

MEASUREMENT ERROR, INSTRUMENTAL VARIABLES AND CORRECTIONS FOR ATTENUATION WITH APPLICATIONS TO META-ANALYSES

R. J. Carroll
Department of Statistics
Texas A&M University
College Station, TX 77843

L. A. Stefanski
Department of Statistics
North Carolina State University
Raleigh, NC 27695

March 25, 1996

ABSTRACT

MacMahon, et al. (1990) present a meta-analysis of the effect of blood pressure on coronary heart disease, as well as new methods for estimation in measurement error models for the case when a replicate or second measurement is made of the fallible predictor. The correction for attenuation used by these authors is compared to others already existing in the literature, as well as to a new instrumental variable method. The assumptions justifying the various methods are examined and their efficiencies are studied via simulation. Compared to the methods we discuss, that of MacMahon, et al. (1990) may have bias in some circumstances because it does not take into account: (i) possible correlations among the predictors within a study; (ii) possible bias in the second measurement; or (iii) possibly differing marginal distributions of the predictors and/or measurement errors across studies.

1 INTRODUCTION

In this paper we discuss some problems that arise in regression meta-analysis when the predictor of interest is measured with nonnegligible error. Motivating our study is a recent paper by MacMahon, et al. (1990) presenting a meta-analysis of the effect of blood pressure on stroke and coronary heart disease. The methodology employed by MacMahon, et al. (1990) has been publicized in the press (Palca, 1990a,b), and it is likely to promote the use of measurement-error-models and meta-analysis in future studies.

Underlying the method proposed by MacMahon, et al. (1990) is a correction for attenuation due to measurement error that employs both baseline and post-baseline measurements of blood pressure from one of the studies; see also Ederer (1972). We compare their correction for attenuation to some of the standard methods in the statistical literature for adjusting regression coefficients for the effects of measurement error. In addition, we introduce a new instrumental variables estimator for generalized linear models. The assumptions justifying the various methods are examined in light of the type of violations that are likely to arise in a meta-analysis, and the estimated corrections for attenuation are studied via simulation experiments.

A necessary feature of a meta-analysis is that the individual studies share sufficient common ground to warrant the combination of information from the different data sets. With respect to measurement error modeling this imposes some restrictions on the relationship between the so-called true predictors and the surrogate predictors actually measured, especially when replicate measurements and/or validation data are limited. Implicit in the MacMahon, et al. (1990) method is the assumption that a single correction for attenuation is adequate for all studies in the meta-analysis. We show that this is not appropriate in general and describe the estimation of study-specific corrections.

In §2 we establish notation and discuss the effects of measurement error on regression meta-analyses. In §3 we present and compare some corrections for attenuation due to measurement error. Simulation studies illustrating some of the results is given in §4. In §5 we apply the various methods to Framingham data, with some comments about meta-analysis. We conclude in §6.

2 GENERAL THEORY

2.1 Study Data, Models and Meta-Analysis in the Absence of Measurement Error

Let Y denote the response variate and X the risk factor that is to be investigated in the meta-analysis. We suppose the availability of data from \mathcal{K} studies, with Y and X common to all studies. In addition, data from the k^{th} study includes a vector Z_k of study-specific covariates.

Justification for the meta-analysis depends on the assumption that the effect of X on Y is the same in all study populations after appropriate covariate adjustments. Thus as a model for the expected value of Y in the k^{th} population we have

$$E(Y | X, Z_k) = f(\alpha_k + \beta X + \gamma_k^T Z_k), \quad k = 1, \dots, \mathcal{K}. \quad (1)$$

The form of f is application dependent. For example, for linear regression f is the identity function, for binary regression f is commonly the logistic distribution function. In some models, *e.g.*, logistic regression, (1) completely specifies the model once the type of variation (Bernoulli, exponential, Poisson, *etc.*) in Y is specified. In other models there are additional variance parameters to model the residual variation which may be homoscedastic in the simplest cases or involve the mean function in addition to other variance parameters. Thus we allow for the possibility that accompanying (1) there is a variance-function model of the form

$$V(Y | X, Z_k) = \sigma_k^2 v(\alpha_k + \beta X + \gamma_k^T Z_k, \tau_k), \quad k = 1, \dots, \mathcal{K}. \quad (2)$$

Together (1) and (2) comprise a generalized quasilielihood/variance-function model with linear effects, and includes, for example, generalized linear models and heteroscedastic nonlinear models; see Carroll & Ruppert (1988) for details.

Let $\hat{\beta}_k$, $k = 1, \dots, \mathcal{K}$ denote the estimates of β obtained by fitting the model to the k^{th} study data. The combined-study estimate of β is obtained as a weighted average

$$\hat{\beta} = \sum_{k=1}^{\mathcal{K}} \hat{w}_k \hat{\beta}_k, \quad (\hat{w}_1 + \dots + \hat{w}_{\mathcal{K}} = 1).$$

In the absence of special considerations, the natural choice of weights has $\hat{w}_k \propto s_k^{-2}$ where s_k is the standard error of $\hat{\beta}_k$.

2.2 The Effect of Measurement Error

Now suppose that the risk factor X is not measured accurately. Let W denote the measured risk factor and assume the representation $W = X + U$ where U is a measurement error independent of Y , X and the other covariates. Furthermore assume that in the k^{th} study $\text{Var}(U) = \sigma_U^2$, independent of k .

In this paper we focus primarily on the simple additive measurement error model just described, although we point out some problems that may arise when the model is inadequate. The acceptability of the model for the epidemiologic application motivating the present paper is difficult to assess with the data available to us. As a referee noted, it fails to account for improvements and standardization in blood pressure measurement methods that have occurred since the start of the Framingham study. Thus a more realistic model might have heteroscedastic measurement errors with variances decreasing over time. We discuss this problem later in the paper (§5.2) in an example.

When the simple additive error model is known to be inadequate it may be necessary to allow for more complex dependencies between the proxy, W , and X and possibly the other covariates as well; see Fuller (1987) and Carroll & Stefanski (1990).

Now suppose that the models (1) and (2) are fit to the data with W substituted for X . The study-specific and combined-study estimators so obtained are denoted $\tilde{\beta}_k$, $k = 1, \dots, \mathcal{K}$ and $\tilde{\beta}$ respectively. In general neither $\tilde{\beta}_k$, $k = 1, \dots, \mathcal{K}$ nor $\tilde{\beta}$ are consistent for β ; see Stefanski (1985).

In the case that (1) and (2) define common homoscedastic linear models it is well known that $\tilde{\beta}_k$ consistently estimates $\lambda_k^{-1}\beta$ where

$$\lambda_k = \frac{\sigma_{W,k}^2}{\sigma_{W,k}^2 - \sigma_U^2}, \quad (3)$$

and $\sigma_{W,K}^2$ is the limiting value, assumed to exist, of $s_{W,k}^2 =$ the mean square error from the linear regression of W on Z_k in the k^{th} study data. Since $\sigma_{W,k}^2 = \sigma_{X,k}^2 + \sigma_U^2$ where $\sigma_{X,k}^2$ is the residual variation from the linear regression of X on Z_k , the attenuation factor for the k^{th} study is

$$\lambda_k^{-1} = \frac{\sigma_{X,k}^2}{\sigma_{X,k}^2 + \sigma_U^2}. \quad (4)$$

It is evident from (4) that attenuation generally varies across study groups, and that collinearity between X and Z_k accentuates attenuation due to measurement error. Note that $\sigma_{W,k}^2 = \text{Var}(W)$

and $\sigma_{X,k}^2 = \text{Var}(X)$ only in the absence of covariates or when X and Z_k are uncorrelated.

It follows that for linear models the combined-study estimator $\tilde{\beta}$ converges in probability to $\lambda^{-1}\beta$ where

$$\lambda^{-1} = \sum_{k=1}^{\mathcal{K}} w_k \lambda_k^{-1},$$

where w_k are the limiting values of weights \tilde{w}_k .

Assuming that data are available for consistent estimation of λ_k , by say $\tilde{\lambda}_k$, $k = 1, \dots, \mathcal{K}$, study-specific estimators of β corrected for attenuation are obtained as $\tilde{\beta}_{k,CA} = \tilde{\lambda}_k \tilde{\beta}_k$, $k = 1, \dots, \mathcal{K}$. A combined-study estimator can be obtained by either taking a weighted average of $\{\tilde{\beta}_{k,CA}\}$ or as $\tilde{\lambda} \tilde{\beta}$ where $\tilde{\lambda}$ is a consistent estimator of λ . The latter estimator is just a particular weighted average of $\{\tilde{\beta}_{k,CA}\}$.

The asymptotically most precise way to combine the study-specific estimators $\tilde{\lambda}_{k,MM}$ and $\tilde{\beta}_k$ to produce an efficient and consistent estimator of β will depend of the specific nature of the $\tilde{\lambda}_{k,MM}$'s, *i.e.*, exactly how these corrections are obtained. This is an important problem but one that we will not discuss in this paper.

Starting with (1) and (2) and the simple measurement error model $W = X + U$, the following approximations to $E(Y|W)$ and $\text{Var}(Y|W)$ can be derived:

$$E(Y|W, Z_k) \approx f\{\alpha_k + \beta E(X | W, Z_k) + \gamma_k^T Z_k\} \approx f(\alpha_k^* + \lambda_k^{-1} \beta W + \gamma_k^{*T} Z_k); \quad (5)$$

$$V(Y|W, Z_k) \approx \sigma_k^2 v\{\alpha_k + \beta E(X | W, Z_k) + \gamma_k^T Z_k, \tau_k\} \approx \sigma_k^2 v(\alpha_k^* + \lambda_k^{-1} \beta W + \gamma_k^{*T} Z_k, \tau_k). \quad (6)$$

The first approximation in (5) follows via a Taylor series expansion of (1) in X around $E(X | W, Z_k)$. The second approximation is obtained by replacing $E(X | W, Z_k)$ with the best linear approximation to this regression function. The approximations in (6) are similarly obtained. Estimation based on substituting $E(X | W, Z_k)$ for X is discussed by Carroll & Stefanski (1990), Gleser (1990), Fuller (1987), Pierce, et al. (1991), Prentice (1982), Rosner, et al. (1989, 1990) and Rudemo, et al. (1989), among others.

Equations (5) and (6) show that if the models (1) and (2) are fit to the data with W substituted for X , then the asymptotic bias in $\tilde{\beta}_k$ will be approximately the same as if linear models had been fit to the data. That is, $\tilde{\beta}_k$ converges in probability to some value, say β_k^\dagger , that is approximately equal to $\lambda_k^{-1}\beta$. It follows that whenever the approximations in (5) and (6) are justified, the k^{th} study estimator can be corrected for attenuation just as in the case of linear models, *viz.*, $\tilde{\beta}_{k,CA} = \tilde{\lambda}_k \tilde{\beta}_k$.

Similarly a combined-study estimator corrected for attenuation is obtained as a weighted average of $\tilde{\beta}_{k,CA}$, $k = 1, \dots, \mathcal{K}$.

When the variation in $\tilde{\lambda}_k$ is small relative to that in $\tilde{\beta}_k$, $k = 1, \dots, \mathcal{K}$, $\text{Var}(\tilde{\beta}) \approx \sum_{k=1}^{\mathcal{K}} \tilde{w}_k^2 \tilde{\lambda}_k^2 \tilde{s}_k^2$ where \tilde{s}_k is the usual standard error of $\tilde{\beta}_k$. In this case the best choice of weights has approximately $\tilde{w}_k \propto (\tilde{\lambda}_k \tilde{s}_k)^{-2}$ for which the standard error of $\tilde{\beta}$ is approximately $\{\sum_{k=1}^{\mathcal{K}} (\tilde{\lambda}_k \tilde{s}_k)^{-2}\}^{-1/2}$. If the variation in $\tilde{\lambda}_k$ is not negligible compared to that of $\tilde{\beta}_k$, $k = 1, \dots, \mathcal{K}$, then calculation of $\text{Var}(\tilde{\beta})$ is more difficult and will depend on the particular form of the estimators.

3 ESTIMATING CORRECTIONS FOR ATTENUATION

3.1 Introduction

The composition of the data, especially with regard to replicate measurements, validation data and the presence of instrumental variables, generally dictates the appropriate method of estimating λ_k , $k = 1, \dots, \mathcal{K}$. We will discuss only methods that are applicable to the epidemiologic application motivating the paper, (MacMahon *et al.*, 1990).

In that application all studies measured diastolic blood pressure (DBP) at baseline; this is W in the established notation. In addition, one study, Framingham, measured DBP at two-years and four-years pre and post baseline. So now in addition to having available (Y, W, Z_k) in all k studies, there is available in one study, taken as the first, another variate, call it T . In the application under consideration T is a second measurement of DBP; more generally we regard T as a *second measurement* of X .

We make a distinction between a *second measurement* and a *replicate measurement*. The former implies only that T and X are correlated. The latter embodies the usual statistical notion of replicates; W and T are replicate measurements of X when $W = X + U_1$, $T = X + U_2$ and U_1 and U_2 are independent and identically distributed. The distinction is useful for it dictates when T should be employed as an instrumental variable. See Fuller (1987, p. 52) for a completely general definition of an instrumental variable, and Buzas (1993) for an exposition on instrumental variable estimation in probit and logistic regression. We note here that the essential requirements are that: i) T is correlated with X ; ii) T is uncorrelated with $W - X$; and iii) T is conditionally uncorrelated with Y given X . The importance and use of instrumental variables will be evident in §3.3.

The data from the first study contain most of the information for estimating σ_U^2 . These data are used either to provide a direct estimate of σ_U^2 or an indirect estimate by first estimating λ_1

directly and then obtaining an estimate of σ_U^2 via (3), *viz.*, $\hat{\sigma}_U^2 = \{(\tilde{\lambda}_1 - 1)/\tilde{\lambda}_1\} s_{W,1}^2$. In either case λ_k , $k = 2, \dots, \mathcal{K}$ are estimated by $\tilde{\lambda}_k = s_{W,k}^2 / (s_{W,k}^2 - \hat{\sigma}_U^2)$.

3.2 When W and T are Replicates

For the model with $W = X + U_1$ and $T = X + U_2$ where U_1 and U_2 are independent, identically distributed and independent of Z_1 , the coefficient of W in the linear regression of T on (W, Z_1) , denoted $\beta_{T|W, Z_1}$, is equal to λ_1^{-1} . Thus an estimator of λ_1 is

$$\bar{\lambda}_{1, RM} = \frac{1}{\hat{\beta}_{T|W, Z_1}}, \quad (7)$$

where the designation ‘‘RM’’ refers to regression to the mean.

Although statistical justification for this estimator is not strong, it has much intuitive appeal. In particular, it makes clear the connection between attenuation due to measurement error and the more widely understood phenomenon of regression to the mean. Apart from differences due to grouping and the inclusion of covariates, $\bar{\lambda}_{1, RM}$ corresponds to the estimator employed by MacMahon, et al. (1990), see §3.5 for additional discussion.

Objections to this estimator arise because it is not symmetric in T and W , while the statistical model is. Under the replication model is it natural to estimate σ_U^2 by

$$\hat{\sigma}_U^2 = (1/2) \text{ sample variance of the } (W_i - T_i), \quad (8)$$

$\sigma_{W,k}^2$ by $s_{W,k}^2 =$ the mean square error from the linear regression of W_k on Z_k , and then λ_k by

$$\tilde{\lambda}_{k, MM} = \frac{s_{W,k}^2}{s_{W,k}^2 - \hat{\sigma}_U^2}, \quad k = 1, \dots, \mathcal{K}, \quad (9)$$

where the designation ‘‘MM’’ refers to method of moments. The variance component estimate in (8) differs from the usual ANOVA within-subjects variance component estimate, $(2n)^{-1} \sum_{i=1}^n (W_i - T_i)^2$. Both are unbiased and they are asymptotically equivalent, and thus equally efficient in large samples. Our preference for (8) over the usual ANOVA variance components estimate is based on model robustness considerations. Departures from the replicate-measurements model in the direction of the instrumental variable model (§3.3) have a greater effect on the ANOVA variance component estimate than they do on (8).

Even the latter procedure is not completely satisfying, for in the replication model the best measurement of X in the first study is $W^* = (T + W)/2$ and logic dictates first regressing Y_1 on

W^* and Z_1 obtaining $\widehat{\beta}_1^*$ with corresponding attenuation factor

$$\lambda_1^{*-1} = \frac{\sigma_{X,1}^2}{\sigma_{X,1}^2 + \sigma_U^2/2}.$$

The measurement error variance, σ_U^2 , again is estimated as in (8), and the mean square error from the regression of W^* on Z_1 , denote it $s_{W,1}^{*2}$, consistently estimates $\sigma_{X,1}^2 + \sigma_U^2/2$. Thus

$$\tilde{\lambda}_{1,MM}^* = \frac{s_{W,1}^{*2}}{s_{W,1}^{*2} - \widehat{\sigma}_U^2/2} \quad (10)$$

is a consistent estimator of λ_1^* .

The latter procedure makes more efficient use of the data but may be objected to on the grounds that it treats the first study differently from the rest. Greater similarity among studies, in this case having the study-specific analyses depend on baseline data only, makes it easier to present and defend the meta-analysis via nontechnical arguments.

Treating baseline and post-baseline measurements equally may be objectionable on statistical grounds as well. For example, one might find differences in cohort distributions of DBP measurements taken four years apart, especially among study participants. In general, when the assumption that W and T are replicates cannot be verified empirically, one may wish to investigate the applicability of using T as an instrumental variable.

3.3 T as an Instrumental Variable

The following is a brief discussion of the theory of approximate instrumental variable estimation in generalized quasilielihood/variance-function models and a discussion of its application in meta-analysis of measurement error models; see Stefanski and Buzas (1992) for a detailed discussion of approximate instrumental variable estimation in binary regression models.

If (1) and (2) are expanded around $E(X | T, Z_k)$ instead of $E(X | W, Z_k)$, then analogous to (5) and (6) we obtain, after replacing $E(X | T, Z_k)$ with its best linear approximant, the approximations

$$\begin{aligned} E(Y|T, Z_k) &\approx f\{\alpha_k + \beta E(X | T, Z_k) + \gamma_k^T Z_k\} \approx f(\alpha_k^* + \delta_1 \beta T + \gamma_k^{*T} Z_k); \\ V(Y|T, Z_k) &\approx \sigma_k^2 v\{\alpha_k + \beta E(X | T, Z_k) + \gamma_k^T Z_k, \tau_k\} \approx \sigma_k^2 v(\alpha_k^* + \delta_1 \beta T + \gamma_k^{*T} Z_k, \tau_k), \end{aligned}$$

where δ_1 is the coefficient of T in the best linear approximation to the regression of X on T and Z_1 .

Thus if the model (1) and (2) is fit to the data with T replacing X , the estimated coefficient of T , denoted $\widehat{\beta}_{Y|\underline{T},Z_1}$, is approximately consistent for $\delta_1\beta$. In other words, $\widehat{\beta}_{Y|\underline{T},Z_1}$ converges in probability to some constant that is approximately equal to $\delta_1\beta$.

Now for the additive model $W = X + U_1$, it is easy to establish that δ_1 is also the coefficient of T in the best linear approximation to the regression of W on T and Z_1 , and thus can be consistently estimated by $\widehat{\beta}_{W|\underline{T},Z_1}$ = the estimated coefficient of T in the least squares regression of W on T and Z_1 .

This leads to the approximate instrumental variable estimator

$$\tilde{\beta}_{1,IV} = \frac{\widehat{\beta}_{Y|\underline{T},Z_1}}{\widehat{\beta}_{W|\underline{T},Z_1}},$$

from which is derived the estimator of λ_1

$$\tilde{\lambda}_{1,IV} = \frac{\tilde{\beta}_{1,IV}}{\widehat{\beta}_{Y|\underline{W},Z}}. \quad (11)$$

3.4 Comparing the Estimators of Attenuation

The four estimators $\bar{\lambda}_{1,RM}$, $\tilde{\lambda}_{1,MM}$, $\tilde{\lambda}_{1,MM}^*$ and $\tilde{\lambda}_{1,IV}$, are all consistent for λ_1 when W and T are replicate measurements of X . We now examine the effect of departures from the replicate measurement error model on the four estimators.

We assume that $W = X + U_1$ as before, but that

$$T = \xi + \eta X + U_2^* \quad (12)$$

where U_2^* is a random error independent of U_1 and Z_1 , but not necessarily having the same distribution as U_1 . The model for T can be motivated as follows.

Let X and X_* denote the ‘true’ DBP at baseline and four years earlier or later respectively, of a randomly selected patient. If there is no change in true DBPs over the study period then $X = X_*$. If there is change, then it is reasonable to assume that X and X_* are jointly normal, in which case the regression of X_* on X is linear. Provided T is an unbiased measurement of the true DBP at follow-up, then $T = E(X_* | X) + U_2^*$ where $E(X_* | X) = \xi + \eta X$ and U_2^* is the sum of the measurement error and the residual error $X_* - E(X_* | X)$.

For this model $\eta = \rho\sigma_{X_*}\sigma_X^{-1}$, where $\rho = \text{corr}(X, X_*)$. Note that $\eta < 1$ unless $\text{Var}(X_*) \geq \rho^{-2}\text{Var}(X)$. So unless the variation in true DBPs increases over time, we expect $\eta < 1$.

Now consider $\bar{\lambda}_{1,RM}$ defined in (7). For the model described above, $\beta_{T|W,Z_1}$ = the coefficient of W in the linear regression of T on (W, Z_1) , is $\eta\lambda_1^{-1}$, and thus $\bar{\lambda}_{1,RM}$ is a consistent estimator of λ_1/η . The correction for attenuation is overestimated in the common situation that $\eta < 1$ and underestimated when $\eta > 1$.

The second correction for attenuation, $\tilde{\lambda}_{1,MM}$ given in (9) depends on the post-baseline measurements only via (8). If the T_i in (8) follow the model in (12) then $\hat{\sigma}_U^2$ is a consistent estimator of

$$\frac{1}{2} \left\{ \sigma_{U_1}^2 + \sigma_{U_2^*}^2 + (\eta - 1)^2 \sigma_X^2 \right\}.$$

This is greater than $\sigma_{U_1}^2$, and thus results in over correction for attenuation, when

$$\sigma_{U_2^*}^2 + (\eta - 1)^2 \sigma_X^2 > \sigma_{U_1}^2. \quad (13)$$

For the model described above, U_1 is the measurement error at baseline and U_2^* is the sum of the measurement error at post-baseline and the residual error $X_* - E(X_* | X)$. Thus under constant measurement error variance, $\sigma_{U_2^*}^2 > \sigma_{U_1}^2$ and the inequality in (13) holds.

The third correction for attenuation, $\tilde{\lambda}_{1,MM}^*$ in (10), depends on the post-baseline measurements via $\hat{\sigma}_U^2$ as well as through $s_{W,1}^{*2}$. This makes it difficult to assess the effect of departures from the replicate measurements model. However, the calculations are manageable in the absence of covariates. In this case $\tilde{\lambda}_{1,MM}^*$ approaches asymptotically

$$g(\eta) = \frac{(\eta + 1)^2 \sigma_X^2 / 4 + (\sigma_{U_1}^2 + \sigma_{U_2^*}^2) / 4}{\eta \sigma_X^2}.$$

Since $g(1) > \lambda_1^*$ when $\sigma_{U_2^*}^2 > \sigma_{U_1}^2$, and $\partial g(\eta) / \partial \eta < 0$ whenever $\eta^2 \leq 1$, the net effect of departures from the replicate measurements model in the direction of (12) in the likely situation that η is less than 1 but positive, is to inflate the correction for attenuation, λ_1^* . Regardless of the presence or absence of covariates, the bias in $\tilde{\lambda}_{1,MM}^*$ affects the corrections for attenuation in the other studies only through $\hat{\sigma}_U^2$, which is generally overestimated under (12). Thus the corrections for attenuation in studies $k = 2, \dots, \mathcal{K}$, are positively biased as well.

The instrumental variable estimator, $\tilde{\lambda}_{1,IV}$, depends only on a nonzero correlation between T and X and linearity in the regressions of W and X on (T, Z_k) , $k = 1, \dots, \mathcal{K}$, and is therefore robust to departures from the replicate-measurements model in the direction of (12).

Summarizing these results we have: (i) all of the corrections for attenuation are consistent when the replicate-measurements model holds; (ii) only the instrumental-variable correction for

attenuation is consistent under the more general second-measurement error model (12); and (iii) excluding the instrumental variable correction, the general effect of departures from the replicate-measurements model is to inflate the corrections for attenuation.

3.5 The Method of MacMahon, et al. (1990)

The method of MacMahon, et al. (1990) is closely related to the regression method (7) and is described as follows. Let \mathcal{C}_1 and \mathcal{C}_2 be extreme intervals, i.e., $\mathcal{C}_1 = \{W \leq \text{lower bound}\}$ and $\mathcal{C}_2 = \{W \geq \text{upper bound}\}$, and for $p = 1, 2$, define

$$\begin{aligned}\hat{C}_{p1} &= \frac{n_1^{-1} \sum_{i=1}^{n_1} W_i I(W_i \in \mathcal{C}_p)}{n_1^{-1} \sum_{i=1}^{n_1} I(W_i \in \mathcal{C}_p)}; \\ \hat{C}_{p2} &= \frac{n_1^{-1} \sum_{i=1}^{n_1} T_i I(W_i \in \mathcal{C}_p)}{n_1^{-1} \sum_{i=1}^{n_1} I(W_i \in \mathcal{C}_p)}\end{aligned}$$

Then their correction for attenuation estimate is

$$\hat{\lambda}_{1,GR} = \frac{\hat{C}_{21} - \hat{C}_{11}}{\hat{C}_{22} - \hat{C}_{12}}, \quad (14)$$

the designation ‘‘GR’’ referring to the grouping inherent in the method.

Upon replacing the numerators and denominators in \hat{C}_{p1} and \hat{C}_{p2} ($p = 1, 2$), by their expectations, it is easily shown that that when T and W are replicates as defined in §3.2, and X is independent of Z , then $\hat{\lambda}_{1,GR}$ consistently estimates λ_1 . However, violation of these assumptions can result in inconsistent estimators.

For example, suppose that we continue to assume normality and continue to assume that T is a replicate, but now allow X and Z to be correlated. Then (14) estimates not λ_1 but instead estimates $\text{Var}(W) / \{\text{Var}(W) - \sigma_U^2\}$, leading to a correction which is generally too *small* since $\text{Var}(W) > \sigma_U^2$.

On the other hand, according to our analysis, the effect of T not being a replicate is that the correction (14) is generally too *large*, see §3.4.

In summary, the appropriateness of the correction (14) proposed by MacMahon, et al. rests fundamentally on the two assumptions that T is a replicate and that X is unrelated to all the other covariates, assumptions which appear to be reasonable in the Framingham data (§5). Significant violation of these assumptions means that this correction should not be used.

4 SIMULATIONS AND FURTHER DISCUSSION

In this section, we report some small linear and logistic regression simulations.

4.1 Linear Regression

The consistency robustness of the instrumental-variable method to departures from the replicate-measurements model is obtained at the expense of greater finite-sample variability in the estimated corrections for attenuation. Table 1 displays the results of a simulation study designed to compare the four estimators $\bar{\lambda}_{1,RM}$, $\tilde{\lambda}_{1,MM}$, $\hat{\lambda}_{1,GR}$ and $\tilde{\lambda}_{1,IV}$ and the corresponding estimators of β . The four methods are designated RM (regression to the mean), MM (method of moments), GR (the grouping method in §3.5) and IV (instrumental variable) respectively.

The model for the simulation study was:

$$Y | X, Z \sim N(\alpha + \beta X + \gamma^T Z, 1), \quad \alpha = 0, \beta = 1, \gamma = (0, 0)^T,$$

$$(X, Z)^T \sim N(0_{3 \times 1}, I_3), \quad W | X \sim N(X, \sigma_U^2),$$

$$T | X \sim N(\xi + \eta X, 1 - \rho^2 + \sigma_U^2), \quad \xi = 0, \eta = \rho.$$

The measurement error variance and ρ were investigated at two levels $\sigma_U^2 = 0.25, 1.00$ and $\rho^2 = 1.00, 0.90$. Sample size was set at $n = 100$, and 1000 independent data sets were generated at each factor level combination. Note that for methods RM, MM and IV, $\lambda = 1.25, 2.00$ when $\sigma_U^2 = 0.25, 1.00$ respectively, while for method MM*, $\lambda = 1.125, 1.50$ when $\sigma_U^2 = 0.25, 1.00$.

Monte Carlo means and mean squared errors are reported for the estimates of β and λ . The instrumental variable estimators of λ and β have generally slightly smaller biases than the other estimators in the study. Furthermore the biases for the cases of $\rho^2 = 1.00$ and 0.90 are comparable, confirming the consistency robustness noted above. In terms of mean squared error $\tilde{\beta}_{1,IV}$ performs well also. However, the mean squared error of $\tilde{\lambda}_{1,IV}$ is consistently larger than the mean squared errors of the other three estimators of λ_1 indicating greater sampling variability in this estimator.

4.2 Logistic Regression

Because the Framingham data can be analyzed by a logistic regression, we performed a small logistic regression simulation. We assumed that there were no additional variables Z , and we observe the response Y , the surrogate W and the second measurement T . The parameters in the simulation were chosen to correspond roughly to those reported in the Framingham data. The sample size was $n = 1600$. We standardized so that X was normally distributed with mean 0.0 and variance 1.0.

With this normalization, our simulations were constructed under the distributional assumptions that $W|X \sim N(X, \sigma_U^2)$ and $T|X \sim N(\xi + \eta X, 1 - \rho^2 + \sigma_U^2)$, with $\xi = 0$, $\eta = \rho$, $\sigma_U^2 = .60$, $\rho^2 = .9, 1.0$. The binary responses followed a logistic linear model with intercept -2.25 and slope 0.35. We also performed, but do not report on here, simulations with for slope parameters 0.17 and 0.70. The results of the simulation are given in Table 2, which is based on 1000 repetitions of the experiment.

In reading Table 2, one should note that there is no “correct” value of λ , because in logistic regression the corrections are only approximate. However, some conclusions are possible for the set of circumstances defined by the simulation. With regard to estimation of λ , Table 2 is consistent with the theoretical results that, in terms of the medians, all methods are approximately unbiased in the replicate measurements model, ($\rho^2 = 1$), but that the method of moments and the regression to the mean methods over estimate λ relative to the instrumental variable method when $\rho^2 < 1$. The means differ from and are larger than the medians because of the finite-sample skewness of the distributions of the estimates of the corrections. The same conclusions apply to estimation of β . The medians of the instrumental variable estimator are similar at $\rho^2 = 1.00$ and 0.90, whereas the other procedures exhibit a positive median bias at $\rho^2 = 0.90$.

There is a large difference in the variability of the estimates of λ and β . The instrumental variable estimate of λ is many times more variable than the other two estimators, whereas for estimation of β the instrumental variable estimator has comparable variability. This may perhaps be due to the negative correlation we observed in our simulations between $\tilde{\lambda}_{1,IV}$ and $\tilde{\beta}_1 = \hat{\beta}_{Y|\underline{W},Z}$. When the latter is small in absolute value, the former is necessarily larger, but the instrumental variable estimator of β , being the product of the two, achieves a rough stability.

5 DISCUSSION OF THE META-ANALYSIS OF CHD AND DBP

5.1 The Corrections in the Framingham Data

MacMahon, et al. (1990) describe analysis of the Framingham study. We give here analyses which are meant to illustrate the issues discussed in the previous sections. The Framingham data consist of measurements at different examinations spaced two years apart, so that, for example, Exam 5 takes place 4 years after Exam 3. In what follows, we define X to be the true diastolic blood pressure (DBP), W to be diastolic blood pressure as measured at Exam 5 and T to be diastolic

blood pressure measured four years earlier, at Exam 3. The other predictors Z used here are age (at Exam 3), serum cholesterol (at Exam 3) and cigarettes/day (at Exam 1). Only those healthy and alive at Exam 5 were considered in the analysis. When we eliminated observations with incomplete data, we were left with a sample size of $n = 1369$, of whom 183 were found to have developed coronary heart disease (CHD) within 10 years of Exam 5.

In these data, W had a sample variance of 126.2, while the mean squared error from regressing W on Z was 126.1, indicating the near independence of these predictors. The resulting method of moments correction is $\tilde{\lambda}_{1,MM} = 1.53$, since the estimate of σ_U^2 equals 43.4.

The coefficient for W in regressing T on (Z, W) is .6310, leading to a regression correction of $\bar{\lambda}_{1,RM} = 1.58$, essentially the same as the moments correction. See the bottom right part of Figure 1 for a plot of this regression.

The sample means and variances of W and T are (84.2, 126.2) and (82.7, 121.7), respectively, indicating that treating T as a replicate is not entirely unreasonable. In bottom left part of Figure 1 we plot a kernel density estimate of $W - T$, noting that it is centered approximately at zero.

For the instrumental variable method, we find that $\hat{\beta}_{W|Z} = .6654$, while $\hat{\beta}_{Y|W,Z} = .01569$ and $\hat{\beta}_{Y|Z} = .01878$. This yields a correction of $\tilde{\lambda}_{1,IV} = 1.80$. The grouping method described in §3.5 yielded $\tilde{\lambda}_{1,M} = 1.62$.

As noticed in the simulations, the instrumental variable method's correction estimate is much more variable than the others. To check this, we used a bootstrap simulation and computed 400 bootstrap samples and the resulting parameter estimates. In top left part of Figure 1, we plot bootstrap kernel density estimates of $\tilde{\lambda}_{1,IV}$ and $\bar{\lambda}_{1,RM}$, noting that the former is much more variable; numerical values are given in Table 3.

While the instrumental variable correction is more variable, the actual estimate of the corrected logistic slope is not. The parameter estimates themselves are quite similar: .0240, .0243, .0254 and .0282 for the moments, regression to the mean, grouping and instrumental variable estimates, respectively. A bootstrap simulation (Table 3) found that the instrumental variable estimator of the logistic slope was in fact no more variable than any of the others, nor was the bootstrap bias much larger, see the top right part of Figure 1.

The bootstrap here is extremely easy to implement (programming time) although somewhat slow to compute (computer time). It is also possible to construct asymptotic standard errors using estimating equations and the delta-method. These results, which appear to be new, are described

in the appendix (§7).

5.2 Implications for Meta-Analyses

We highlight the issues that arise in meta-analyses, using as a second study the MRFIT data, see Kannel, et al. (1986). MacMahon, et al. (1990) compute their correction (14) in the Framingham data, and then apply it to all the other data sets in their meta-analysis, including the MRFIT data. As illustrated by (3), this is not always appropriate since the correction for attenuation need not be constant across studies even when the measurement error variance is.

The following numbers are purely illustrative. We will ignore the covariates Z as the evidence suggests that they are at best weakly predictive of W , i.e., we will assume that X is independent of Z and that T is a replicate. Then, for Framingham men, the sample variance of W is 126.2, $\hat{\sigma}_U^2 = 43.4$ from (8) and hence $\tilde{\lambda}_{1,MM} = 1.53$. For the MRFIT data, Kannel, et al. state that the sample variance of W is 110.2, so that $\tilde{\lambda}_2 = 1.65$. In other words, the fact that the predictor W is less variable in the MRFIT study means that its regression coefficient should have been corrected by the factor 1.65, not 1.53 as suggested by the method of moments estimator, although this is a minor difference in practice.

Of course these conclusions are highly dependent on the assumption of constant measurement error variance across studies. We note that the MRFIT measurements were taken in 1973–75, whereas the Framingham measurements date to 1955. Thus one might expect greater reliability in the MRFIT measurements. If instead we assume that the variances of X in the Framingham and MRFIT study populations are equal, then the difference between the respective variances of W (126.2 - 110.3), is an estimate of the difference in the measurement error variances. That is, with $\hat{\sigma}_U^2 = 43.4$ for the Framingham study, the estimate of the measurement error variance for MRFIT is $\hat{\sigma}_U^2 = 43.4 - (126.2 - 110.3) = 27.5$. This results in an estimated correction for attenuation of $\tilde{\lambda}_{2,MM} = 110.3/83.0 = 1.33$, a 17% decrease relative to the correction (1.60) reported by MacMahon, et al. (1990) and a 13% decrease relative to the moments correction (1.53) reported here.

6 CONCLUSIONS

We have considered corrections for attenuation in semilinear regression models. There is a tendency for users of measurement error methods to base corrections for attenuation on the variance of the fallible covariate W . We have noted that the correction depends on the size of the measurement

error σ_U^2 and on the size of the regression MSE, σ_W^2 , from regressing the surrogate W on all the other predictors Z , see (3). Failing to take into account the presence of other covariates can lead to an undercorrection of the regression coefficients. These comments are relevant to single-study measurement error analyses as well as to meta-analyses.

In correcting the results of a single study, we have distinguished between *replicate measurements* and *second measurements* of a fallible covariate. For replicates, the regression to the mean (RM) method (7), the method of moments (MM) methods (9)–(10), the grouping method (14) and the instrumental variable (IV) method (11) all yield consistent estimates of the attenuation.

For those cases that the second measurement is biased for the fallible covariate, only the IV method consistently estimates the attenuation. We have shown that in this case, the usual effect of using the others is to *overestimate* the correction for attenuation.

We have also noted that the correction for attenuation proposed by MacMahon, et al. (1990) yields a consistent estimate only if the second measurement is a replicate *and* the true and surrogate predictors X and W are unrelated to all the other covariates Z . Failure of these assumptions generally causes under- and over-corrections, respectively.

We have also discussed the use of corrections for attenuation in meta-analysis. We have stressed in (3)–(4) that even when the measurement error variance is constant across studies, *the proper correction for attenuation may vary from study to study*, depending on the marginal distribution of the predictors through the mean squared error from the linear regression of W on Z . Also, as the example in §5.2 demonstrates, a single correction for attenuation is not possible when the measurement error variances differ across studies. Thus, in general, study-specific corrections are necessary, and using the same correction for attenuation across studies generally leads to biased estimates. Furthermore, neither the direction nor the magnitude of the bias is predictable.

ACKNOWLEDGEMENT

Carroll's research was supported by a grant from the National Cancer Institute, while that of Stefanski was supported by a grant from the National Science Foundation. We are indebted to Paul Sorlie for help on an earlier version of this paper.

REFERENCES

- Carroll, R. J. & Ruppert, D. (1988). *Transformation and Weighting in Regression*. Chapman & Hall, London.
- Carroll, R. J. & Stefanski, L. A. (1990). Approximate quasilikelihood estimation in models with

- surrogate predictors. *Journal of the American Statistical Association*, 85, 652–663.
- Buzas, J. S. (1993). Instrumental variable estimation in generalized linear measurement error models. Ph.D. Thesis, Department of Statistics, North Carolina State University.
- Cornfield, J. (1962). Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: A discriminant function analysis. *Federal Proceedings*, 21, 58–61.
- Ederer, F. (1972). Serum cholesterol changes: effects of diet and regression toward the mean. *Journal of Chronic Diseases*, 25, 277–289.
- Fuller, W. A. (1987). *Measurement Error Models*. Wiley, New York.
- Gleser, L. J. (1990). Improvements of the naive approach to estimation in nonlinear errors-in-variables regression models. In *Statistical Analysis of Measurement Error Models and Application*, P. J. Brown and W. A. Fuller, editors. American Mathematics Society, Providence.
- Kannel, W. B., Neaton, J. D., Wentworth, D., Thomas, H. E., Stamler, J., Hulley, S. B. & Kjelsberg, M. O. (1986). Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for MRFIT. *American Heart Journal*, 112, 825–836.
- MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A., & Stamler, J. (1990). Blood pressure, stroke and coronary heart disease: Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*, 335, 765–774.
- Palca, J. (1990a). Getting to the heart of the cholesterol debate. *Science*, 24, 1170–71.
- Palca, J. (1990b). Why statistics may understate the risk of heart disease. *Science*, 24, 1171.
- Pierce, D. A., Stram, D. O., Vaeth, M., Schafer, D. (1990). Some insights into the errors in variables problem provided by consideration of radiation dose–response analyses for the A–bomb survivors. *Journal of the American Statistical Association*, 87, 351–359.
- Prentice, R. L. (1982). Covariate measurement errors and parameter estimation in a failure time regression model. *Biometrika*, 69, 331–342.
- Rosner, B., Willett, W. C. & Spiegelman, D. (1989). Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Statistics in Medicine*, 8, 1051–1070.
- Rosner, B., Spiegelman, D. & Willett, W. C. (1990). Correction of logistic regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error. *American Journal of Epidemiology*, 132, 734–745.
- Rudemo, M., Ruppert, D. & Streibig, J. C. (1989). Random effect models in nonlinear regression with applications to bioassay. *Biometrics*, 45, 349–362.
- Stefanski, L. A. (1985). The effect of measurement error on parameter estimation. *Biometrika*, 72, 583–592.
- Stefanski, L. A. & Buzas, J. S. (1992). Instrumental variable estimation in binary regression measurement error models. Institute of Statistics Mimeo Series, No. 2239, North Carolina

7 APPENDIX

In this appendix, we provide directions for constructing asymptotic covariance formulae for the methods described in the main text. In practice, we find it convenient to use the bootstrap to construct standard errors and confidence intervals, see §4.2 for an example.

We first review some basic facts about M-estimators (unbiased estimating equations), see Carroll & Ruppert (1988, Chapter 7 and references within). If we have $k = 1, \dots, \mathcal{K}$ populations, the ensemble of parameters is denoted by Θ , and there are $i = 1, \dots, n_k$ observations in the k^{th} population, M-estimators solve estimating equations of the form

$$0 = \sum_{k=1}^{\mathcal{K}} \sum_{i=1}^{n_k} \Psi_{ik}(\hat{\Theta}). \quad (15)$$

for some function Ψ which depends on the data for the i^{th} person in the k^{th} population. The dimension of Ψ_{ik} is the same as that of Θ .

Set $n = \sum_k n_k$. If the estimating equation (15) is unbiased, i.e., the terms each have mean zero when evaluated at the true parameter, then in general $\hat{\Theta}$ is asymptotically normally distributed with mean Θ and covariance matrix $n^{-1}A^{-1}BA^{-t}$, where

$$\begin{aligned} A &= n^{-1} \sum_{k=1}^{\mathcal{K}} \sum_{i=1}^{n_k} E \left\{ \left(\partial / \partial \Theta^t \right) \Psi_{ik}(\Theta) \right\}; \\ B &= n^{-1} \sum_{k=1}^{\mathcal{K}} \sum_{i=1}^{n_k} E \left\{ \Psi_{ik}(\Theta) \Psi_{ik}^t(\Theta) \right\}. \end{aligned}$$

Usually, one will want to estimate a function $g(\Theta)$. Let $g_{\Theta}(\Theta)$ be the vector of partial derivatives of $g(\Theta)$ with respect to Θ . By the delta-method, $g(\hat{\Theta})$ is asymptotically normally distributed with mean $g(\Theta)$ and variance $n^{-1}g_{\Theta}^t(\Theta)A^{-1}BA^{-t}g_{\Theta}(\Theta)$.

It remains to estimate the matrices A and B . There are at least two standard devices for doing so. The most general is the co-called sandwich method, which simply eliminates the expectation signs:

$$\begin{aligned} \hat{A}_s &= n^{-1} \sum_{k=1}^{\mathcal{K}} \sum_{i=1}^{n_k} \left(\partial / \partial \Theta^t \right) \Psi_{ik}(\hat{\Theta}); \\ \hat{B}_s &= n^{-1} \sum_{k=1}^{\mathcal{K}} \sum_{i=1}^{n_k} \Psi_{ik}(\hat{\Theta}) \Psi_{ik}^t(\hat{\Theta}). \end{aligned}$$

Under very broad conditions, the sandwich method yields consistent estimates, but they can be inefficient.

A second method is to try to compute the elements of A and B explicitly and then make obvious substitutions. Write $\hat{C}_{pj} = \hat{C}_{pju} / \hat{C}_{pd}$. The unknown parameters in the \mathcal{K} studies are $\Theta = (\Theta_1, \dots, \Theta_{\mathcal{K}})$, where $\Theta_1 = (\Theta_{11}, \Theta_{12})$,

$$\Theta_{11} = (\mu_U, \sigma_U^2, C_{11u}, C_{12u}, C_{1d}, C_{21u}, C_{22u}, C_{2d}, \mathcal{B}_{W|T,Z,1}, \mathcal{B}_{T|W,Z,1}, \mathcal{B}_{Y|T,Z,1}),$$

$\Theta_{12} = (\mathcal{B}_{Y|W,Z,1}, \mathcal{B}_{W|Z,1}, \sigma_{w,1}^2)$ and for $k \geq 2$, $\Theta_k = (\mathcal{B}_{Y|T,Z,k}, \mathcal{B}_{Y|W,Z,k}, \mathcal{B}_{W|Z,k}, \sigma_{w,k}^2)$. In this framework, μ_U is the mean of $(W - T)/2^{1/2}$, which equals zero in the replication model. Also, $\mathcal{B}_{Y|W,Z,k}$ are the intercept, the slope for W and the slope for Z in the regression of Y on (Z, W) , and similarly for the other regression parameters. The predicted value from the regression of Y on (W, Z) is denoted by $\mu_{Y|W,Z,i,k}$.

Make the following definitions:

$$\psi_{i1}(\Theta) = \begin{bmatrix} (W_{i1} - T_{i1})/2^{1/2} - \mu_U \\ \left\{ (W_{i1} - T_{i1})/2^{1/2} - \mu_U \right\}^2 - \sigma_U^2 \\ W_{i1}I(W_{i1} \in C_1) - C_{11u} \\ T_{i1}I(W_{i1} \in C_1) - C_{21u} \\ I(W \in C_1) - C_{1d} \\ W_{i1}I(W_{i1} \in C_2) - C_{12u} \\ T_{i1}I(W_{i1} \in C_2) - C_{22u} \\ I(W_{i1} \in C_2) - C_{2d} \\ (1, T_{i1}, Z_{i1}^t)^t (W_{i1} - \mu_{W|T,Z,i,1}) \\ (1, W_{i1}, Z_{i1}^t)^t (T_{i1} - \mu_{T|W,Z,i,1}) \\ (1, T_{i1}, Z_{i1}^t)^t (Y_{i1} - \mu_{Y|T,Z,i,1}) \\ (1, W_{i1}, Z_{i1}^t)^t (Y_{i1} - \mu_{Y|W,Z,i,1}) \\ (1, Z_{i1}^t)^t (W_{i1} - \mu_{W|Z,i,1}) \\ [n_1 / (\{n_1 - 1 - \dim(Z)\})] (W_{i1} - \mu_{W|Z,i,1})^2 - \sigma_{w,1}^2 \end{bmatrix},$$

while for $k \geq 2$,

$$\psi_{ik}(\Theta) = \begin{bmatrix} (1, W_{ik}, Z_{ik}^t)^t (Y_{ik} - \mu_{Y|W,Z,i,k}) \\ (1, Z_{ik}^t)^t (W_{ik} - \mu_{W|Z,i,k}) \\ [n_k / (\{n_k - 1 - \dim(Z)\})] (W_{ik} - \mu_{W|Z,i,k})^2 - \sigma_{w,k}^2 \end{bmatrix},$$

The Ψ_{ik} is a vector all of whose elements are zero except for a block of terms corresponding to ψ_{ik} , namely

$$\Psi_{i1} = \begin{bmatrix} \psi_{i1} \\ 0 \\ \cdot \\ \cdot \\ 0 \end{bmatrix}; \quad \Psi_{i2} = \begin{bmatrix} 0 \\ \psi_{i2} \\ \cdot \\ \cdot \\ 0 \end{bmatrix}; \dots \quad (16)$$

Because of its special form, we do not need to use the sandwich formula to estimate A . We will concentrate on linear and logistic regression. By (16), A is a block diagonal matrix consisting of \mathcal{K} blocks, those being the appropriate sums of expectations of the ψ_{ik} with respect to Θ_k . We will evaluate each of these blocks.

Define $\xi_{T,Z,i,k} = (1, T_{ik}, Z_{ik}^t)^t$. In linear regression for Y , let $\mu^{(1)} = 1$, while in logistic regression for a binary Y , let $\mu^{(1)} = \mu(1 - \mu)$. Let I_8 be the eight by eight identity matrix. Then the expectation

of the matrix of derivatives of ψ_{i1} with respect to Θ_1 is

$$- \begin{bmatrix} I_8 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & R_{i,1,1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & R_{i,1,2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & R_{i,1,3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & R_{i,1,4} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & R_{i,1,5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix},$$

where

$$\begin{aligned} R_{i,1,1} &= \xi_{T,Z,i,1} \xi_{T,Z,i,1}^t; & R_{i,1,2} &= \xi_{W,Z,i,1} \xi_{W,Z,i,1}^t; & R_{i,1,3} &= \xi_{T,Z,i,1} \xi_{T,Z,i,1}^t \mu_{Y|T,Z,i,1}^{(1)}; \\ R_{i,1,4} &= \xi_{W,Z,i,1} \xi_{W,Z,i,1}^t \mu_{Y|W,Z,i,1}^{(1)}; & R_{i,1,5} &= \xi_{Z,i,1} \xi_{Z,i,1}^t. \end{aligned}$$

The expectation of the matrix of derivatives of ψ_{ik} with respect to Θ_k is

$$- \begin{bmatrix} \xi_{W,Z,i,k} \xi_{W,Z,i,k}^t \mu_{Y|W,Z,i,k}^{(1)} & 0 & 0 \\ 0 & \xi_{Z,i,k} \xi_{Z,i,k}^t & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

One estimates these terms by replacing terms such as $\mu_{Y|T,Z,k}$ by its estimate, thus yielding a consistent version of \hat{A} . We recommend using this over the sandwich estimate.

We next turn to estimating B . By (16) this is block diagonal, and we can use the sandwich formula to evaluate the blocks. The sandwich formula has the feature that it is consistent even when the various linear regressions are heteroscedastic.

Application of the formulae discussed above requires access to the data for all the studies under question, which may sometimes prove impossible to gain in practice. In some cases, however, reasonable standard errors can still be constructed.

For example, consider the case that the response is binary, and one has data for the first population, while the other populations ($k \geq 2$) contain only the naive logistic regression parameter estimate $\tilde{\beta}_k$, an estimate of its standard error $\hat{s}_{\beta,k}$ and an estimate $s_{W,k}^2$. From the first study, we obtain this information plus an estimate $\hat{\sigma}_U^2$, its estimated standard error \hat{s}_u and an estimate of the covariance between the naive logistic regression estimate and $\hat{\sigma}_U^2$, say $\hat{s}_{\beta,u}$. In most instances, the variation of $s_{W,k}^2$ will be much smaller than that of the other estimates, especially the logistic regression parameter estimates, and may be ignored. For a fixed set of weights (w_1, \dots, w_K) , the pooled coefficient estimate is

$$\tilde{\beta} = \sum_{k=1}^K w_k \tilde{\beta}_k s_{W,k}^2 / (s_{W,k}^2 - \hat{\sigma}_U^2).$$

Ignoring the variation in $s_{W,k}^2$, an estimate of the asymptotic variance of $\tilde{\beta}$ is

$$\begin{aligned} & \sum_{k=1}^K w_k^2 \left(\frac{s_{W,k}^2}{s_{W,k}^2 - \hat{\sigma}_U^2} \right)^2 \hat{s}_{\beta,k}^2 + \left[\sum_{k=1}^K w_k \tilde{\beta}_k \left\{ \frac{s_{W,k}^2}{(s_{W,k}^2 - \hat{\sigma}_U^2)^2} \right\} \right]^2 \hat{s}_u^2 \\ & + 2w_1 \frac{s_{W,1}^2}{s_{W,1}^2 - \hat{\sigma}_U^2} \left[\sum_{k=1}^K w_k \tilde{\beta}_k \left\{ \frac{s_{W,k}^2}{(s_{W,k}^2 - \hat{\sigma}_U^2)^2} \right\} \right] \hat{s}_{\beta,u}. \end{aligned}$$

$\rho^2 = 1.00$	$\beta[214z]$	$\sigma_U^2 = 0.25$				$\sigma_U^2 = 1.00$			
		1.00	1.01	1.00	1.00	1.02	1.05	1.02	1.03
		.0167	.1084	.0174	.1080	.0478	.0854	.0517	.0593
	λ	1.25	1.26	1.25	1.26	2.06	2.11	2.08	2.07
		.0091	.0042	.0141	.0115	.1641	.2442	.3169	.2130
		.0627	.0408	.0755	.0709	.2330	.2377	.3144	.2508
$\rho^2 = 0.90$	β	$\sigma_U^2 = 0.25$				$\sigma_U^2 = 1.00$			
		1.06	1.06	1.00	1.06	1.08	1.12	1.02	1.09
		.0242	.0264	.0194	.0262	.0674	.1303	.0588	.0849
	λ	1.32	1.33	1.25	1.33	2.18	2.25	2.09	2.20
		.0190	.0138	.0174	.0228	.2484	.4178	.3544	.3229
		.0870	.0668	.0825	.0879	.2502	.2583	.3224	.2729

Table 1: *This simulation is described in §4.1. Here “RM” denotes the regression to the mean method correction, “MM” denote the method of moments corrections, “GR” is the grouping method and “IV” is the instrumental variable correction. The first row is the mean, the second the mean squared error and, for λ , the third row is the median absolute error.*

Results for λ					
	$\rho^2 = 0.90$	MM	RM	IV	GR
Mean		1.688	1.688	1.686	1.689
Median		1.686	1.685	1.589	1.685
S.D.		.056	.053	.718	.064
MAD		.036	.035	.318	.040
	$\rho^2 = 1.00$	MM	RM	IV	GR
Mean		1.601	1.601	1.688	1.602
Median		1.600	1.599	1.596	1.598
S.D.		.050	.044	.702	.056
MAD		.031	.030	.300	.035
Results for β					
	$\rho^2 = 0.90$	MM	RM	IV	GR
Mean		.365	.364	.345	.365
MSE		.0135	.0133	.0136	.0136
Median AE		.078	.078	.076	.079
	$\rho^2 = 1.00$	MM	RM	IV	GR
Mean		.346	.346	.346	.346
MSE		.0119	.0119	.0124	.0120
Median AE		.074	.074	.073	.072

Table 2: This simulation is described in §4.2. Here “RM” denotes the regression to the mean method correction, “MM” denote the method of moments corrections, “GR” is the grouping method and “IV” is the instrumental variable correction. The approximate standard error for the MSE’s for estimating β is .0006. MAD is median absolute deviation from the median, while Median AE is the median absolute error.

	Framingham Data	Bootstrap			
		Mean	Median	std. dev.	MAD
Sample Size	1369	–	–	–	–
Number of cases of CHD	183	–	–	–	–
W	DBP Exam 5	–	–	–	–
T	DBP Exam 3	–	–	–	–
Z_1	Age	–	–	–	–
Z_2	Cholesterol	–	–	–	–
Z_3	Cigs/Smoked	–	–	–	–
\overline{W}	84.2	84.1	84.1	.32	.22
Sample Variance(W)	126.2	126.2	126.3	5.84	3.77
\overline{T}	82.7	82.7	82.7	.29	.20
Sample Variance(T)	121.7	121.8	121.7	5.49	3.63
s_W^2	126.1	125.3	125.1	5.85	3.80
$\hat{\sigma}_U^2$	43.4	43.5	43.2	2.11	1.34
$100 \times \hat{\beta}_{Y W,Z}$	1.57	1.60	1.64	.70	.44
$100 \times \hat{\beta}_{Y \underline{T},Z}$	1.88	1.97	1.97	.69	.46
$\hat{\beta}_{T W,Z}$.63	.63	.63	.021	.015
$\hat{\beta}_{W \underline{T},Z}$.67	.67	.67	.026	.018
$\tilde{\lambda}_{1,MM}$	1.53	1.53	1.53	.054	.030
$\tilde{\lambda}_{1,RM}$	1.58	1.59	1.58	.048	.036
$\tilde{\lambda}_{1,IV}$	1.80	2.37	1.81	6.16	.421
$\tilde{\lambda}_{1,M}$	1.62	1.63	1.63	.065	.046
$100 \times \tilde{\beta}_1$	2.40	2.46	2.53	1.10	.685
$100 \times \overline{\beta}_1$	2.43	2.54	2.62	1.08	.704
$100 \times \tilde{\beta}_{1,IV}$	2.82	2.96	2.99	1.04	.702
$100 \times \tilde{\beta}_{1,M}$	2.54	2.60	2.70	1.13	.728

Table 3: Results of analysis of Framingham data. The bootstrap simulation was based upon 400 bootstrap samples.

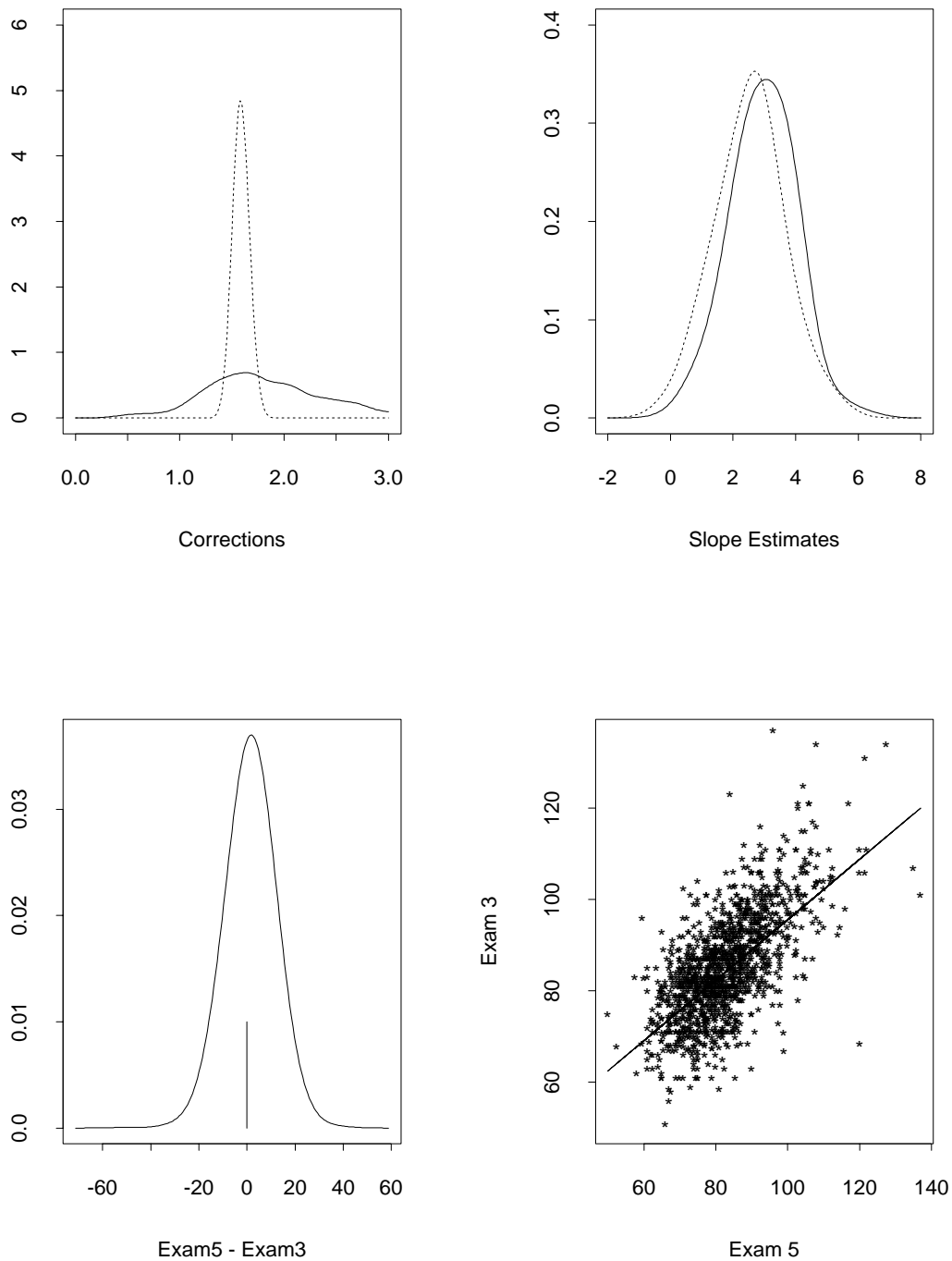


Figure 1: *Top left: bootstrap kernel density estimates for the instrumental variable correction (solid) and the RM (regression to the mean) method (dashed). Top right: same as above, but for the slope estimates. Bottom left: kernel density estimates of Exam 5 DBP minus Exam 3 DBP. Bottom right: scatterplot of Exam 3 DBP versus Exam 5 DBP.*