Assessing the impact of measurement error in modeling change. A sensitivity analysis approach.

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Abstract

Measurement error in predictors is known to cause bias in estimated regression coefficients and also leads to a loss of power for detecting associations. Methods commonly used to correct for bias require auxiliary data (e.g., replicates, validation data). We develop a procedure for investigating the associations between the change in an imprecisely measured outcome and precisely measured predictors, adjusting for the baseline value of the outcome, when auxiliary data are not available. The procedure employs sensitivity analysis and large-sample theory to investigate both the associations between change and the predictors and to assess the impact of the measurement error. An illustration investigating the associations between three-year change in the intima-media thickness of the common carotid artery and known cardiovascular disease risk factors is provided.

KEYWORDS: Linear regression; Method of moments; Sensitivity analysis; Errors in variables; Measurement reliability; Measurement error variance.

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1 Introduction

In this paper we provide a sensitivity analysis-based procedure to investigate the associations between the change in an imprecisely measured outcome and precisely measured predictors when auxiliary data (e.g., replicates, validation data, instrumental variables) are not available. Change is defined to be the difference in some measured outcome variable, $\Delta = W_2 - W_1$, where W_2 denotes the outcome at time t_2; W_1 denotes the outcome at time t_1 with $t_2 > t_1$. We refer to W_1 as the *baseline* and W_2 as the *follow-up* values of the outcome. Analyses of change, Δ, are often conducted in biomedical research. Whether one adjusts for the baseline is critical from a scientific or causal perspective. This fact is independent of the problems due to measurement error. Including the baseline value of the outcome in a model for change will yield different causal effect estimates than a model that omits it [9]. Investigations that do not require adjusting for the baseline will not be affected by measurement error bias. We focus upon the situation where adjusting for the baseline is appropriate to obtain the desired causal effect estimates.

The effects of measurement error in regression have been known for more than 130 years [1]. There is an extensive literature for both linear [8] and non-linear measurement error models [2, 3]. Including an imprecisely measured predictor (e.g., the baseline outcome) in a regression model not only causes a bias in the estimated regression coefficient of the offending predictor, but can also cause a bias in the estimated regression coefficient of another predictor if those predictors are correlated. Yanez et al. [14] investigated the problem of modeling change in linear regression. They showed how failing to correct for measurement error could lead to totally spurious associations. They employed a method-of-moments approach to correct for measurement error bias in the regression coefficients and used a bootstrap approach [5] to obtain valid standard error estimates for use in hypothesis testing.

Other approaches are available to correct for measurement error bias. These include Regression Calibration (RC) [2], simulation extrapolation (SIMEX) [4], Generalized Linear Covariate Measurement Error Models (CME) [12], Generalized Non-Parametric Corrected Scores [10], Corrected Estimating Equations [11], and more recently, Moment Reconstruction [6]. Programs for RC,

SIMEX and CME are available in popular statistical software packages such as Stata (e.g., `rcal, simex, cme`) and R (`simex`). Some approaches are only available in specialized programs written in high-level languages (e.g., FORTRAN, C++) and would be difficult for the non-technical data analyst to implement. All these approaches, including the method-of-moments, require auxiliary data on at least a subset of the data to perform a measurement error correction. Unfortunately, most studies lack auxiliary data. They may not have been collected for any one of several reasons (e.g., prohibitive costs, lack of appropriate planning). In those situations, measurement error could be assessed indirectly using independent data collected from other data sources called *external datasets*. Using external datasets has drawbacks. One must assume the data are appropriate to assess the measurement error or that the model is *transportable* [2]. If this (untestable) assumption is false, bias may be introduced as well.

Another alternative to using external datasets involves the specification of parameters associated with the measurement error. If the variance of the measurement error were known, for example, measurement error correction may be reduced to a rescaling of the estimated regression coefficients and estimated standard errors in some models. The `eivreg` program in Stata employs such a procedure for measurement error-correction when the measurement *reliability* of an imprecisely measured predictor is assumed known and provides a reasonable first step for investigating the impact of measurement error. It may not be reasonable, however, to assume knowledge of the measurement reliability precisely. Often times investigators may be able to more reasonably specify a range of plausible values for the measurement reliability or the variance of the measurement error for an imprecisely measured variable. The procedure we developed allows for the specification of a range of values for either the measurement reliability or the measurement error variance to assess the impact of the measurement error. This assessment may be performed by examination of the fitted model or tests of associations for model predictors for the specified range of the measurement error parameter. It may also be assessed graphically using the R program provided. We present a model for change, a bias-corrected estimator and large-sample variance estimate of the bias-corrected estimator in Section 2. In Section 3, we provide an illustration for the problem that motivated this

work. The example analysis examines the impact of measurement error in analyzing the change in intima-media thickness (IMT) of the common carotid artery and known cardiovascular disease (CVD) risk factors. A discussion is given in Section 4. The Appendix provides derivations for the asymptotic variances for the measurement error-corrected estimates. We also provide instructions for implementing our procedure in the R statistical software package. The program and its point-and-click graphical interface are available upon request from the the first author of this paper.

2 A Model for Change

2.1 The model

Suppose that for $i = 1, 2, \ldots, n$, we write the model for *true* change, D_i, as

$$D_i = Y_{2i} - Y_{1i} = \mathbf{z}_i'\boldsymbol{\beta} + \alpha Y_{1i} + \varepsilon_i \tag{1}$$

where $\mathbf{z}_i = (1, z_{1i}, z_{2i}, \ldots, z_{pi})'$ are precisely measured predictors, $\boldsymbol{\beta} = (\beta_0, \beta_1, \ldots, \beta_p)'$ and α are the model regression coefficients, ε_i is a mean zero random error with constant variance and Y_{1i} and Y_{2i} are the true values of the outcome at baseline and at follow-up. The outcomes, $Y_{ji}\,(j = 1, 2)$, are unobservable. We observe $W_{ji} = Y_{ji} + U_{ji}$, where U_{ji} are the measurement errors of Y_{ji}, and have mean zero and constant variance, σ_u^2. We assume the measurement errors are uncorrelated with the model error, ε_i, the predictor variables, $\mathbf{z}_i$, and the outcomes Y_{ji}.

Let $\Delta_i = W_{2i} - W_{1i}$ denote the *observed* change in the outcome variable. The model for the observed change, Δ_i, is

$$\Delta_i = W_{2i} - W_{1i} = \mathbf{z}_i'\boldsymbol{\beta}^o + \alpha^o W_{1i} + \epsilon_i. \tag{2}$$

Yanez et al. [14] showed that fitting model (2) yields biased estimated regression coefficients relative to the regression coefficients of model (1). The least squares estimator for the regression coefficients of model (2), $(\hat{\boldsymbol{\beta}}^{o\prime}, \hat{\alpha}^o)'$, can be written as

$$\begin{pmatrix} \hat{\boldsymbol{\beta}}^o \\ \hat{\alpha}^o \end{pmatrix} = \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{zz} & \hat{\boldsymbol{\Sigma}}_{zW_1} \\ \hat{\boldsymbol{\Sigma}}_{W_1 z} & \hat{\Sigma}_{W_1 W_1} \end{pmatrix}^{-1} \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{z\Delta} \\ \hat{\Sigma}_{W_1\Delta} \end{pmatrix}, \tag{3}$$

where

$$\hat{\mathbf{\Sigma}}_{zz} = n^{-1}\sum_{i=1}^{n} \boldsymbol{z}_i \boldsymbol{z}_i', \qquad \hat{\mathbf{\Sigma}}_{zW_1} = n^{-1}\sum_{i=1}^{n} \boldsymbol{z}_i W_{1i},$$

$$\hat{\mathbf{\Sigma}}_{W_1 z} = n^{-1}\sum_{i=1}^{n} W_{1i} \boldsymbol{z}_i', \qquad \hat{\Sigma}_{W_1 W_1} = n^{-1}\sum_{i=1}^{n} W_{1i}^2,$$

$$\hat{\mathbf{\Sigma}}_{z\Delta} = n^{-1}\sum_{i=1}^{n} \boldsymbol{z}_i \Delta_i, \qquad \hat{\Sigma}_{W_1 \Delta} = n^{-1}\sum_{i=1}^{n} W_{1i} \Delta_i.$$

The asymptotic expectation of $(\hat{\boldsymbol{\beta}}^{o\prime}, \hat{\alpha}^o)'$ is

$$\lim_{n\to\infty} \begin{pmatrix} \hat{\boldsymbol{\beta}}^o \\ \hat{\alpha}^o \end{pmatrix} = \begin{pmatrix} \mathbf{\Sigma}_{zz} & \mathbf{\Sigma}_{zY_1} \\ \mathbf{\Sigma}_{Y_1 z} & \Sigma_{Y_1 Y_1} + \sigma_u^2 \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{\Sigma}_{zD} \\ \Sigma_{Y_1 D} - \sigma_u^2 \end{pmatrix}, \tag{4}$$

where

$$\hat{\mathbf{\Sigma}}_{zY_1} = n^{-1}\sum_{i=1}^{n} \boldsymbol{z}_i Y_{1i}, \qquad \mathbf{\Sigma}_{zY_1} = \lim_{n\to\infty} \hat{\mathbf{\Sigma}}_{zY_1},$$

$$\hat{\mathbf{\Sigma}}_{Y_1 z} = n^{-1}\sum_{i=1}^{n} Y_{1i} \boldsymbol{z}_i', \qquad \mathbf{\Sigma}_{Y_1 z} = \lim_{n\to\infty} \hat{\mathbf{\Sigma}}_{Y_1 z}$$

$$\hat{\Sigma}_{Y_1 Y_1} = n^{-1}\sum_{i=1}^{n} Y_{1i}^2, \qquad \Sigma_{Y_1 Y_1} = \lim_{n\to\infty} \hat{\Sigma}_{Y_1 Y_1},$$

$$\hat{\mathbf{\Sigma}}_{zD} = n^{-1}\sum_{i=1}^{n} \boldsymbol{z}_i D_i, \qquad \mathbf{\Sigma}_{zD} = \lim_{n\to\infty} \hat{\mathbf{\Sigma}}_{zD},$$

$$\hat{\Sigma}_{Y_1 D} = n^{-1}\sum_{i=1}^{n} Y_{1i} D_i, \qquad \Sigma_{Y_1 D} = \lim_{n\to\infty} \hat{\Sigma}_{Y_1 D},$$

$$\mathbf{\Sigma}_{zz} = \lim_{n\to\infty} \hat{\mathbf{\Sigma}}_{zz}.$$

The resulting bias in $\hat{\boldsymbol{\beta}}^o$ can be written as

$$\lim_{n\to\infty} \hat{\boldsymbol{\beta}}^o = \boldsymbol{\beta} + (\frac{\sigma_u^2}{\sigma_{Y_1|\mathbf{z}}^2 + \sigma_u^2})(1+\alpha)\boldsymbol{\gamma},$$

where $\sigma_{Y_1|\mathbf{z}}^2$ is the error variance of regressing Y_1 on $\mathbf{z}$, σ_u^2 is the measurement error variance of U_1, and $\boldsymbol{\gamma}$ are the regression coefficients in the regression of Y_1 on $\mathbf{z}$, i.e., $E[Y_1 \mid \mathbf{z}] = \mathbf{z}'\boldsymbol{\gamma}$. One

sees the bias in $\hat{\boldsymbol{\beta}}^o$ persists even if the baseline regression coefficient, α, is zero. The estimated coefficient for the observed baseline outcome, $\hat{\alpha}^o$, is also biased for α. Its asymptotic expectation is $\lim_{n\to\infty} \hat{\alpha}^o = \alpha(\frac{\sigma^2_{Y_1|\mathbf{z}}}{\sigma^2_{Y_1|\mathbf{z}}+\sigma^2_u}) - (\frac{\sigma^2_u}{\sigma^2_{Y_1|\mathbf{z}}+\sigma^2_u})$. In the following section, we propose an estimator that corrects for measurement error bias.

2.2 A regression estimator

Using the result of equation (4) and a method-of-moments approach, the proposed estimator,

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\alpha} \end{pmatrix} = \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{zz} & \hat{\boldsymbol{\Sigma}}_{zW_1} \\ \hat{\boldsymbol{\Sigma}}_{W_1 z} & \hat{\Sigma}_{W_1W_1} - \sigma^2_U \end{pmatrix}^{-1} \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{z\Delta} \\ \hat{\Sigma}_{W_1\Delta} + \sigma^2_U \end{pmatrix}, \tag{5}$$

provides unbiased estimates for the regression coefficients in model (1) if the variance of the measurement error, σ^2_u, were known. One could also re-parameterize the estimator in equation (5) in terms of a measure of the reliability, e.g., $\lambda = \sigma^2_{Y_1}/\sigma^2_{W_1}$, where $\sigma^2_{W_1} = \text{var}\,(W_{1i}) = \sigma^2_{Y_1} + \sigma^2_u$. The two occurrences of the measurement error variance, σ^2_u, in equation (5) would simply be replaced by $(1-\lambda)\sigma^2_{W_1}$. Specification of either λ or σ^2_u in equation (5) allows one to obtain unbiased estimates for the association between the change in the outcome, D, and the predictors, $\mathbf{z}$, adjusting for the baseline outcome.

2.3 A variance estimator

It can be shown that the proposed estimator in equation (5), $(\hat{\boldsymbol{\beta}}', \hat{\alpha})$, converges in distribution to a normal random variable,

$$n^{1/2}\left\{ \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\alpha} \end{pmatrix} - \begin{pmatrix} \boldsymbol{\beta} \\ \alpha \end{pmatrix} \right\} \xrightarrow{\mathcal{L}} N(\mathbf{0}, \boldsymbol{\Sigma}_{\beta\alpha}), \tag{6}$$

for covariance matrix $\boldsymbol{\Sigma}_{\beta\alpha}$. It is not difficult to obtain a consistent estimator for $\boldsymbol{\Sigma}_{\beta\alpha}$ for known σ^2_u or λ. Details of the formulae and derivations are provided in the Appendix. By having an unbiased estimator of $(\boldsymbol{\beta}', \alpha)'$ and a consistent estimator of its asymptotic variance, one is in a position to more fully investigate the association between the true change in the outcome, D, and the predictors, $\mathbf{z}$, adjusting for the baseline outcome, in the absence of auxiliary data. One

still must specify either σ_u^2 or λ. We recommend specifying a range of values for either of the two parameters to assess the impact of measurement error. An illustration that investigates the association between three-year change in the intima-media thickness of the common carotid artery and known cardiovascular disease risk factors is presented in the following section.

3 Illustration

3.1 Change in intima-media thickness of the common carotid artery

We illustrate the approach proposed in this paper using data from the Cardiovascular Health Study (CHS) [7, 13]. The CHS is a population-based, longitudinal study of coronary heart disease and stroke in people aged 65 years and older. This research was motivated, in part, by the problems encountered when analyzing change in the intima-media wall thickness (IMT) of the common carotid artery (as measured by ultrasonography) in models that included cardiovascular disease (CVD) risk factors: age, high density lipoproteins (HDL), low density lipoproteins (LDL), systolic blood pressure (SBP) , diabetes, gender, and current smoking status. These variables were originally selected for inclusion in our analysis as they were determined to be strong correlates of IMT at baseline.

3.2 Naive results

Of the 5201 original CHS study participants, 4044 had IMT measured at baseline and three years later. Naive (uncorrected) analyses were conducted and the results are shown in Table 1 and Table 2. An analysis that adjusted for baseline IMT showed highly significant associations between change and the CVD risk factors (Table 1). Table 2 shows an analysis without adjustment for the baseline IMT. There were no significant associations whatsoever. The results for the two analyses seem quite contradictory. While it is plausible that the inclusion or exclusion of baseline IMT in a model for change should yield different causal effect estimates, it seemed unlikely that the differences would be so extreme. These results led us to investigate the issue further. Quality control experiments conducted at the ultrasound center for CHS made it clear there was considerable measurement error in the carotid IMT measurements.

3.3 Bias-corrected results with auxiliary data

Auxiliary data in the form of replicate measures on baseline IMT were available on a subset of 40 CHS participants. These data were used to estimate the measurement error variance, $\hat{\sigma}_u^2 = 0.0376$ and the measurement reliability, $\hat{\lambda} = 0.697$. Bias-corrected estimates were obtained using the method-of-moments estimator in equation (5). Standard error estimates were obtained using a bootstrap procedure [5]. The results are shown in Table 3. There were no significant associations between change and the CVD risk factors. These results appeared similar to the results in Table 2, possibly suggesting that adjusting for baseline IMT was unnecessary. It is possible that the bias-corrected results were suspect. Even though the CHS sample dataset was large ($n = 4044$), the number of subjects with replicate data was small ($m = 40$). The sampling distribution of method-of-moments estimators can often be skewed in small samples. Examination of the bias-corrected bootstrap estimates supports this notion. Further, the size of the observed p-values were all greater than 0.68. If none of the predictors were associated with change in IMT, one should expect the p-values to be uniformly distributed between zero and one. In the third and final analysis of these data, we used the auxiliary (replicate) data only to pick bounds for the measurement reliability to assess the impact of measurement error in our fitted models.

3.4 Bias-corrected results without auxiliary data

We investigated the association between the CVD risk factors, $\mathbf{z}$, and *true* change in carotid IMT, by specifying a range of plausible values for the measurement reliability, $\lambda = \{0.60, 0.70, 0.80\}$. We selected this range as the estimated measurement reliability from the replicate data was approximately 0.70. Discussions with radiologists with expertise in ultrasound measurement supported this choice. Summaries of the fitted models are shown in Table 4. Corresponding graphical plots of the estimated regression coefficients and confidence bands, as a function of λ, are presented in Figure 1 through Figure 8.

For reliability $\lambda = 0.60$, age, systolic blood pressure, HDL cholesterol and baseline IMT were significantly associated with IMT change. Age, systolic blood pressure and baseline IMT are

inversely associated with IMT change while HDL cholesterol was positively associated with IMT change. Diabetic status, gender, LDL cholesterol and smoking status are not significantly associated with IMT change. The associations change dramatically for $\lambda = 0.70$. Risk factors that were associated with IMT change for $\lambda = 0.6$ are no longer associated with IMT change (i.e., age, systolic blood pressure, baseline IMT) or had their association reverse direction (HDL cholesterol). Risk factors that were not associated with IMT change for $\lambda = 0.6$ (i.e., diabetic status, gender, LDL cholesterol and current smoking status) are now significantly and positively associated with IMT change. For reliability $\lambda = 0.80$, all risk factors were significantly associated with IMT change. The directions of the associations between the CVD risk factors and IMT change are similar to those observed in the naive model (Table 1), where measurment error was ignored.

Figures 1 through 8 demonstrate more concisely the associations between the CVD risk factors and IMT change as a function of the measurement reliability, λ. The solid curves show the magnitudes of the estimated regression coefficients and the dashed lines are the 95 percent confidence intervals for the estimated regression coefficients for varying values of λ. It was interesting to note that the direction of the associations between IMT change and the CVD risk factors, $\mathbf{z}$ almost appear to "pivot" around the point estimate of the reliability, $\hat{\lambda} = .0697$.

4 Discussion

In this paper, we presented a method to investigate the associations between change in some imprecisely outcome and precisely measured predictors when (a) adjustment for the baseline value of the imprecisely measured outcome is appropriate, and (b) there are not auxiliary data to correct for measurement error. Adjusting for the baseline value of the outcome variable as a covariate (equation (2)), can cause a measurement error bias. Not correcting for the bias can lead to spurious findings.

The approach presented here does not take into account sampling variability of the specification of the measurement reliability or the variance of the measurement error in equation (5) or its estimated variance or standard error estimate. Hence, the Wald test statistic, $\hat{\beta}_k / \hat{se}(\hat{\beta}_k)$, used to

test the association between the k-th predictor variable, z_k, and the true change in the outcome, D, will likely be anti-conservative. The purpose of the approach is not to provide an omnibus test for these associations, but to provide insight on the behavior of these associations depending upon the amount of measurement error. In the illustration above, one sees how measurement error, as a function of reliability, affected the direction and magnitude of the associations between change in carotid IMT and the CVD risk factors.

Appendix

A.1 Asymptotic variance estimator

Assume the measurement reliability, λ is known and is defined as $\lambda = \frac{\sigma^2_{Y_1}}{\sigma^2_{W_1}} = \frac{\sigma^2_{Y_1}}{\sigma^2_{Y_1}+\sigma^2_{U_1}}$. The proposed estimator, $(\hat{\boldsymbol{\beta}}', \hat{\alpha})'$ in equation (5) can be re-written as

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\alpha} \end{pmatrix} = \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{zz} & \hat{\boldsymbol{\Sigma}}_{zW_1} \\ \hat{\boldsymbol{\Sigma}}_{W_1 z} & \hat{\Sigma}_{W_1W_1} - (1-\lambda)\hat{\sigma}^2_{W_1} \end{pmatrix}^{-1} \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{z\Delta} \\ \hat{\Sigma}_{W_1\Delta} + (1-\lambda)\hat{\sigma}^2_{W_1} \end{pmatrix},$$

where $\sigma^2_{W_1} = \text{var}\,(W_{1i}) = \sigma^2_{Y_1} + \sigma^2_{U_1}$. An asymptotically consistent estimator for $\sigma^2_{W_1}$ is

$$\hat{\sigma}^2_{W_1} = n^{-1}\sum_{i=1}^{n}(W_{1i} - \bar{W}_1)^2.$$

Let $\boldsymbol{\Sigma}_{ab} = \lim \hat{\boldsymbol{\Sigma}}_{ab}$ for any a and b. Also let

$$\hat{\boldsymbol{\Sigma}} = \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{zz} & \hat{\boldsymbol{\Sigma}}_{zW_1} \\ \hat{\boldsymbol{\Sigma}}_{W_1 z} & \hat{\Sigma}_{W_1W_1} - (1-\lambda)\hat{\sigma}^2_{W_1} \end{pmatrix}, \qquad \boldsymbol{\Sigma} = \lim_{n\to\infty} \hat{\boldsymbol{\Sigma}} = \begin{pmatrix} \boldsymbol{\Sigma}_{zz} & \boldsymbol{\Sigma}_{zW_1} \\ \boldsymbol{\Sigma}_{W_1 z} & \Sigma_{W_1W_1} - (1-\lambda)\sigma^2_{W_1} \end{pmatrix},$$

$$\hat{\boldsymbol{\mu}} = \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{z\Delta} \\ \hat{\Sigma}_{W_1\Delta} + (1-\lambda)\hat{\sigma}^2_{W_1} \end{pmatrix}, \qquad \boldsymbol{\mu} = \lim_{n\to\infty} \hat{\boldsymbol{\mu}} = \begin{pmatrix} \boldsymbol{\Sigma}_{z\Delta} \\ \Sigma_{W_1\Delta} + (1-\lambda)\sigma^2_{W_1} \end{pmatrix}.$$

Then

$$n^{1/2}\left\{\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\alpha} \end{pmatrix} - \begin{pmatrix} \boldsymbol{\beta} \\ \alpha \end{pmatrix}\right\} = n^{1/2}(\hat{\boldsymbol{\Sigma}}^{-1}\hat{\boldsymbol{\mu}} - \boldsymbol{\Sigma}^{-1}\boldsymbol{\mu}) = n^{1/2}\hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}} - \boldsymbol{\mu}) + n^{1/2}(\hat{\boldsymbol{\Sigma}}^{-1} - \boldsymbol{\Sigma}^{-1})\boldsymbol{\mu}.$$

We can see that

$$n^{1/2}(\hat{\boldsymbol{\mu}} - \boldsymbol{\mu}) = n^{1/2} \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{z\Delta} - \boldsymbol{\Sigma}_{z\Delta} \\ \hat{\Sigma}_{W_1\Delta} - \Sigma_{W_1\Delta} + (1-\lambda)(\hat{\sigma}^2_{W_1} - \sigma^2_{W_1}) \end{pmatrix}$$

$$= n^{-1/2} \sum_{i=1}^{n} \begin{pmatrix} \boldsymbol{z}_i\Delta_i - \boldsymbol{\Sigma}_{z\Delta} \\ W_{1i}\Delta_i - \Sigma_{W_1\Delta} + (1-\lambda) r_i \end{pmatrix},$$

where

$$r_i = (W_{1i} - \bar{W}_1)^2 - \sigma^2_{W_1}. \tag{7}$$

We have $n^{1/2}\hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\mu}} - \boldsymbol{\mu}) = n^{-1/2}\sum_{i=1}^{n} \boldsymbol{u}_i + o_p(\mathbf{1})$, where

$$\boldsymbol{u}_i = \boldsymbol{\Sigma}^{-1} \begin{pmatrix} \boldsymbol{z}_i\Delta_i - \boldsymbol{\Sigma}_{z\Delta} \\ W_{1i}\Delta_i - \Sigma_{W_1\Delta} + (1-\lambda) r_i \end{pmatrix}.$$

It is easy to see that

$$\hat{\boldsymbol{\Sigma}}^{-1} - \boldsymbol{\Sigma}^{-1} = \hat{\boldsymbol{\Sigma}}^{-1}\boldsymbol{\Sigma}\boldsymbol{\Sigma}^{-1} - \hat{\boldsymbol{\Sigma}}^{-1}\hat{\boldsymbol{\Sigma}}\boldsymbol{\Sigma}^{-1} = -\hat{\boldsymbol{\Sigma}}^{-1}(\hat{\boldsymbol{\Sigma}} - \boldsymbol{\Sigma})\boldsymbol{\Sigma}^{-1}.$$

Since

$$n^{1/2}(\hat{\boldsymbol{\Sigma}} - \boldsymbol{\Sigma}) = n^{1/2} \begin{pmatrix} \hat{\boldsymbol{\Sigma}}_{zz} - \boldsymbol{\Sigma}_{zz} & \hat{\boldsymbol{\Sigma}}_{zW_1} - \boldsymbol{\Sigma}_{zW_1} \\ \hat{\boldsymbol{\Sigma}}_{W_1 z} - \boldsymbol{\Sigma}_{W_1 z} & \hat{\boldsymbol{\Sigma}}_{W_1W_1} - \Sigma_{W_1W_1} - (1-\lambda)(\hat{\sigma}^2_{W_1} - \sigma^2_{W_1}) \end{pmatrix}$$

$$= n^{-1/2} \sum_{i=1}^{n} \begin{pmatrix} \boldsymbol{z}_i\boldsymbol{z}_i' - \boldsymbol{\Sigma}_{zz} & \boldsymbol{z}_i W_{1i} - \boldsymbol{\Sigma}_{zW_1} \\ W_{1i}\boldsymbol{z}_i' - \boldsymbol{\Sigma}_{W_1 z} & W_{1i}^2 - \Sigma_{W_1W_1} - (1-\lambda) r_i \end{pmatrix},$$

where r_i is defined in (7), we know that $n^{1/2}(\hat{\boldsymbol{\Sigma}}^{-1} - \boldsymbol{\Sigma}^{-1})\boldsymbol{\mu} = n^{-1/2}\sum_{i=1}^{n} \boldsymbol{v}_i + o_p(\mathbf{1})$, where

$$\boldsymbol{v}_i = -\boldsymbol{\Sigma}^{-1} \begin{pmatrix} \boldsymbol{z}_i\boldsymbol{z}_i' - \boldsymbol{\Sigma}_{zz} & \boldsymbol{z}_i W_{1i} - \boldsymbol{\Sigma}_{zW_1} \\ W_{1i}\boldsymbol{z}_i' - \boldsymbol{\Sigma}_{W_1 z} & W_{1i}^2 - \Sigma_{W_1W_1} - (1-\lambda) r_i \end{pmatrix} \boldsymbol{\Sigma}^{-1}\boldsymbol{\mu}.$$

Hence

$$n^{1/2} \left\{ \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\alpha} \end{pmatrix} - \begin{pmatrix} \boldsymbol{\beta} \\ \alpha \end{pmatrix} \right\} = n^{-1/2} \sum_{i=1}^{n} (\boldsymbol{u}_i + \boldsymbol{v}_i) + o_p(\mathbf{1}) \xrightarrow{\mathcal{L}} N(\mathbf{0}, \boldsymbol{\Sigma}_{\beta\alpha}),$$

where $\boldsymbol{\Sigma}_{\beta\alpha} = \text{var}\,(\boldsymbol{u}_i + \boldsymbol{v}_i)$. To obtain a consistent estimator for $\boldsymbol{\Sigma}_{\beta\alpha}$, we first define $\hat{r}_i$ by replacing $\sigma^2_{W_1}$ by $\hat{\sigma}^2_{W_1}$ in the definition of r_i. We then define $\hat{\boldsymbol{u}}_i$ and $\hat{\boldsymbol{v}}_i$ in the same way as we define $\boldsymbol{u}_i$

and $\boldsymbol{v}_i$, only with $\boldsymbol{\Sigma}$, $\boldsymbol{\Sigma}_{ab}$, r_i and $\boldsymbol{\mu}$ replaced by $\hat{\boldsymbol{\Sigma}}$, $\hat{\boldsymbol{\Sigma}}_{ab}$, $\hat{r}_i$ and $\hat{\boldsymbol{\mu}}$, respectively. Then we let $\hat{\boldsymbol{\Sigma}}_{\beta\alpha} = n^{-1}\sum_{i=1}^{n}(\hat{\boldsymbol{u}}_i + \hat{\boldsymbol{v}}_i)^{\otimes 2}$. It is not hard to see that $\hat{\boldsymbol{\Sigma}}_{\beta\alpha}$ is consistent for $\boldsymbol{\Sigma}_{\beta\alpha}$. The estimated asymptotic covariance matrix for $(\hat{\boldsymbol{\beta}}', \hat{\alpha})$ is then $\hat{\boldsymbol{\Sigma}}_{\beta\alpha}/n$.

One can easily obtain the asymptotic covariance matrix for $(\hat{\boldsymbol{\beta}}', \hat{\alpha})'$ as a function of the measurement error variance by starting with the proposed estimator in (5) and proceeding with the derivations outlined here.

A.2 Statistical software – *(in progress)*

A.2.1 Introduction

We provide instructions on how to install and use the measurement error correction approach presented in this paper. The function, `changelm`, and its point-and-click interface, `changelmGUI`.

The `changelm` function is written in the R statistical language. The point-and-click interface, `changelmGUI`, is written using a library in R called TCL/TK. Both programs must be loaded directly into R to be able to implement our measurement error correction approach.

A.2.2 Installing `changelm` and `changelmGUI`

`changelm` runs on top of the free statistical software program R. Please go to to the website http://cran.r-project.org/ for specific details on how to install R on your computer. The `changelm` program can run on several platforms (e.g., Windows, Linux/UNIX, Macintosh). To run the point-and-click interface `changelmGUI`, the TCL/TK library need to be installed on your particular platform.

http://www.biostat.washington.edu/ yanez/changelm/

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Table 1: Naive results for modeling observed change (with adjustment for baseline IMT).

Variable	Coefficient	Std. Error	P-value
Age	2.48×10^{-3}	5.30×10^{-4}	0.0001
Syst bp	5.65×10^{-4}	1.30×10^{-4}	0.0001
Diabetes	1.84×10^{-2}	6.67×10^{-3}	0.0058
Gender	3.55×10^{-2}	5.96×10^{-3}	0.0001
HDL	-5.64×10^{-4}	1.86×10^{-4}	0.0024
LDL	2.69×10^{-4}	7.57×10^{-5}	0.0004
Smoker	2.73×10^{-2}	8.70×10^{-3}	0.0017
baseline	-3.65×10^{-1}	1.41×10^{-2}	<.0001

Table 2: Naive estimates for modeling observed change (without adjustment for baseline IMT).

Variable	Coefficient	Std. Error	P-value
Age	-2.18×10^{-4}	5.61×10^{-4}	0.698
Syst bp	-5.10×10^{-5}	1.38×10^{-4}	0.711
Diabetes	5.20×10^{-3}	7.18×10^{-3}	0.469
Gender	9.18×10^{-3}	6.34×10^{-3}	0.148
HDL	-8.81×10^{-5}	1.99×10^{-4}	0.659
LDL	7.31×10^{-5}	8.13×10^{-5}	0.368
Smoker	6.94×10^{-3}	9.35×10^{-3}	0.458

Table 3: Bias corrected estimates for modeling observed change (with adjustment for baseline IMT).

Variable	Coefficient	Std. Error	P-value
Age	-2.89×10^{-3}	2.41×10^{-2}	0.9044
Syst bp	-5.61×10^{-5}	5.60×10^{-4}	0.9188
Diabetes	4.72×10^{-3}	1.35×10^{-2}	0.7273
Gender	8.79×10^{-3}	2.38×10^{-2}	0.7099
HDL	-8.24×10^{-5}	4.58×10^{-4}	0.8576
LDL	7.31×10^{-5}	2.78×10^{-4}	0.6829
Smoker	6.35×10^{-3}	1.92×10^{-2}	0.7417
baseline	4.42×10^{-3}	0.44×10^{-1}	0.9887

Table 4: Bias corrected estimates (sensitivity analysis method).

$\lambda = 0.60$			
Variable	Coefficient	Std. Error	P-value
Age	-1.73 x 10^{-3}	3.38 x 10^{-4}	<.0001
Syst bp	-3.95 x 10^{-4}	7.73 x 10^{-5}	<.0001
Diabetes	-2.16 x 10^{-3}	2.47 x 10^{-3}	0.3815
Gender	-5.50 x 10^{-3}	3.28 x 10^{-3}	0.0936
HDL	1.78 x 10^{-4}	7.03 x 10^{-5}	0.0114
LDL	-3.64 x 10^{-5}	3.01 x 10^{-5}	0.2269
Smoker	-4.45 x 10^{-3}	3.45 x 10^{-3}	0.1967
baseline	2.04 x 10^{-1}	4.44 x 10^{-2}	<.0001

$\lambda = 0.70$			
Variable	Coefficient	Std. Error	P-value
Age	-9.63 x 10^{-5}	1.85 x 10^{-4}	0.6030
Syst bp	-2.33 x 10^{-5}	4.34 x 10^{-5}	0.5923
Diabetes	5.79 x 10^{-3}	1.48 x 10^{-3}	0.0001
Gender	1.04 x 10^{-2}	1.90 x 10^{-3}	<.0001
HDL	-1.10 x 10^{-4}	4.05 x 10^{-5}	0.0069
LDL	8.20 x 10^{-5}	1.79 x 10^{-5}	<.0001
Smoker	7.86 x 10^{-3}	2.09 x 10^{-3}	0.0002
baseline	-1.64 x 10^{-2}	2.27 x 10^{-2}	0.4691

$\lambda = 0.80$			
Variable	Coefficient	Std. Error	P-value
Age	1.03 x 10^{-3}	1.59 x 10^{-4}	<.0001
Syst bp	2.33 x 10^{-4}	3.79 x 10^{-5}	<.0001
Diabetes	1.13 x 10^{-2}	1.85 x 10^{-3}	<.0001
Gender	2.13 x 10^{-2}	1.78 x 10^{-3}	<.0001
HDL	-3.08 x 10^{-4}	4.57 x 10^{-5}	<.0001
LDL	1.53 x 10^{-4}	2.10 x 10^{-5}	<.0001
Smoker	1.64 x 10^{-2}	2.58 x 10^{-3}	<.0001
baseline	-1.68 x 10^{-1}	6.44 x 10^{-3}	<.0001

Figure 1: Age (in years).

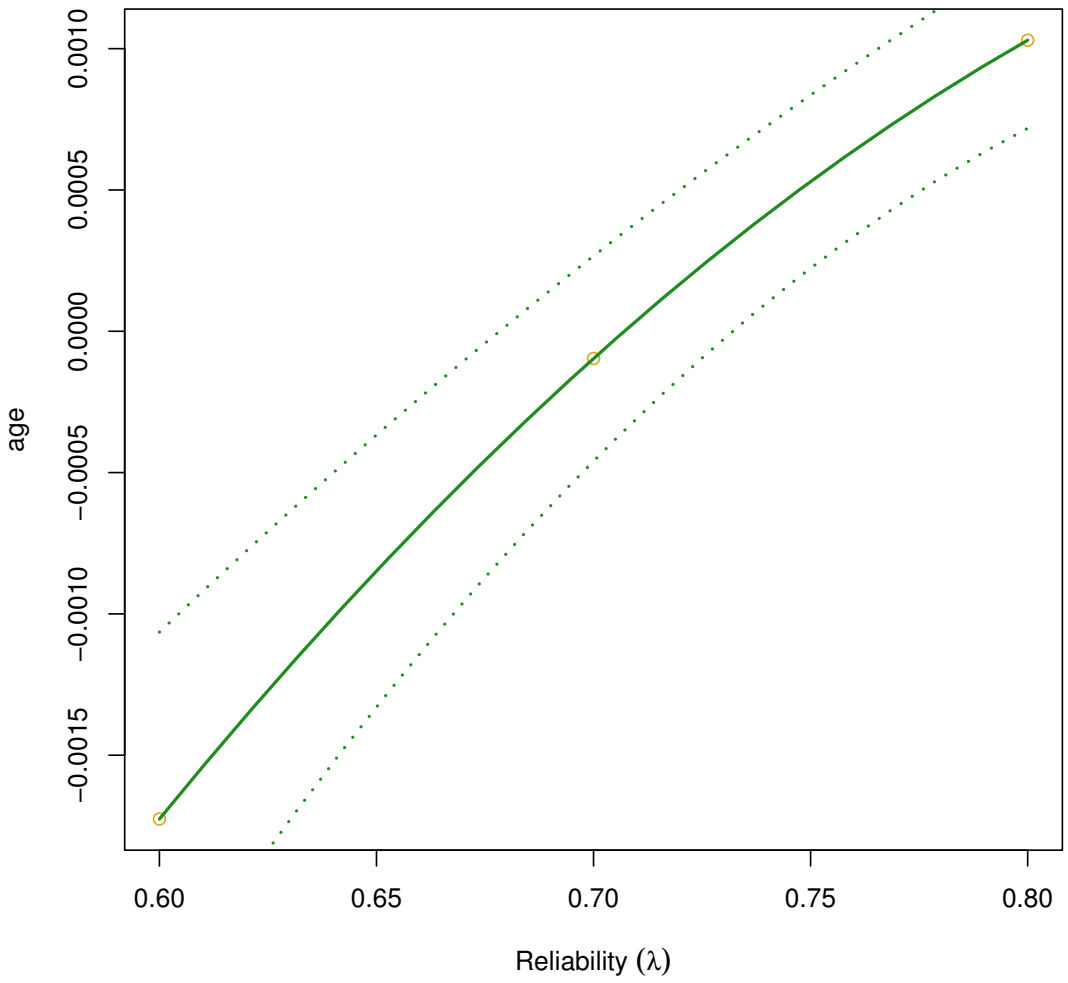

Figure 2: Systolic Blood Pressure (mmHg).

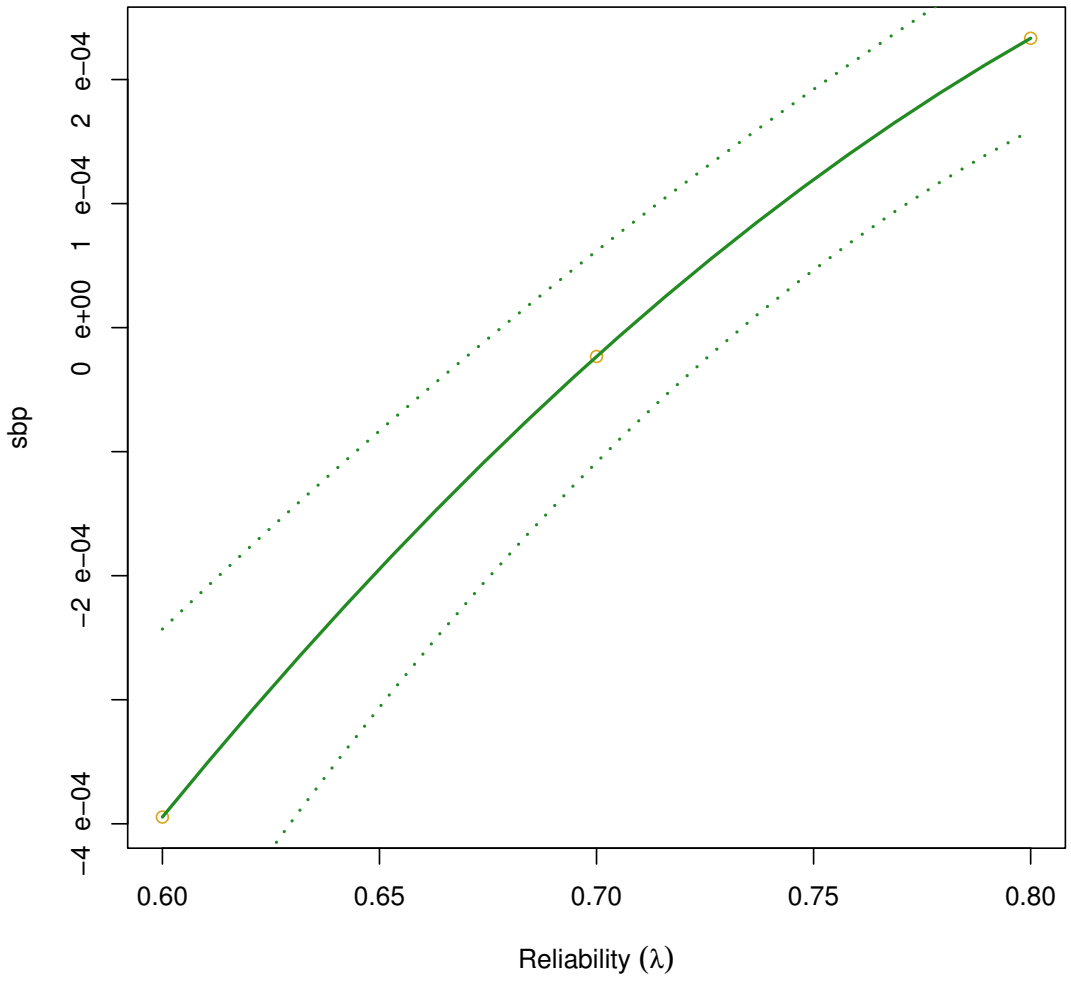

Figure 3: Diabetes.

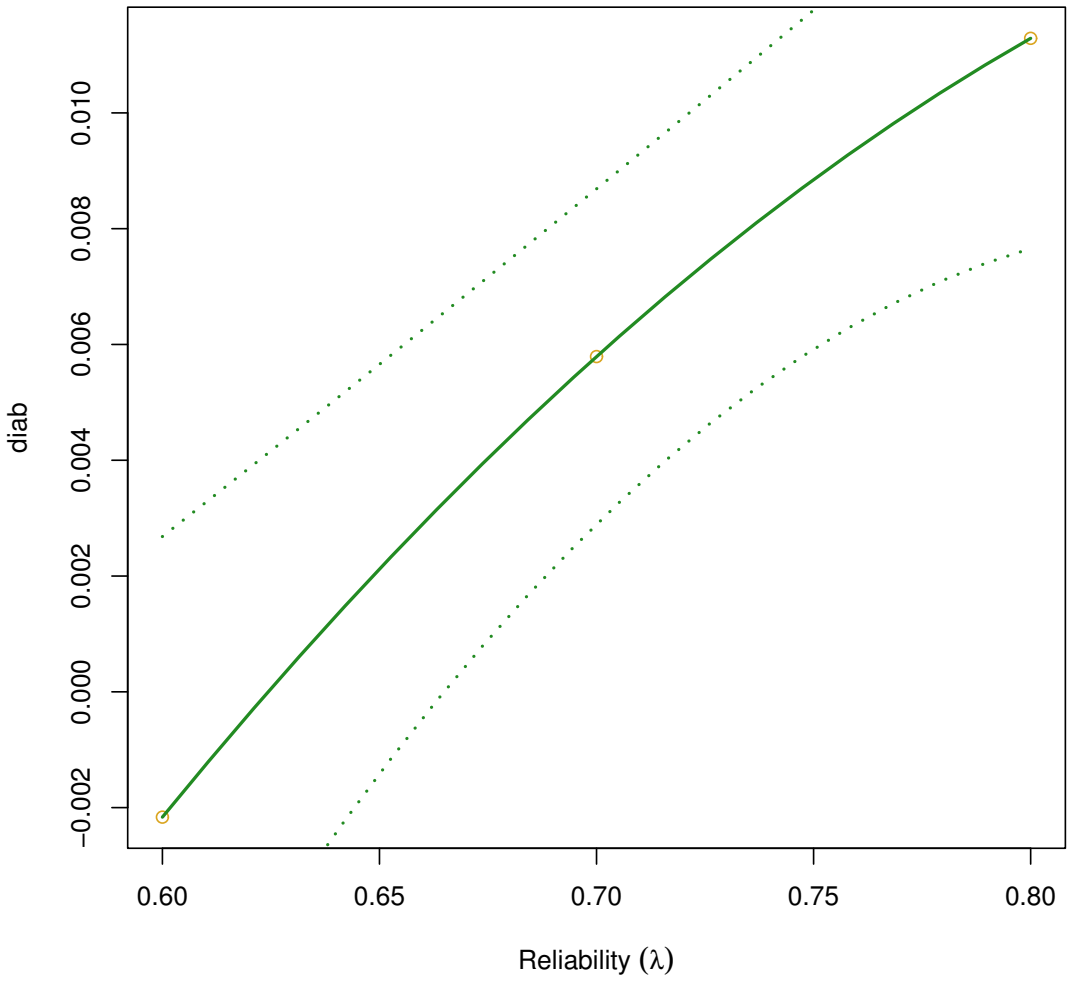

Figure 4: Male gender.

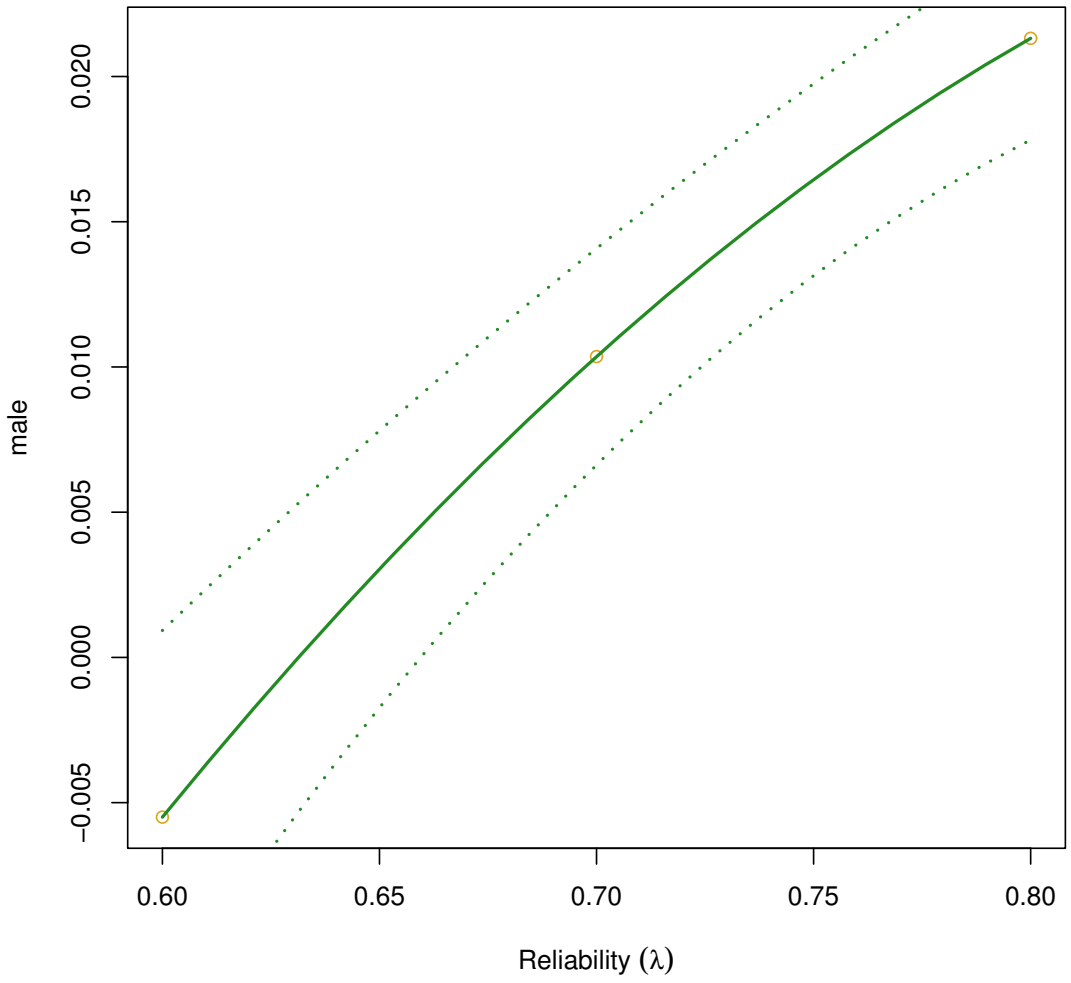

Figure 5: High Density Lipoproteins (mg/dL).

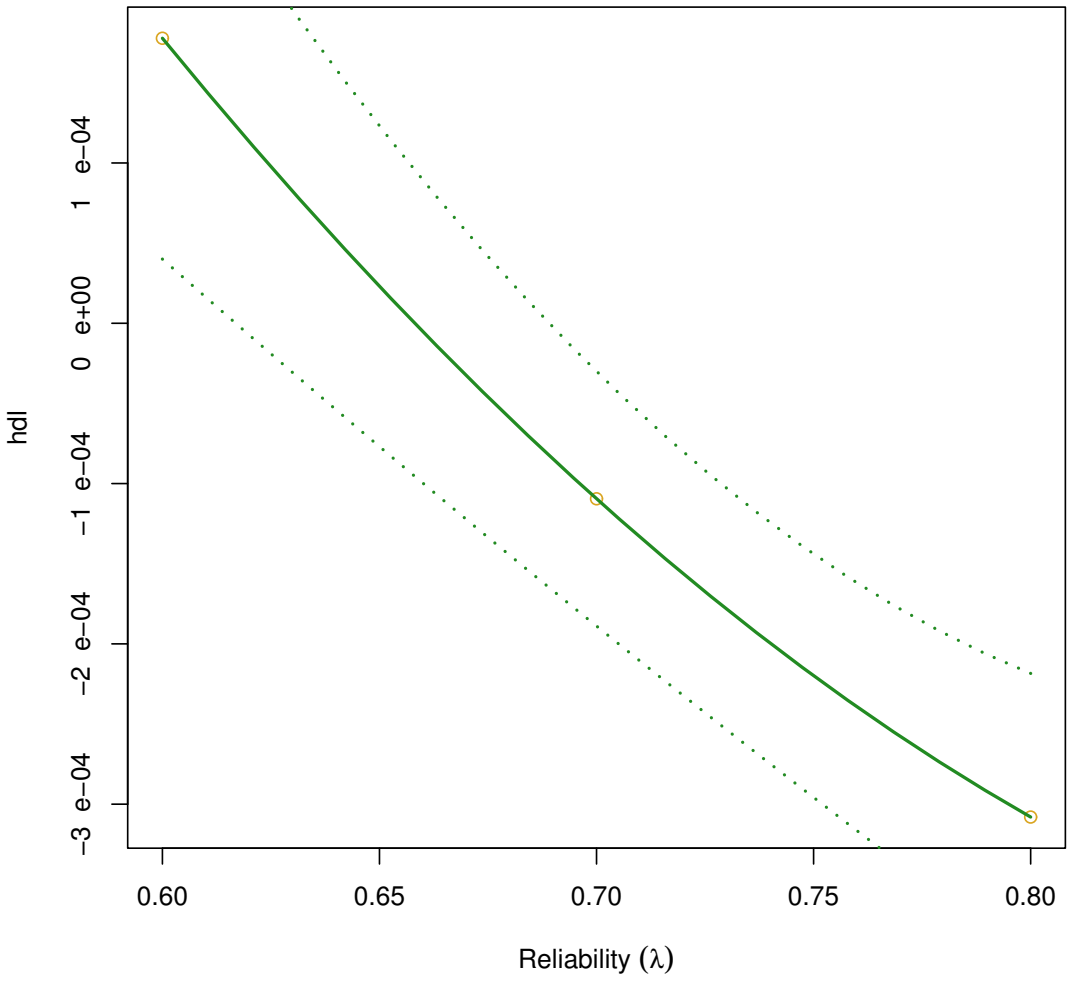

Figure 6: Low Density Lipoproteins (mg/dL).

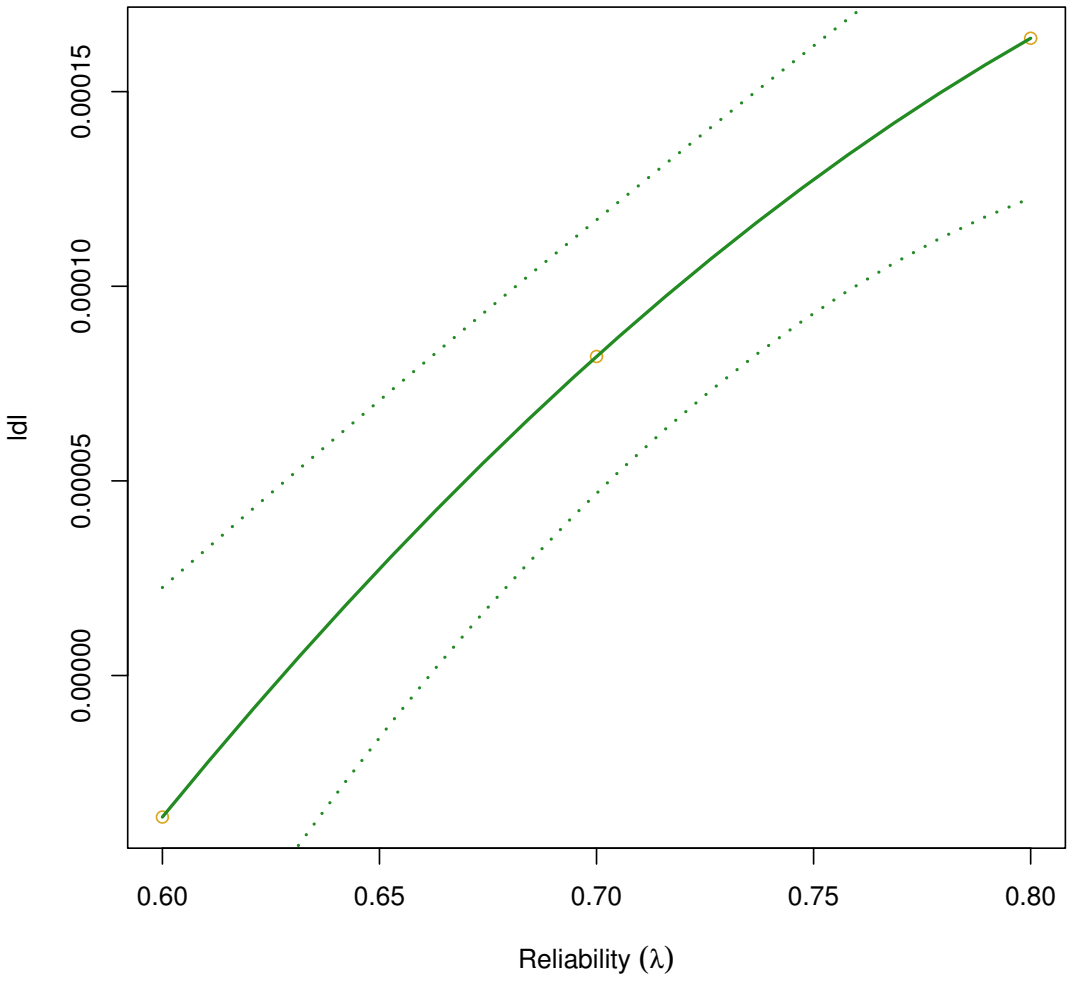

Figure 7: Current smoker.

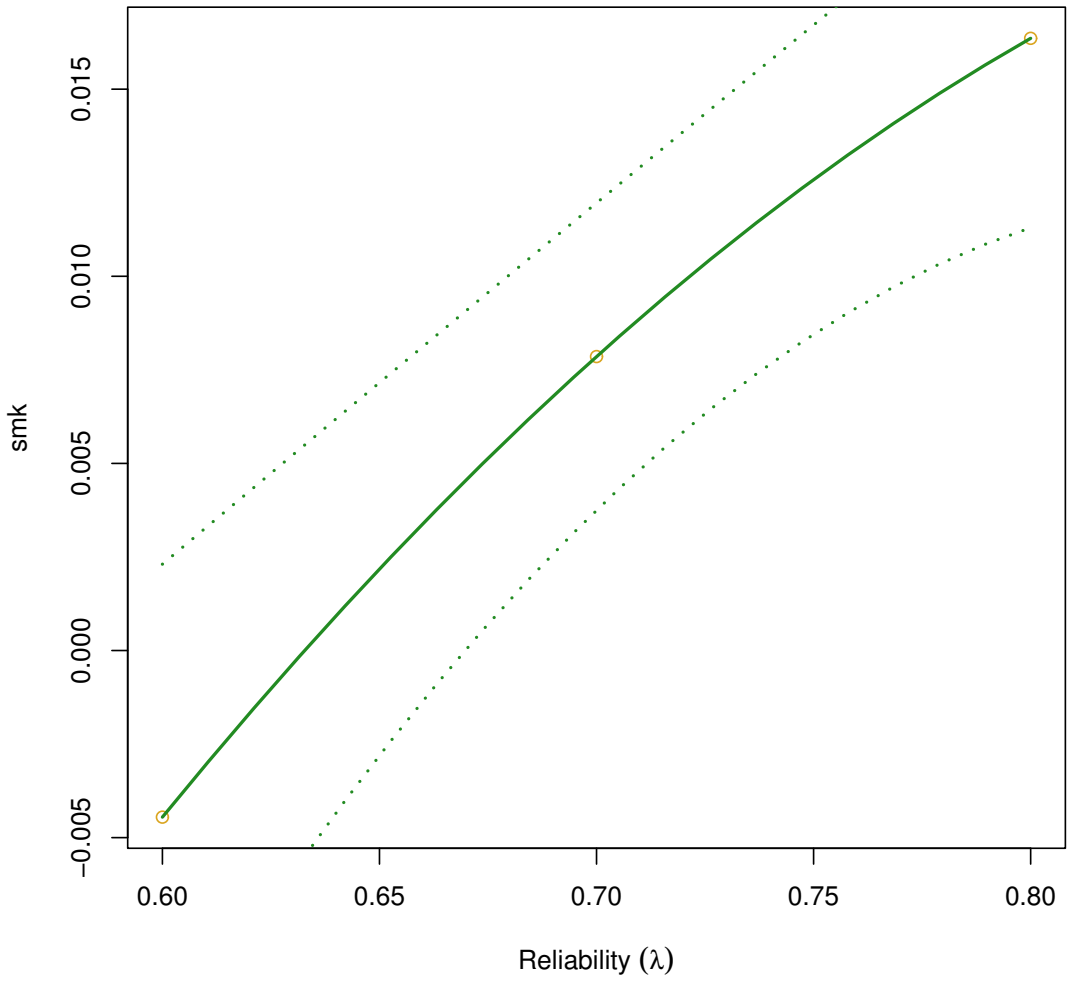

Figure 8: Baseline IMT.