Association of Serum Total Cholesterol with Coronary Disease and All-Cause Mortality: Multivariate Correction for Bias Due to Measurement Error

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Measurement error in the exposure under investigation is an important but often ignored source of bias in observational studies. The authors examined the impact of measurement error in the association between total serum cholesterol and 16-year coronary heart disease and all-cause mortality in a cohort of 6,137 middle-aged men of Japanese descent in the Honolulu Heart Program (1973-1988). A Cox regression model that enables modeling of survival time with correction for measurement errors in multiple covariates was employed. After controlling for age, body mass index, systolic blood pressure, smoking status, alcohol consumption, dietary cholesterol, and total calorie intake, a difference of one standard deviation (38 mg/dL) in total cholesterol was associated with a significant increase in the risk of coronary disease death (uncorrected hazard ratio = 1.35). After correction for measurement errors in total cholesterol and covariates (except smoking and age), the estimated hazard ratio increased to 1.65 (a 22% increase). A U-shaped relation was observed between total cholesterol levels and the risk of all-cause mortality. This association was then examined with a quadratic model and with a two-slope or V-shaped regression model. In the quadratic fit, the magnitude of the quadratic total cholesterol term increased threefold after the adjustment for measurement error. In the V fit, the hazard ratio of all-cause death corresponding to a change in one standard deviation above 214 mg/dL (the nadir of the V) was 1.15, and increased to 1.49 (by 29%) after the correction. The corresponding hazard ratio of a change in one standard deviation below 214 mg/dL was 1.11, and increased to 1.37 (by 23%) after the correction. The authors conclude that the impact of elevated total cholesterol on the risk of coronary disease and all-cause mortality may be greater than previously estimated with standard methods of analysis. In addition, the correction for measurement error in total cholesterol and covariates did not explain the excess mortality associated with low total cholesterol. More research is needed to elucidate the fundamental issues underlying the U-shaped association, i.e., confounding versus causal implications. Am J Epidemiol 1996;143:463-71.

bias (epidemiology); cohort studies; coronary disease; mortality; regression analysis; risk factors

A common problem in observational studies is that measured biologic or behavioral risk factors are only surrogate indicators of the individual's true level of exposure (1). A well-known consequence of the error in measurement is that the slope of the simple regression of y (disease) on x (exposure) is attenuated (2, 3).

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Abbreviations: CI, confidence interval; ICD-8, International Classification of Diseases, 8th revision; SE, standard error.
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This phenomenon has been called “regression dilution bias” by MacMahon et al. (4).

Because total serum cholesterol concentrations are subject to intraindividual fluctuations and to laboratory error (5, 6), it follows that the univariate relation of total cholesterol level with mortality will be subject to the effect of regression dilution bias. In consequence, previous estimates of the relation of total cholesterol with risk of coronary heart disease or all-cause mortality may be attenuated relative to the true extent of the association (7-9). However, when multivariate models are used and two or more variables included in the model are measured with error, the situation becomes more complex and the observed regression coefficients may underestimate or overestimate the corresponding true regression coefficients (3). Recently, a number of papers have appeared (3, 10-13) that describe methods to assess and correct for measurement error.
The aim of this report is to present two empirical examples of a method for correcting for measurement error bias using multiple Cox proportional hazards regression. The method is an extension of a logistic procedure described by Rosner et al. (13). In the first example, and as previously shown in the Lipid Research Clinics Mortality Follow-up Study (14) and the British United Provident Association Study (15), we hypothesized that the crude (uncorrected) association of elevated total cholesterol with the risk of coronary disease death is an underestimation of the true extent of the hazard of elevated total cholesterol. The second example involved the application of the correction procedure to the U-shaped relation of total cholesterol with all-cause mortality. We hypothesized that the quadratic relation and thus both arms of a V-shaped fit will become steeper after the correction. It is anticipated that measurement error is not a likely explanation of the excess death rate in cohort members with low total cholesterol.

**MATERIALS AND METHODS**

**The cohort**

The Honolulu Heart Program was established in 1965–1968 with the examination of 8,006 Japanese-American men born between 1900 and 1919 and who lived on the island of Oahu, Hawaii. About 12 percent of the cohort were migrant farmers from southern Japan. The principal focus of the study has been the identification of predictors of coronary disease and stroke. Specifics of the design, study population, and methodological procedures have been previously published (16, 17). On entry into the study (1965–1968) and during the third examination 6 years later (1971–1974), the following data were obtained from each subject: sociodemographic factors, individual and family medical history, weight, height, blood pressure, non-fasting total cholesterol, as well as cigarette smoking and alcohol consumption habits. At each examination, blood pressure was measured once by a physician and twice by a trained nurse, and the average of the three readings was used in the analysis. Usual diet was assessed at the first examination with the 24-hour dietary recall method (18). In 1970, a random sample of 261 men were invited to participate in a dietary intake validation study involving the completion of 7-day dietary records. The purpose of this validation study was to assess within-person variability of nutrient intake (19). In 1965–1968, non-fasting total cholesterol concentrations were measured by the Autoanalyzer N-24A method (Technicon Instruments Corp., Tarrytown, New York) at the US Public Health Service Laboratory in San Francisco, California (20). In 1971–1974, non-fasting total cholesterol was determined by the same method, but sera specimens were processed in a different laboratory (Kuakini Medical Center, Honolulu, Hawaii). Deaths during the period 1973–1988 were then ascertained through hospital surveillance, state health department records, and newspaper obituaries. The underlying cause of death was assigned by a mortality review panel, and coded following the eighth revision of the International Classification of Diseases (ICD-8) (21).

The principal endpoints for this analysis were deaths due to coronary disease (rubrics 410–414 of the ICD-8) and all-cause mortality. Less than 2 percent of the cohort was lost to follow-up during the study period. Of the total 8,006 men enrolled in the study, 231 had prevalent coronary disease, 68 had cerebrovascular disease, and 58 had cancer at the time of baseline measurements, and were excluded from the study. Of the remaining 7,515 men, 1,378 had missing values in total cholesterol and/or study covariates, or did not attend examination 3. Thus, the final sample for analysis comprised 6,137 participants.

**Statistical analysis**

We first obtained descriptive statistics and Pearson correlations among the study variables. Age-adjusted mortality rates for coronary disease and all causes were computed by quintiles of total cholesterol using the direct method with the entire cohort as the standard population.

To model survival time as a function of total cholesterol, we used the Cox proportional hazards model (22, 23). Hazard ratios and 95 percent confidence intervals are given for corresponding increases of one standard deviation in each continuous predictor variable and for contrasted levels of categorical predictors. To remove the effect of age, regression models were stratified on age at baseline (in individual’s years, and assumed to contain no error).

Tests for linear or quadratic (U-shaped) associations between total cholesterol and mortality outcomes were performed with age-adjusted Cox regression on linear total cholesterol only and with age-adjusted Cox regression of linear plus total cholesterol squared terms, respectively. A U-shaped relation indicates that the risk across the independent variable (in this case, total cholesterol) is elevated at low and at high values of the predictor and is minimum at the middle range.

One way to parametrize a quadratic risk relation is to fit a “two-piece” or “V-shaped” regression line to the data. This parametrization has been described in the literature as “broken” or “piece-wise” regression (24). The nadir or breakpoint of the “V” was estimated as the minimum of the U-curve (25), and was equal to 214 mg/dL.
To correct for the effect of measurement error in total cholesterol and selected life-style (alcohol consumption, dietary cholesterol, and total calorie intake) and physiologic characteristics (body mass index and systolic blood pressure), we employed a multivariate method described by Rosner et al. (13), and a matrix-based algorithm developed by Dwyer and Sun (Institute for Prevention Research, Department of Preventive Medicine, University of Southern California, unpublished). The Dwyer-Sun program is a generalization of the Rosner method that applies to different forms of regressions: linear, probit, logistic, and proportional hazards. In the current analysis, smoking status (past, continuing smoking, and quitting, relative to never smokers) was also included in the multivariate models, but no attempt was made to correct for possible errors in the ascertainment of smoking status. We entered a categorical variable for alcohol abstinence (presumed fully accurate), because abstainers have been shown to be a group with compromised health (26). The Dwyer-Sun algorithm yields measurement error corrected point and confidence limit estimates of proportional hazards regression coefficients with covariates assumed to be measured with or without error. This analytic approach requires the availability of estimates of between- and within-person components of variance. These are usually determined via analysis of repeated measures or by validation studies. In our analysis, we used two observations of total cholesterol and covariates (examinations 1 and 3, 6 years apart), and two observations of dietary cholesterol and total calorie intake (one the baseline 24-hour dietary recall, and the other the average of seven consecutive daily food records supplied by a random subsample of 261 cohort members about 2 or 3 years later).

The method of Rosner et al. (13) for measurement error correction involves four steps. First, uncorrected or crude Cox regression coefficients are estimated for each study outcome using the main study data (examination 1 and 24-hour dietary recall). Second, a multivariate quadratic model (linear total cholesterol, total cholesterol squared, plus covariates); and second, a segmented multivariate V-shaped regression model (converging near the estimated total cholesterol value of minimal mortality), plus covariates).

RESULTS

Table 1 presents descriptive statistics of all the predictor variables in the main sample of 6,137 men,

<p>| TABLE 1. Descriptive statistics of study variables among a cohort of 6,137 middle-aged men of Japanese descent in the Honolulu Heart Program* |</p>
<table>
<thead>
<tr>
<th>Non-dietary variables</th>
<th>Main sample (n = 6,137)</th>
<th>At baseline (1965–1966)</th>
<th>At examination 3 (1971–1974)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>53.9 (5.4)</td>
<td>59.9 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL), mean (SD)</td>
<td>218 (36)</td>
<td>216 (36)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>23.9 (3.0)</td>
<td>23.7 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>133 (20)</td>
<td>136 (20)</td>
<td></td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>45.3</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (oz/month†), mean (SD)</td>
<td>13.6 (23.6)</td>
<td>13.5 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Alcohol abstainers (%)</td>
<td>35.5</td>
<td>30.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary variables</th>
<th>Dietary validation sample (n = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour dietary recall (1965–1968)</td>
<td>542 (317)</td>
</tr>
<tr>
<td>7-day dietary records (1970)</td>
<td>2,318 (662)</td>
</tr>
</tbody>
</table>

* Men with prevalent coronary disease, stroke, or cancer at baseline, or with missing values on study covariates at baseline or examination 3 variables are excluded.
† SD, standard deviation.
‡ 1 oz = 28.35 g.
together with the intake of dietary cholesterol and total calories in the validation sample of 261 men. There were slight reductions in average levels of serum cholesterol and body mass index, and a small increase in average systolic blood pressure from examination 1 to examination 3. The standard deviations of dietary cholesterol and total calorie intake measured by 7-day dietary records were appreciably smaller than the corresponding standard deviations of the same dietary variables measured with a 24-hour dietary recall (18.2 vs. 31.2 and 727 vs. 511, respectively). Results in table 1 also indicate a smaller proportion of current smokers and a tendency toward less alcohol abstinence in examination 3.

Total cholesterol at baseline showed a weak positive correlation with body mass index ($r = 0.12$), systolic blood pressure ($r = 0.07$) and dietary cholesterol ($r = 0.06$), and a weak negative correlation with alcohol consumption ($r = -0.05$). Autocorrelations (i.e., correlation of a variable at examination 1 with the same variable at examination 3) were high for body mass index ($r = 0.89$) and alcohol consumption ($r = 0.72$), and moderate for total cholesterol ($r = 0.61$) and systolic blood pressure ($r = 0.64$). The correlation between dietary cholesterol and total calories from the 24-hour dietary recall method and the same variables measured by 7-day records were $r = 0.33$ and $r = 0.46$, respectively, in the 261 participants in the collection of 7-day dietary records.

Example 1: total cholesterol and coronary mortality

There were 197 documented coronary disease deaths, comprising about 13 percent of all deaths and 50 percent of all cardiovascular disease deaths. Age-adjusted coronary disease mortality rates per 100 men increased consistently with the level of total cholesterol: 1.7 (<189 mg/dL), 2.7 (189–207 mg/dL), 3.2 (208–226 mg/dL), 3.1 (227–247 mg/dL), and 5.9 (>247 mg/dL), respectively ($p$ linear trend = 0.0001).

Table 2 presents the uncorrected and measurement error corrected multivariate hazard ratios of coronary disease death associated with differences of one standard deviation in continuous variables, and the corresponding hazards of former smokers, continuing smokers, and quitters, relative to never smokers. The risk from alcohol abstinence is given in relation to any alcohol consumption.

A difference of one standard deviation (38 mg/dL) of total cholesterol was associated with a 1.35 “crude” increase in coronary disease mortality. When the correction for measurement error was performed, the hazard increased to 1.65 (a 22 percent increase). The association of systolic blood pressure with the risk of death from coronary disease was also considerably augmented after the correction for measurement error (1.57 uncorrected vs. 1.98 corrected). Dietary cholesterol was a weak (and non-statistically significant)
positive risk factor for fatal coronary disease. It is noteworthy that the relative risk associated with an increase of 300 mg/day in dietary cholesterol (holding the total calorie intake constant) rose from 1.05 to 1.26 after the multivariate correction for measurement error bias (about 20 percent increase). However, this deattenuation was accompanied by an extremely wide 95 percent confidence interval, including unity. Conversely, correction for errors of measurement did not have an appreciable impact on the direct relation between body mass index and the inverse relation of alcohol consumption with the risk of coronary death.

Among the variables assumed to contain no error, it was found that smoking quitters, continuing smokers (in relation to never smokers), and abstainers from alcohol (in relation to any alcohol consumption) were at increased risk of coronary disease mortality.

Example 2: total cholesterol and all-cause mortality

There were a total of 1,490 deaths in the 16 years of follow-up among the study subjects. Age-adjusted mortality rates (per 100 persons) by quintiles of total cholesterol at baseline were 25.5, 22.0, 22.1, 25.4, and 26.3, respectively, evidencing a quadratic relation of all-cause mortality with the level of total cholesterol ($\beta$ for total cholesterol squared = 0.0000339; standard error (SE) = 0.0000093; $t = 3.6$). To facilitate the interpretation of the U-shaped relation, we estimated the hazard ratios for changes of 1 standard deviation (SD) (38 mg/dL) above and below the nadir of the V (that is, the intersection of the slopes at 214 mg/dL) using a V-shaped regression model (table 3). An increase of 38 mg/dL above 214 mg/dL was associated with a hazard ratio of 1.15. A decrease of 38 mg/dL from the breaking point of the V predicted a hazard ratio of 1.11. Corresponding corrected estimates were about 29 percent higher for the hazard derived from the right slope (total cholesterol change toward higher level), and 23 percent higher for the hazard derived from the left slope (total cholesterol change toward lower level).

When the correction was applied to the multivariate quadratic model, the coefficient for total cholesterol squared became about three times larger ($\beta = 0.000113$; SE = 0.000044; $t = 2.5$).

Systolic blood pressure and alcohol consumption were significant risk factors for all-cause mortality among men of the Honolulu cohort. After the correction, the risk associated with these variables increased by a moderate amount (11 percent for systolic blood pressure and 6 percent for alcohol consumption). No impact on all-cause mortality was observed for body mass index, dietary cholesterol, and total calorie intake. On the other hand, all smoking categories (rela-

<table>
<thead>
<tr>
<th>Predictor variables (1 SD change)</th>
<th>Hazard ratio† (95% CI)</th>
<th>% Change‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol +38 mg/dL above 214 mg/dL</td>
<td>1.15 (1.07-1.24)</td>
<td>29.5</td>
</tr>
<tr>
<td>-38 mg/dL below 214 mg/dL</td>
<td>1.11 (1.00-1.22)</td>
<td>23.4</td>
</tr>
<tr>
<td>Body mass index (3.1 kg/m²)</td>
<td>1.02 (0.96-1.07)</td>
<td>-0.02</td>
</tr>
<tr>
<td>Systolic blood pressure (21 mmHg)</td>
<td>1.25 (1.19-1.31)</td>
<td>11.2</td>
</tr>
<tr>
<td>Alcohol consumption (24 oz/month)</td>
<td>1.10 (1.04-1.16)</td>
<td>-6.3</td>
</tr>
<tr>
<td>Dietary cholesterol (300 mg/day)</td>
<td>1.02 (0.97-1.08)</td>
<td>5.8</td>
</tr>
<tr>
<td>Total calories (700 calories)</td>
<td>0.92 (0.87-0.97)</td>
<td>9.6</td>
</tr>
<tr>
<td>Past smoking vs. never smoking</td>
<td>1.18 (1.02-1.37)</td>
<td>2.4</td>
</tr>
<tr>
<td>Continuing smoking vs. never smoking</td>
<td>2.10 (1.84-2.40)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Quitting smoking vs. never smoking</td>
<td>1.78 (1.50-2.11)</td>
<td>-4.5</td>
</tr>
<tr>
<td>Alcohol abstinence vs. any alcohol</td>
<td>1.22 (1.08-1.36)</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Men with prevalent coronary disease, stroke, or cancer at baseline are excluded.
† Hazard ratios are estimated for 1 SD (standard deviation) change in continuous variables, and relative to never smokers and any alcohol consumption, respectively, for smoking status and alcohol abstinence.
‡ % change is estimated as ((corrected - uncorrected)/uncorrected) x 100.
§ 1 oz = 28.35 g.

tive to never smokers) and alcohol abstinence were important determinants of death.

DISCUSSION

The aim of this analysis was to reduce the effect of measurement error in the association between total cholesterol and coronary disease mortality and between total cholesterol and all-cause mortality in the Honolulu Heart Program. The corrected relative risk estimates can be interpreted as the true measure of association given that only random (unbiased) but not systematic (biased) within-person errors were present in total cholesterol and related confounders (body mass index, systolic blood pressure, alcohol consumption, dietary cholesterol, and total calorie intake).

The sources of random within-person error in the assessment of total cholesterol level are well documented. They consist of within-person seasonal (28), day-to-day (29), or diurnal variation (30), as well as possible technical errors in the laboratory (e.g., omissions in the protocol, variability of reagents, or faulty instruments). The principal source of systematic error in total cholesterol is actual physiologic change due to life-style modification or disease.

Within-person random error and consequent regression dilution are closely related to the phenomenon of regression toward the mean, a problem first described by Galton (31) after he observed the stature of parents and their offspring. Galton concluded that the stature of the offspring tended toward values closer to the mean population height. Regression toward the mean in total cholesterol level implies that extreme readings at baseline are more likely than not to shift toward central values at a subsequent reexamination. This phenomenon can be illustrated in the Honolulu cohort. Men with total cholesterol values in the lowest quintile at baseline had a mean total cholesterol concentration of 170 mg/dL in 1965–1968, but the same men had a mean value of 186 mg/dL at examination 3. Similarly, the mean total cholesterol concentration in men in the highest quintile at baseline was 272 mg/dL, and had regressed 6 years later to 249 mg/dL.

In corroboration of the first hypothesis of the study, we noted an increase in the hazard ratio of fatal coronary disease associated with a difference of 38 mg/dL in total cholesterol after correction for measurement error (from 1.35 to 1.65, a 22 percent increase). A systolic blood pressure higher by 21 mmHg was associated with a crude 1.6 hazard ratio. However, when measurement errors were accounted for, the hazard ratio for the same difference in systolic blood pressure was estimated to be about 2.0 (26 percent change in the hazard ratio). The increased importance of blood pressure as a coronary disease risk factor after correction for measurement error has been reported by MacMahon et al. (4).

Total calorie intake had a weak protective effect on coronary death risk, a circumstance that was unchanged after correction for measurement error. On the other hand, the corrected risk associated with an increase of 300 mg/day of dietary cholesterol was 20 percent greater than the uncorrected risk (1.26 vs. 1.05). Because the blood level of total cholesterol is likely to be in the causal pathway of the dietary cholesterol-coronary disease relation, we also estimated the risk of coronary disease death associated with this nutrient without adjusting for total cholesterol in the multivariate model. The corresponding crude estimate was 1.07 (95 percent CI 0.92–1.24) and the corrected estimate was 1.32 (95 percent CI 0.59–2.93).

Connor and Connor (32) demonstrated a significant correlation between cholesterol intake and death rates from arteriosclerotic and degenerative heart disease in 24 countries. In the Western Electric Study (33), the Ireland - Boston Diet - Heart Study (34), and the Zutphen Study (35), dietary cholesterol was an independent risk factor of coronary disease mortality. In the Honolulu Heart Program, dietary cholesterol intake was significantly higher among incident cases of definite coronary disease (nonfatal myocardial infarction, coronary disease death, or sudden death within one hour of coronary disease-type chest pain) after 10 years of follow-up than among non-cases (36). Other studies, however, have failed to find associations between dietary lipids and the risk of coronary disease within defined populations (37). Interestingly, our corrected results support the evidence a role of dietary cholesterol in the development of coronary disease, as previously reported in ecologic and population-based data.

A controversy exists about the U-shaped association between total cholesterol and all-cause mortality, arising from a (causal) positive association between high total cholesterol and atherosclerotic disease, and a negative association (of uncertain nature) between low total cholesterol and nonatherosclerotic conditions (apparently in men but not in women) (38). In this paper, we focused on the potential impact of measurement error in this U-shaped association between total cholesterol and mortality. Regression dilution bias has been cited as an unlikely mechanism behind the U-shaped association between total cholesterol and all-cause mortality (39) because, if present, it may increase rather than reduce the U-shape of the association. The current analysis is an empirical dem-
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A few methodological shortcomings of the current analysis should be pointed out. First, within-person variability in serum cholesterol and the covariates was assumed to be solely due to random fluctuation. In reality, however, it is likely that systematic together with random fluctuations in serum cholesterol and related risk factors may have occurred. For example, since the repeated measures used in this analysis were taken an average of 6 years apart, it is likely that some true biologic change may have taken place. If this is the case, the correction procedure is anticonservative and may actually have led to overcorrection of the risk estimates. Second, all the exposures need to conform to the normal or Gaussian distribution. All of the variables used in the analysis were approximately normal, with the exception of alcohol consumption. As a check of robustness in this instance, the continuous alcohol intake variable was logarithmically transformed and the models reestimated. The risk estimates and confidence intervals were very similar. Finally, in the case of the dietary variables, it was necessary to assume that the errors from the two dietary measures (24-hour dietary recall and the average of the 7-day records) were uncorrelated (e.g., that they fluctuate randomly with respect to each other). This assumption implies that participants who completed both the 24-hour and the 7-day dietary records were unlikely to either overreport or underreport their dietary intake in both occasions. The random error in dietary measures includes actual variation over time, imprecise recall of foods consumed, and errors in portion size, as well as random recording and data entry errors (43).

In the current analysis, we chose to include only dietary cholesterol and total calories because of the high intercorrelation (i.e., multicollinearity) of macro-nutrients, which makes it difficult to separate out independent effects of fat, protein, carbohydrate, or dietary cholesterol in multivariate models (19, 36).

Recently, several studies have been published that employ methods to correct for exposure measurement error in chronic disease epidemiology: colon cancer and diet (44); breast cancer and dietary fat, calories, and alcohol (13); blood pressure, stroke, and coronary disease (4); and total cholesterol and risk of coronary disease (14, 15, 45). As recognized by a recent review on this topic (3), a much wider application of these methods, particularly in the area of nutritional epidemiology, is desirable.

However, this analytical method is not without some liabilities. It enables the estimation of deattenuated risk relations, but at the expense of increased variance. Furthermore, as seen in the examples presented here, this effect is sensitive to the size of the validation cohort.

Nevertheless, the question of measurement error may have important consequences for conducting epidemiologic research. First, it underscores the need for reproducibility and validation studies, therefore establishing some potential new priorities when planning and implementing studies. Second, from an etiologic point of view, measurement error correction may help clarify causal mechanisms of disease, or may support existing ones. Finally, correcting for regression dilution bias in associations between risk factors and disease may have public health implications, because corrected estimates could substantially alter population attributable risks. Therefore, there is a growing consensus that the design, implementation, and analytical phases of future studies should consider the possibility and consequences of exposure measurement errors.

In conclusion, the example presented here illustrates the feasibility and the precautions that one should bear in mind when implementing procedures for measurement error correction. Our data suggest that the influence of elevated serum total cholesterol may have a more important influence on the risk of coronary heart disease and all-cause mortality than has been previously estimated with the use of standard methods of analysis. In addition, correction for measurement error in total cholesterol and study covariates did not explain the excess mortality associated with low total cholesterol level. On the contrary, the hazard of low total cholesterol became larger after the correction.

More experience and careful application of methods for correcting for measurement error will allow researchers to balance the deattenuation of associations with the increased uncertainty introduced by the correction procedure.
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