groups A (mean, 5.2 mmol/L; men less than 35 and women less than 45 years old) and C (mean, 6.4 mmol/L; women 55 years and older). Solid line indicates the estimated true level; dashed lines, 80% confidence intervals. The faint diagonal line is an equivalence line.
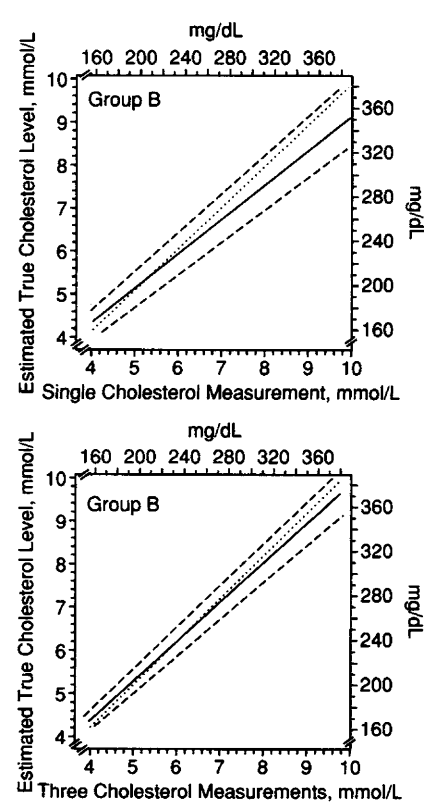

Fig 2.—Estimated true cholesterol level for one or three measurements for group B (mean, 5.8 mmol/L; men 35 years and older and women 45 through 54 years). Solid line indicates the estimated true level; dashed lines, 80% confidence intervals. The faint diagonal line is an equivalence line.

Mean Age and Sex-Specific Cholesterol Levels in the United States[14] and United Kingdom[17]*

	Mean Cholesterol Level by Group					
	A (5.2 mmol/L [200 mg/dL])		B (5.8 mmol/L [225 mg/dL])		C (6.4 mmol/L [245 mg/dL])	
Age, y/Sex	United States	United Kingdom	United States	United Kingdom	United States	United Kingdom
25-34/M	5.15	5.35	...	...	...	...
25-34/F	4.97	5.15	...	...	...	...
35-44/M	...	...	5.61	5.90	...	...
35-44/F	5.35	5.45	...	...	...	...
45-54/M	...	...	5.87	6.10	...	...
45-54/F	...	...	6.00	6.15	...	...
55-64/M	...	...	5.92	6.10	...	...
55-64/F	...	...	...	...	6.44	6.70
65-74/M†	...	...	5.72	...	...	...
65-74/F†	...	...	...	...	6.36	...

*See the "Methods" section for explanation.
†Data are not available for the United Kingdom.

ment, the estimated true level is 8.4 mmol/L, with a CI of 7.7 to 9.2 mmol/L. If the value of 9.0 mmol/L is obtained as the mean of three measurements, the estimated true level is 8.8 mmol/L, with

a CI of 8.3 to 9.3 mmol/L.

Probability of Misclassification. — Figure 3 shows the probability of having a true level above the NCEP thresholds of 5.2 mmol/L (200 mg/dL) and 6.2
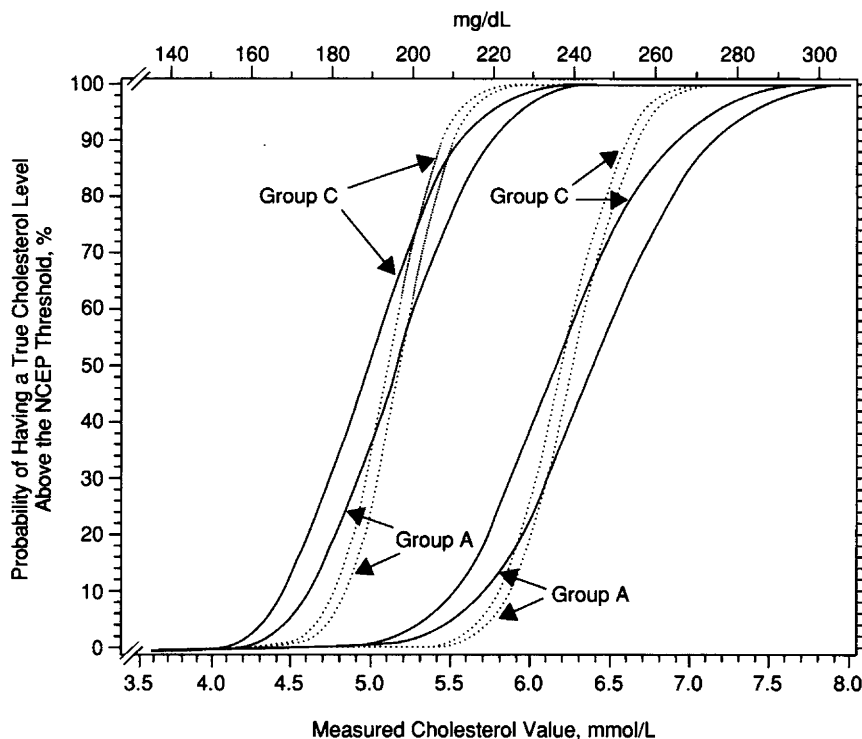
Fig 3.—Probability of having a true cholesterol level that exceeds the National Cholesterol Education Program (NCEP) threshold, by measured cholesterol value. Curves on the left indicate the probability of having a true cholesterol level above 5.2 mmol/L (200 mg/dL). Curves on the right indicate the probability of having a true cholesterol level above 6.2 mmol/L (240 mg/dL). Solid lines indicate one measurement; dotted lines, the mean of three measurements.
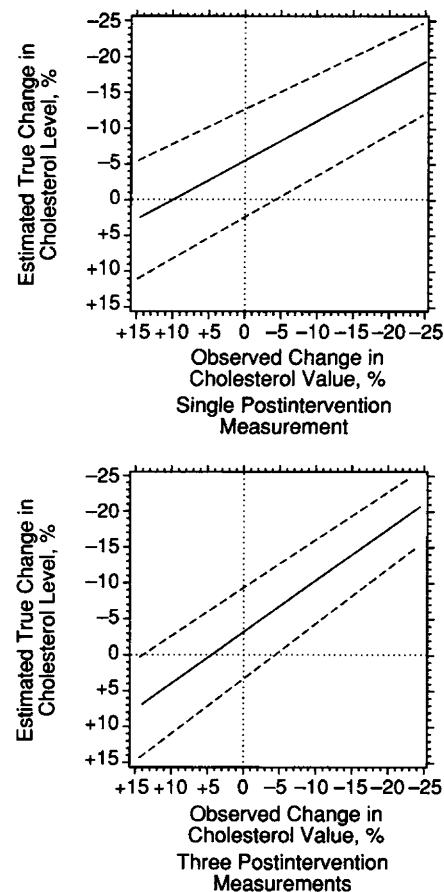
Fig 4.—Estimated true change in cholesterol value by observed change in cholesterol level for group B, with a preintervention value of 7.8 mmol/L, based on three measurements. Solid line indicates estimated true change; dotted lines, 80% confidence intervals.

mmol/L (240 mg/dL) for a range of measured values in populations with mean cholesterol values of 5.2 mmol/L (group A) and 6.4 mmol/L (group C). Probabilities for group B are approximately equivalent to the mean of those for groups A and C. Individuals have more than a 10% probability of having a true level above the lower NCEP threshold if their measured cholesterol value is 4.7 mmol/L (180 mg/dL) and they belong to group A or if the measurement is 4.5 mmol/L (175 mg/dL) and they belong to group C (solid lines in left-hand family of curves, Fig 3). An individual whose screening cholesterol value is 4.9 mmol/dL has a 26% probability of having a true level above the threshold from group A and a 42% probability from group C. The probability of someone with a screening measurement below 5.2 mmol/L (200 mg/dL) actually having a true level above 6.2 mmol/L (240 mg/dL) is extremely small.

People with screening measurements above a threshold may also be misclassified. For example, there is a 10% probability that an individual's true level is 5.2 mmol/L or less if the screening measurement is 5.8 mmol/L and the individ-

ual is in group A or if the screening measurement is 5.5 mmol/L and the individual is in group C. According to NCEP guidelines, such individuals should have three measurements before consideration of treatment. Therefore, Fig 3 also shows the probability of a true level above one of the thresholds given a cholesterol value calculated as the mean of three measurements (dotted line). In general, a mean value more than 0.4 mmol/L (15 mg/dL) away from a threshold has less than a 10% probability of being misclassified.

Assessing the Effect of an Intervention

Estimating the True Change.—Figure 4 shows the estimated true percentage decrease in the cholesterol level and its 80% CI for a given observed percentage decrease. For this example we used the results from a trial of dietary intervention that was found to reduce cholesterol values in over 90% of people, with a mean reduction of 13%.[19] The figure is for group B and an arbitrarily chosen preintervention cholesterol value of 7.8 mmol/L (300 mg/dL), calculated as the mean of three measurements. Data for

groups A and C (ie, with different population means) or for individuals with alternative preintervention measurements ranging from 6.5 mmol/L (250 mg/dL) to 9.1 mmol/L (350 mg/dL) are very similar, the estimated true reductions always being well within 1% of those shown for group B.

Figure 4, top, shows results when there is only one postintervention measurement. When the observed decrease is greater than the mean of 13% (eg, 25%), the estimated true decrease (19% in this example) is less than that observed. On the other hand, when the observed decrease is smaller than the mean, eg, 0%, the estimated true decrease is 5%. An estimate of no true change occurs only when there is an observed increase of over 10%. This is an effect of the use of prior information about the efficacy of intervention. The CI of the estimated actual change is large. For example, if no change in cho-

lesterol measurement is observed, the CI is between a true decrease of 13% and a true increase of 3%. Across the range of observed changes, the upper confidence limit is always well above the horizontal line, representing no true change. Thus, even up to a 15% observed increase, there is a reasonable probability of a true decrease. The most clinically useful line is the lower confidence limit. As this is the lower boundary of an 80% CI, it represents the level at which one is 90% certain of a true decrease. To be 90% certain of any true decrease, there needs to be at least a 5% observed decrease in the cholesterol value.

Figure 4, bottom, shows the effect of using a postintervention value calculated as the mean of three measurements. The estimated true decrease is closer to the observed value than in the case of a single postintervention measurement, and the CI is smaller. The lower confidence limit shows that a 5% observed decrease in the cholesterol value is needed to be 90% certain of a true decrease; surprisingly, this is the same result as if there is only a single postintervention measurement. A more extreme observed decrease of 25% reflects 90% certainty of a true cholesterol decrease of about 15%. This true decrease is somewhat but not appreciably larger than that obtained (12%) if the observed decrease is based on one postintervention measurement. Any advantage to be gained by increasing the number of postintervention measurements is limited by the fact that there are only three preintervention measurements. Even with an infinite number of postintervention measurements, there still needs to be a 5% observed decrease to be 90% certain of a true decrease, while an observed decrease of 25% reflects 90% certainty of a true cholesterol decrease of about 18%. It is important to note that CIs would be wider if we had not used the prior information about response.

Probability of Misclassification.— Figure 5 is an alternative representation of the information in Fig 4, showing the probability of true decreases in cholesterol level of 5% and 10% after dietary intervention, given a range of observed changes. Figure 5, like Fig 4, shows the data for group B, with a preintervention value, based on three measurements, of 7.8 mmol/L (300 mg/dL). Data for groups A and C or for individuals with preintervention measurements of 6.5 and 9.1 mmol/L are always within 5% of those shown. In Fig 5, solid lines show the probability of a true decrease if there is only one postintervention measurement. With no ob-
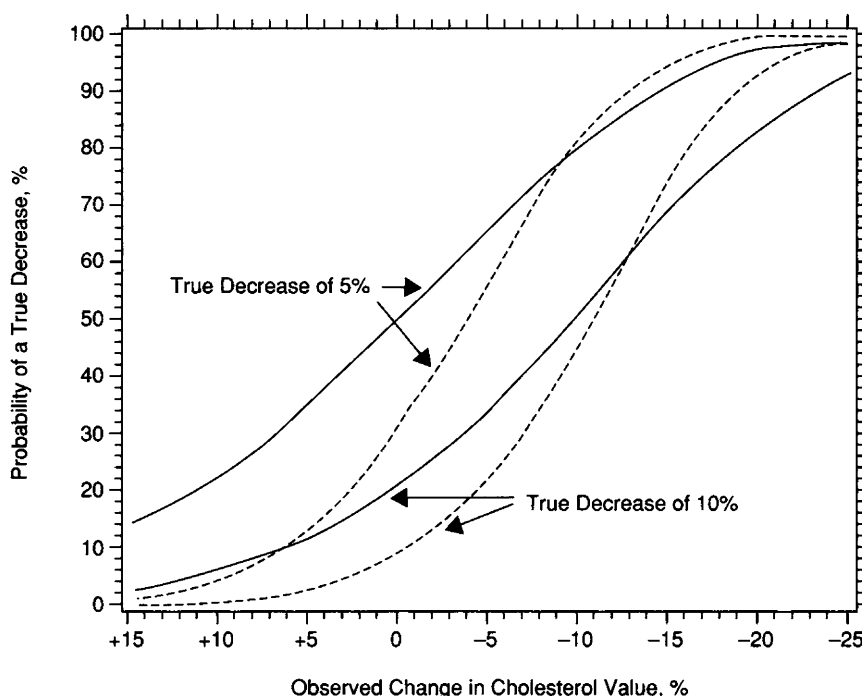

Fig 5.—Probability of a true decrease in cholesterol level of 5% or 10% given an observed change for group B, with a preintervention value of 7.8 mmol/L, based on three measurements. Solid lines indicate one postintervention measurement; dotted lines, the mean of three postintervention measurements.

served change, there is a 22% probability of a real decrease of 10% or more (right-hand solid line) and a 52% probability of a 5% decrease (left-hand solid line). There needs to be an observed decrease of 22% before one is 90% certain of a true decrease of 10% (a result that can also be read in Fig 4, top). Dotted lines show the probability of a real decrease if the postintervention value is (as for preintervention) calculated as the mean of three measurements.

From a practical point of view, the major effect of altering the number of postintervention measurements is that small decreases (eg, less than 5%) based on multiple measurement are less likely to reflect true reductions than small decreases based on single measurements. This is because less importance is accorded to the prior population information about the efficacy of intervention if it is contradicted by individual information based on multiple measurements. On the other hand, if we wish to be 90% certain of a reduction of 10%, we need an observed decrease of more than 18% using three postintervention measurements (or 16% using an infinite number of postintervention measurements), not appreciably less than the 22% observed decrease in the case of a single measurement.

COMMENT

In interpreting a cholesterol measurement, a clinician usually needs to make one of two decisions: (1) What is an individual's true blood cholesterol level in relationship to decision thresholds? (2) To what extent has blood cholesterol changed in response to an intervention? Although most clinicians are aware that patients' test results vary, regression to the mean and measurement uncertainty are often not considered in any quantitative way in decision making.

We present a series of figures from which a clinician can read off an estimate of an individual's true cholesterol level, given an observed cholesterol value, the number of measurements on which it is based, and the individual's age and sex. Similar figures address the issue of estimating an individual's true change in cholesterol in response to intervention. The figures are based on Bayesian methods, using variance estimates from large studies in the United States[14,15] and population means compatible with those in various age-sex groups in the United States or United Kingdom.[14,17]

In screening, we are primarily concerned with correctly identifying values above a recommended threshold. The NCEP Expert Panel, aware of the problem of measurement error, has incorpo-

rated repeated measurement for individuals with a cholesterol measurement over a threshold of 5.2 mmol/L. However, the importance of misclassification in single measurements below 5.2 mmol/L may have been underestimated. When screening for most risk factors, such as hypertension, the threshold is usually well above the population mean; regression to the mean implies that the true level is generally lower for initial measurements above the threshold. With cholesterol screening the population mean for adults is generally higher than the 5.2 mmol/L threshold. The true level is likely to be higher than an initial measurement that was below the threshold. For example, someone from group C (women 55 years and older) who has a value 0.4 mmol/L below 5.2 mmol/L has a 1 in 3 chance of having a true level above this threshold, whereas someone who has a value 0.4 mmol/L above the threshold has less than a 1 in 10 chance of having a true level below 5.2 mmol/L (Fig 3). The implication is that someone with a truly high level is quite likely to be declared to have a "desirable" cholesterol level and to be told to have a repeated cholesterol measurement in 5 years.[7] We are concerned that the person given this (mis)information is unlikely to be motivated to adopt the dietary recommendations that are promoted to all.[20] This is of particular concern if that person has other cardiovascular risk factors.

When considering the effectiveness of intervention in an individual, the clinician must judge the relevance of observed changes in the cholesterol value. In this situation, the effect of regression to the mean is not widely appreciated; the individual's observed response regresses towards the mean population response to the intervention. Therefore, the interpretation of observed change depends in part on the known response to the intervention and its variability. Figures 4 and 5 show estimates of true decrease for a dietary intervention known to reduce the mean cholesterol level by 13% that causes some reduction in at least 90% of the population.[19] The true cholesterol level is likely to have decreased whatever the observed change, but with wide CIs.

Judgments about true change will be more secure if the differences between preintervention and postintervention measurements are large or, more important, if controlled studies show that response to therapy is likely and has little individual variation.

Monitoring cholesterol values is used to decide on the need for a change in intervention and as a behaviorial reinforcement to motivate patient compli-

ance. Both are problematic: the wide CIs due to within-individual variation imply that one cannot know how much change has truly occurred with sufficient precision to allow monitoring to be useful. Contrary to common practice and, indeed, NCEP recommendations, our findings suggest that monitoring an individual's cholesterol measurements should play only a limited role in decision making and patient feedback. Figures 4 and 5 should help clinicians decide how much reliance to place on an observed change in measurement. When there are good data on the effect of the intervention (as in Figs 4 and 5), we will often conclude that the blood cholesterol level has been reduced even if preintervention and postintervention measurements show no change or even an increase.

Results of our analyses depend on the efficacy of the treatment. We have chosen to use this example of a dietary intervention because the within-individual variance of the response could be ascertained, which is not the case for many other publications on the efficacy of interventions. The size of the mean reduction in blood cholesterol achieved in dietary intervention trials ranges from 3% to 23%.[21,22] Drug trials may achieve more consistent mean reductions in blood cholesterol, ranging from 10% to 34%,[23] with, for example, 13% in the Lipid Research Clinics Coronary Prevention Trial of cholesytramine,[24] 11% in the Helsinki Heart Study of gemfibrozil,[25] and as much as 30% in trials using hydroxymethylglutaryl coenzyme A reductase inhibitors.[26]

It is important to note that our estimates represent an ideal and that the CIs will be wider if the cholesterol measurements are performed in multiple laboratories or using laboratories, staff, and analyzers that do not meet the recommended standards.[5,6,27,28]

In conclusion, we argue that labeling an individual's cholesterol level as desirable if it falls below 5.2 mmol/L at screening is inappropriate because of the substantial probability of misclassification. In the presence of considerable within-individual variability, a screening threshold of 5.2 mmol/L, below which people may be misinformed that their cholesterol level is desirable, seems at odds with a population strategy of dietary recommendations promoted to all regardless of their cholesterol level. When the NCEP recommendations are followed, a clinician should use Figs 1 through 3 plus an assessment of overall cardiovascular risk to decide on further cholesterol measurements and on how to advise those with screening measurements below 5.2 mmol/L. We

have also illustrated the difficulty of providing accurate feedback to individuals about changes in their cholesterol level based only on their measurements; in many circumstances such feedback is misleading. Based on the additional information about the effect of the intervention in the population, our Figures provide the clinician with estimates of the likely true change in the individual. These should guide the decision about therapy and what to tell the patient.

References

1. Cooper GR, Myers GL, Smith SJ, Sampson EJ. Standardization of lipid, lipoprotein, and apolipoprotein measurements. *Clin Chem.* 1988;34:B95-B105.
2. Byers T. Two-test cholesterol screening: computer simulation of a strategy to reduce within-person variance in mass screening programs. *Am J Epidemiol.* 1989;130:853. Abstract.
3. Weissfield JL, Weissfield LA, Holloway JJ, Bernard AM. A mathematical examination of the Expert Panel's guidelines for high blood cholesterol case-finding and treatment. *Med Decis Making.* 1990;10:135-146.
4. Thompson SG, Pocock SJ. The variability of serum cholesterol measurements: implications for screening and monitoring. *J Clin Epidemiol.* 1990;43:783-789.
5. Current status of blood cholesterol measurement in the United States: a report from the Laboratory Standardization Panel of the National Cholesterol Education Program. *Clin Chem.* 1988;34:193-201.
6. Naito HK. Reliability of lipid, lipoprotein, and apolipoprotein measurements. *Clin Chem.* 1988;34:B84-B94.
7. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med.* 1988;148:36-69.
8. Demacker PNM, Schade RWB, Jansen RTP, Van't Laar A. Intra-individual variation of serum cholesterol, triglycerides and high density lipoprotein cholesterol in normal humans. *Atherosclerosis.* 1982;45:259-266.
9. Rotterdam EP, Katan MB, Knuiman JT. Importance of time interval between repeated measurements of total or high-density lipoprotein cholesterol when estimating an individual's baseline concentrations. *Clin Chem.* 1987;33:1913-1915.
10. Roberts L. Measuring cholesterol is as tricky as lowering it. *Science.* 1987;238:482-483.
11. Gardner MJ, Heady JA. Some effects of within-person variability in epidemiological studies. *J Chronic Dis.* 1973;26:781-795.
12. Morrison JA, Laskarzewski P, deGroot I, et al. Diagnostic ramifications of repeated plasma cholesterol and triglyceride measurements in children: regression toward the mean in a paediatric population. *Pediatrics.* 1979;64:197-201.
13. Belsey R, Baer DM. Cardiac risk classification based on lipid screening. *JAMA.* 1990;263:1250-1252.
14. Fulwood R, Kalsbeek W, Rifkind B, et al. *Total Serum Cholesterol Levels of Adults 20-74 Years of Age: United States, 1976-80.* Washington, DC: National Center for Health Statistics. US Dept of

Health and Human Services publication PHS 86-1686. Vital and Health Statistics, ser 11, No. 236.

15. Jacobs DR, Barrett-Connor E. Retest reliability of plasma cholesterol and triglycerides. *Am J Epidemiol.* 1982;116:878-885.

16. Keil U, Kuulasmaa K. WHO MONICA Project: risk factors. *Int J Epidemiol.* 1989;18(suppl 1):S46-S55.

17. Mann JI, Lewis B, Shepherd J, et al. Blood lipid concentrations and other cardiovascular risk factors: distribution, prevalence, and detection in Britain. *BMJ.* 1988;296:1702-1706.

18. Tunstall-Pedoe H, Smith WC, Tavendale R. How-often-that-high graphs of serum cholesterol. *Lancet.* 1989;1:540-542.

19. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. *Lancet.* 1981;2:1303-1313.

20. Kinlay S, Heller RF. Effectiveness and hazards of case finding for a high cholesterol concentration. *BMJ.* 1990;300:1545-1547.

21. Tyroler HA. Review of lipid-lowering clinical trials in relation to observational epidemiological studies. *Circulation.* 1987;76:515-522.

22. Enholm C, Huttunen JK, Pietinen P, et al. Effect of diet on serum lipoproteins in a population with a high risk of coronary heart disease. *N Engl J Med.* 1982;307:850-855.

23. Roberts WC. Lipid-lowering therapy after an atherosclerotic event. *Am J Cardiol.* 1989;64:693-695.

24. The Lipid Research Clinics Coronary Prevention Trial results, II: the relation of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA.* 1984;251:365-374.

25. Manninen V, Elo O, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA.* 1988;260:641-651.

26. O'Brien R, Simon LA, Clifton P, et al. Comparison of simvastatin and cholestyramine in the treatment of primary hypercholesterolaemia. *Med J Aust.* 1990;152:480-483.

27. Naughton MJ, Luepker RV, Strickland D. The accuracy of portable cholesterol analyzers in public screening programs. *JAMA.* 1990;263:1213-1217.

28. Kaufman HW, McNamara JR, Anderson KM, Wilson PWF, Schaefer EJ. How reliably can compact chemistry analyzers measure lipids? *JAMA.* 1990;263:1245-1249.

29. Berger J. *Statistical Decision Theory and Bayesian Analysis.* New York, NY: Springer-Verlag NY Inc; 1985.

30. DeGroot MH. *Probability and Statistics.* 2nd ed. Reading, Mass: Addison-Wesley Publishing Co; 1986.

31. Nunnally JC. *Psychometric Theory.* New York, NY: McGraw-Hill International Book Co; 1967.

32. Shepard DS. Reliability of blood pressure measurements: implications for designing and evaluating programs to control hypertension. *J Chronic Dis.* 1981;34:191-209.

33. Hjermann I. Smoking and diet intervention in healthy coronary high risk men: methods and 5 year follow-up of risk factors in a randomisation trial. *J Oslo City Hosp.* 1980;30:3-17

APPENDIX: THE CORRECTION FORMULAS

Screening

Suppose the "true" values in the population have a mean μ and variance σ_p^2, and suppose the within-individual variance is σ_e^2. The observed variance of the population using a single measurement will be $\sigma_o^2 = \sigma_p^2 + \sigma_e^2$.

If we take a *single* screening measurement, x_i, with measurement vari-

ance σ_e^2, the best estimate of that "true" value, μ_i, for that individual is obtained by combining the two noisy sources of information, the population and the measurement(s), with weightings equal to the inverse of their variances. The estimate of μ_i would be:

$$(1) \quad \hat{\mu}_i = \frac{\left(\frac{1}{\sigma_p^2} \bullet \mu\right) + \left(\frac{1}{\sigma_e^2} \bullet x_i\right)}{\frac{1}{\sigma_p^2} + \frac{1}{\sigma_e^2}}$$

$$(2) \quad = \frac{\left(\sigma_e^2 \bullet \mu\right) + \left(\sigma_p^2 \bullet x_i\right)}{\sigma_p^2 + \sigma_e^2}$$

The variance of this estimate of the true value is:

$$(3)$$

$$\sigma_T^2 = \left[\left(\frac{\sigma_e^2}{\sigma_p^2+\sigma_e^2}\right)^2 Var\ (X)\right] + \left[\left(\frac{\sigma_p^2}{\sigma_p^2+\sigma_e^2}\right)^2 Var\ (X_i)\right]$$

$$= \left[\left(\frac{\sigma_e^2}{\sigma_p^2+\sigma_e^2}\right)^2 \bullet \sigma_p^2\right] + \left[\left(\frac{\sigma_p^2}{\sigma_p^2+\sigma_e^2}\right)^2 \bullet \sigma_e^2\right]$$

$$= \frac{\sigma_p^2 \bullet \sigma_e^2}{\sigma_p^2+\sigma_e^2}$$

where X is an observation from the (accurately measured) population and X_i is an observation from patient i.

If we view the population distribution as a prior distribution and the single measurement as new information about an individual, the above result is the posterior distribution that would result from a Bayesian analysis if the prior distributions of both population and measurement error are normal. The resultant posterior distribution of $\hat{\mu}_i$ is

$$N\left[\frac{(\sigma_e^2 \bullet \mu)+(\sigma_p^2 \bullet x_i)}{\sigma_p^2+\sigma_e^2}, \frac{\sigma_p^2 \bullet \sigma_e^2}{\sigma_p^2+\sigma_e^2}\right],$$

since the sum of (weighted) normals is still normal. For a proof and discussion, see Berger[29] or DeGroot.[30]

The same result for the estimated true value based on a single measurement is given by Nunnally[31] and used by Shepard.[32] Their variance estimate is given as

$$\sigma_o^2 \left(1 - \frac{\sigma_p^2}{\sigma_p^2+\sigma_e^2}\right) = \sigma_e^2.$$

This overstates the variance and hence gives excessively wide confidence intervals. For example, imagine that

most of the variation was due to poor measurement, ie, $\sigma_e^2 \gg \sigma_p^2$. We would largely rely on the population distribution and ignore the measurement. More generally, $\sigma_T \leqslant min(\sigma_e, \sigma_p)$.

If we have *several* screening measurements, n, from individual i with mean $\bar{x}_i$, it follows, by substituting σ_e^2/n for σ_e^2 in equations 2 and 3, that:

$$mean = \frac{\left(\frac{\sigma_e^2}{n}\right)\mu + \sigma_p^2 \bullet x_i}{\sigma_p^2 + \frac{\sigma_e^2}{n}} \quad and \quad variance = \frac{\sigma_p^2 \left(\frac{\sigma_e^2}{n}\right)}{\sigma_p^2 + \frac{\sigma_e^2}{n}}.$$

Thus, with repeated measurements from an individual, the error decreases and the importance of the population distribution becomes less. With infinite samples or a perfect measurement, the population distribution has no influence at all and we simply accept x_i as the result.

Assumptions

The following assumptions must be fulfilled when using the normal distribution version of the above formulas:

1. The within-individual variance must be independent of the underlying cholesterol level.

2. Within-individual variation and cholesterol levels in the population must both be normally distributed.

To determine the within-individual variances we used the published data from the Lipid Research Clinics Prevalence Study,[15] provided to us as individual unidentified records. Within-individual variance was estimated as half the between-occasion variance.

As suggested in the original publication of these data, within-individual variance was dependent on the cholesterol level. However, this dependence was minimized if natural logarithms of cholesterol values were used (Appendix Table 1). Log cholesterol measurements were normally distributed, whereas the distribution of the difference between two (within-individual) measurements was symmetrical but somewhat leptokurtic. The magnitude of this deviation from normality is small and unlikely to be important.

Appendix Table 2 shows that the within-individual variance of log cholesterol measurements was similar in

Appendix Table 1.— Within-Individual Variance of Cholesterol Values by Cholesterol Level

| | Within-Individual Variance | | | | |
| | Cholesterol Level, mmol/L* | | | | |
	<4.14	4.14-5.16	5.17-6.19	>6.20	Overall
Log cholesterol	0.00682	0.00610	0.00566	0.00514	0.00589
Cholesterol	0.0911	0.1335	0.1773	0.2511	0.1614

*Estimated as the mean of two measurements.

	Group A	Group B	Group C	Overall
Within-individual variance	0.00635	0.00548	0.00539	0.00589
Total population variance*	0.04194	0.03964	0.03649	0.03936
Ratio of within-individual variance to total population variance	0.151	0.138	0.148	0.150

*True population variance plus within-individual variance.

groups A, B, and C, as defined in the "Methods" section. Of importance for equation 2, the ratio of within-individual to total population variance is nearly constant across the groups. In all our calculations we have used the mean within-individual variance of 0.00589 derived from the Lipid Research Clinics Prevalence Study data.

The total population variances and means were taken from National Center for Health Statistics data.[14] The SD for each age- and sex-specific group was estimated by dividing the difference between the logs of the 10th and 90th percentiles by 2×1.282. As groups A, B, and C contain several age and sex strata, the between-strata variance for each of the three groups was added, giving variances shown in Appendix Table 2. We used the mean of these, 0.03936, and then subtracted the within-individual variance to obtain a variance for true values in the population of 0.03347.

Estimating Change

We can use a similar process of combining individual and population information to estimate the amount an individual's cholesterol value has changed following an intervention. To do this we treat the *change* in the same way we treated the level: the estimated change is the weighted sum of the individual's observed change and the population change.

If the second measurement is x_{i2}, the observed change is $x_{i2} - x_{i1}$. The adjusted observed change is the postintervention observation minus the predicted preintervention true value: $x_{i2} - \hat{\mu}_{i1}$ (let this be d'), which we would expect to be zero on average if there were no real change. The variance of d' is the sum of the variance of its two components, viz,

$$\frac{\sigma_p^2 \cdot \sigma_e^2}{\sigma_p^2 + \sigma_e^2} + \sigma_e^2 = \sigma_{d'}^2$$

Assuming that, from previous studies of the intervention, we know that the real changes are distributed as $N(\Delta, \sigma_\Delta^2)$, the (inverse variance) weighted sum of Δ and d' is:

$$(4) \quad \hat{d}_i = \frac{\left(\frac{1}{\sigma_\Delta^2} \cdot \Delta\right) + \left(\frac{1}{\sigma_{d'}^2} \cdot d'\right)}{\frac{1}{\sigma_\Delta^2} + \frac{1}{\sigma_{d'}^2}}$$

$$(5) \quad = \frac{\left(\sigma_{d'}^2 \cdot \Delta\right) + \left(\sigma_\Delta^2 \cdot d'\right)}{\sigma_\Delta^2 + \sigma_{d'}^2}.$$

The variance of this estimate of change is then:

$$(6) \quad Var(\hat{d}_i) = \frac{\sigma_\Delta^2 \cdot \sigma_{d'}^2}{\sigma_\Delta^2 + \sigma_{d'}^2}.$$

Note that, if $\sigma_e^2 = 0$, then $\sigma_{d'}^2$ is 0 and, hence, $\hat{d}_i = d'$; ie, if there is no measurement error, the estimated change equals the observed change. If $\sigma_\Delta^2 = 0$, then $\hat{d}_i = \Delta$, since we know for certain a priori what the change will be, and measurement does not help. Of course, all realistic cases are between these two extremes.

If there were n_1 preintervention measurements and n_2 postintervention measurements, then the variance of d' becomes:

$$\frac{\sigma_p^2 \left(\frac{\sigma_e^2}{n}\right)}{\sigma_p^2 + \left(\frac{\sigma_e^2}{n_1}\right)} + \frac{\sigma_e^2}{n_2}.$$

The example intervention we used was the Oslo dietary intervention study. Since the proportional change appeared to be normally distributed (see Fig 3 in Hjermann et al[19]), σ_Δ was estimated on the log scale from the mean decrease and z value of the 90th percentile. The mean decrease was 13% (a log decrease of 0.139), with a variance of 0.0118, based on a preintervention value calculated as the mean of three measurements and a postintervention value calculated as the mean of 10 measurements.[38] Removing the within-individual variance component leaves us with a variance for the true change of $0.0118 - \{0.00589 \times [(1/3) + (1/10)]\} = 0.00924$.