Simple Sensitivity Analysis for Differential Measurement Error

By Tyler J. VanderWeele and Yige Li
Harvard University, Cambridge, MA, U.S.A.

Abstract

Simple sensitivity analysis results are given for differential measurement error of either the exposure or the outcome. In the case of differential measurement error of the outcome it is shown that the true effect of the exposure on the outcome on the risk ratio scale must be at least as large as the observed association between the exposure and the mis-measured outcome divided by the maximum strength of differential measurement error, assessed as the risk ratio of the controlled direct effect of the exposure on mis-measured outcome not through the true outcome. In the case of differential measurement error of the exposure it is shown that the true effect on the risk ratio scale of the exposure on the outcome must be at least as large as the observed association between the mis-measured exposure measurement and the outcome divided by the maximum strength of differential measurement error, assessed as the risk ratio of the effect of the outcome on mis-measured exposure measurement conditional on the true exposure. The results can also be immediately used to indicate the minimum strength of differential measurement error that would be needed to explain away an observed association between an exposure measurement and an outcome measurement.

Key words: Measurement Error, Misclassification, Differential, Bias Analysis, Sensitivity Analysis.
1. Introduction

Measurement error, along with unmeasured confounding and selection bias, are often considered as being the central threats to validity in observational studies. However, measurement error is perhaps more often dismissed as a threat than is bias due to potential unmeasured confounding. Some of this discrepancy may arise from the perception that at least non-differential measurement error often, though not always, biases results towards the null.\textsuperscript{1-6} In such contexts, when biases are towards the null, then when the original estimate is meaningfully large, the true effect will be even larger. While this intuition does not always hold, it is still used with some frequency as justification for ignoring questions of measurement error. However such ignoring of measurement error, can fail, and dramatically so, when measurement error is differential such that the measurement error in the outcome depends on the value of the exposure, or when the measurement error in the exposure in fact depends on the value of the outcome, as may arise in retrospective reporting of the exposure. While various techniques to address non-differential measurement have been put forward\textsuperscript{6-11}, many of these techniques require detailed knowledge on numerous parameters related to conditional sensitivities and specificities for misclassification. These can be difficult to obtain data on, or to specify or interpret in a sensitivity analysis, unless a validation study, with access to the gold-standard measurement, is carried out.

In this paper we address these issues surrounding differential measurement error by proposing very simple sensitivity analysis techniques that assess how strongly the differential measurement error would have to be to completely explain away an observed exposure-outcome association. The parameters in the results given are particularly easy to interpret and essentially correspond, in the case of differential measurement error of the exposure to the effect of the outcome on the exposure measurement conditional on the true exposure, and in the case of differential measurement error of the outcome to the effect of the exposure on the outcome measurement conditional on the true outcome. Analogous results are available for the differential measurement error of the exposure as well.

2. Definitions and Notation

We will give results here for a binary outcome; results for a continuous outcome, which can be derived from the other research literature, are given in the Appendix (Le Cessie et al., 2012). Let $A$ denote a binary exposure and $Y$ denote a binary outcome. Let $C$ denote a set of measured covariates. Let $A^*$ and $Y^*$ denote respectively the measurements of $A$ and $Y$ that may be subject to measurement error. We will first consider the setting of measurement error with respect to the outcome $Y$ and then will turn to the case of measurement error with respect to the exposure $A$. As our focus in this paper is on measurement error, we will assume that the measured covariates $C$ suffice to control for confounding for the effect of true exposure $A$ on the true outcome $Y$. The results given below are stated in terms of probabilities and are thus applicable even if this no unmeasured confounding assumption does not hold, but to interpret the various
expressions below as the effects of the exposure on the outcome, the measured covariates C would have to suffice to control for confounding. Some similar simple sensitivity analysis results for unmeasured confounding have been provided previously.\textsuperscript{12,13}

We will say that the measurement error for the outcome Y is non-differential with respect to exposure A if the distribution of Y* conditional on Y and C is independent of A which we can denote in terms of probability distributions by $P(y^*|a,y,c) = P(y^*|y,c)$. In other words, the measurement error of Y is non-differential with respect to exposure A if, conditional on measured covariates C, the exposure A gives no information about the measurement Y* beyond that in the true value of Y. If this is not the case so that Y* in fact depends on exposure A even conditional on (Y,C) then we say that the measurement error is differential. Non-differential measurement error of the outcome is represented in the diagram in Figure 1a and differential measurement of the outcome is represented in Figure 1b.\textsuperscript{14,15} If the exposure A affects the measurement Y* through pathways other than through its effect on the true outcome Y, then measurement error will be differential. It is this context which, as noted above, can often induce substantial bias away from the null, that will be the focus of the present paper.

In the context of differential measurement error of the outcome we will let $p_{a}=P(Y=1|A=a,C=c)$ denote the probability of the true outcome conditional on the exposure $A=a$ and we will let $p_{a}^{*}=P(Y^*=1|A=a,C=c)$ denote the probability of the outcome measurement $Y^*=1$ conditional on the exposure $A=a$. The true risk ratio for the effect of the exposure on the outcome is then $p_{1}/p_{0}=P(Y=1|A=1,C=c)/P(Y=1|A=0,C=c)$ and the risk ratio obtained with the mismeasured data is then denoted by $p_{1}^{*}/p_{0}^{*}=P(Y^*=1|A=1,C=c)/P(Y^*=1|A=0,C=c)$. The sensitivity analysis results will relate the true risk ratio to the risk ratio obtained with the mismeasured data. In the expressions, $p_{1}/p_{0}$ and $p_{1}^{*}/p_{0}^{*}$, above we have suppressed the conditioning on C=c in the subscripts. The notation and results that follow are all applicable with analyses conditional on the measured covariates C. However, for notational simplicity, we have omitted “c” from the subscripts.

3. Simple Sensitivity Analysis for Differential Measurement Error of the Outcome

In the context of differential measurement error of the outcome let $s_{a}$ denote the sensitivity of the measurement $Y^*$ for Y conditional on $A=a$ and $C=c$, that is, the
probability, conditional on \( A=a \) and \( C=c \) that when \( Y=1 \), we also have that \( Y^*=1 \). In terms of probabilities, \( s_a = P(Y^*=1|Y=1,A=a,C=c) \). Note that with differential measurement error the sensitivity of the measurement \( Y^* \) can vary with the value of the exposure \( A \); the sensitivity may for example be lower for the exposed than for the unexposed. Also let \( f_a \) denote the false positive probability of the measurement \( Y^* \) for \( Y \) conditional on \( A=a \) and \( C=c \), that is, the probability, conditional on \( A=a \) and \( C=c \) that when in fact \( Y=0 \), we have the measurement that \( Y^*=1 \). In terms of probabilities, \( f_a = P(Y^*=1|Y=0,A=a,C=c) \). The false positive probability is also just 1 minus the specificity. Again with differential measurement error, the false positive probabilities of the measurement \( Y^* \) can vary with the value of the exposure \( A \).

Consider now the ratio of the sensitivity parameter conditional on the exposure being present versus absent i.e. \( s_1/s_0 = P(Y^*=1|Y=1,A=1,C=c)/P(Y^*=1|Y=1,A=0,C=c) \). This ratio is essentially the risk ratio for the effect of the exposure \( A \) on the measurement \( Y^* \) conditional on \( Y=1 \) and \( C=c \). It corresponds to the effect represented by arrow from \( A \) to \( Y^* \) in Figure 1b when \( Y=1 \). It assesses how much more likely the measurement of \( Y^* \) is reported to be present, \( Y^*=1 \), when the exposure is present versus absent, in settings in which the true outcome is present. Likewise, consider the ratio of the false positive probabilities \( f_1/f_0 = P(Y^*=1|Y=0,A=1,C=c)/P(Y^*=1|Y=0,A=0,C=c) \). This is essentially the risk ratio for the effect of the exposure \( A \) on the measurement \( Y^* \) conditional on \( Y=0 \) and \( C=c \). It corresponds to the effect represented by arrow from \( A \) to \( Y^* \) in Figure 1b when \( Y=0 \). It assesses how much more likely the measurement of \( Y^* \) is reported to be present, \( Y^*=1 \), when the exposure is in fact present versus absent, in settings in which the true outcome is in fact absent.

We can now state our first sensitivity analysis result.

**Theorem 1.** Under differential measurement error of the outcome, if \( p_1/p_0 \geq 1 \) then \( p_1/p_0 \geq (p_1*/p_0*) / \max(s_1/s_0 , f_1/f_0) \); and if \( p_1/p_0 \leq 1 \) then \( p_1/p_0 \leq (p_1*/p_0*) / \min(s_1/s_0 , f_1/f_0) \).

The proof of this and other results are given in the Appendix. Consider the case of a causative exposure so that the true risk ratio is greater than or equal to 1. The result states that the true effect of the exposure on the outcome on the risk ratio scale, \( p_1/p_0 \), must be at least as large as the observed association between exposure \( A \) and measurement \( Y^* \) on the risk ratio scale, \( p_1*/p_0* \), divided by the maximum of the direct effect of \( A \) on \( Y^* \) not through \( Y \) i.e. the maximum of the sensitivity risk ratio for \( A \) on \( Y^* \), \( s_1/s_0 \), and the false positive probability ratio for the effect of \( A \) on \( Y^* \), \( f_1/f_0 \). This also implies that for the observed association between \( A \) and \( Y^* \) to be completely explained away by differential measurement error so there is no true causative effect, then the strength of the differential measurement error, assessed as the direct effect risk ratio of the effect of \( A \) on \( Y^* \) not through \( Y \) must be at least as large as the observed association between \( A \) and \( Y^* \) for either when \( Y=1 \), which is \( s_1/s_0 \), or when \( Y=0 \), which is \( f_1/f_0 \). This is stated formally in Corollary 1.

**Corollary 1.** Under differential measurement error of the outcome, if the observed association between the exposure and the mis-measured outcome is to be due solely to
differential measurement error, rather than a true effect, then if \( p_1/p_0 > 1 \) it must be the case that either \( s_1/s_0 \geq p_1*/p_0* \) or that \( f_1/f_0 \geq p_1*/p_0* \); and if \( p_1/p_0 < 1 \) then it must be the case that either \( s_1/s_0 \leq p_1*/p_0* \) or \( f_1/f_0 \leq p_1*/p_0* \).

While the proof of Theorem 1, from which Corollary 1 follows, is not entirely straightforward (see Appendix), the result in Corollary 1 is relatively intuitive graphically insofar as if the A-Y arrow in Figure 1b is to be absent and we observe an association between A and Y* then the direct effect arrow from A to Y* not through Y must be at least as large as our observed association between A and Y*. Similar logic can of course be used to assess the extent of measurement error needed to shift the estimate to any other value.

A very simple sensitivity analysis thus consists of specifying the maximum effect that the investigator believes is possible for A to have on Y* independent of Y i.e. how much more likely is the outcome reported to be present, \( Y^* = 1 \), comparing the exposure present to absent, when the true outcome is present, or how much more likely when the true outcome is absent. Once this is specified one simply divides the observed association between A and Y* by this parameter corresponding to the maximum direct effect of A on Y* independent of Y; the true effect of A on Y must be at least this large. Alternatively, one might just report that for differential measurement error to completely explain away the effect of the observed association between exposure A and measurement Y* the magnitude of differential measurement error, assessed by the maximum direct effect of A on Y* not through Y, must be at least as large as the observed association between A and Y*. We will illustrate the use of such an approach below but first we will also consider similar results for differential measurement error of the exposure.

### 4. Simple Sensitivity Analysis for Differential Measurement Error of the Exposure

Now consider measurement error in the exposure A. We will say that the measurement error for the exposure A is non-differential with respect to outcome Y if the distribution of A* conditional on A and C is independent of Y which we can denote in terms of probability distributions by \( P(a^*|y,a,c) = P(a^*|a,c) \). In other words, the measurement error of exposure A is non-differential with respect to outcome Y if, conditional on measured covariates C, the outcome Y gives no information about the measurement A* beyond that in the true value of A. If this is not the case so that A* in fact depends on Y even conditional on (A,C) then we say that the measurement error is differential. Non-differential measurement error of the exposure is represented in the diagram in Figure 2a and differential measurement of the exposure is represented in Figure 2b. If the outcome Y affects the measurement A* through pathways other than through its being affected by true exposure A, then measurement error will be differential. We will now consider simple sensitivity analysis for differential measurement error of the exposure.

As before, we will let \( p_{a} = P(Y=1|A=a,C=c) \) denote the probability of the true outcome conditional on the exposure A=a and we will now let \( p_{a}^* = P(Y=1|A^*=a,C=c) \) denote the probability of the outcome conditional on the measurement A*=a. As before, the true risk ratio for the effect of the exposure on the outcome is then
\( p_1/p_0 = P(Y=1|A=1,C=c)/P(Y=1|A=0,C=c) \) and the risk ratio obtained with the mismeasured data is then denoted by \( p'_1/p'_0 = P(Y=1|A^*=1,C=c)/P(Y=1|A^*=0,C=c) \). The sensitivity analysis results will relate the true risk ratio to the risk ratio obtained with the mismeasured data.

In the context of differential measurement error of the exposure let \( s_y' \) denote the sensitivity of the measurement \( A^* \) for \( A \) conditional on \( Y=y \) and \( C=c \), that is, the probability, conditional on \( Y=y \) and \( C=c \) that when \( A=1 \), we also have that \( A^*=1 \). In terms of probabilities, \( s_y' = P(A^*=1|Y=y,A=1,C=c) \). Note that with differential measurement error the sensitivity of the measurement \( A^* \) can vary with the value of the outcome \( Y \). Also let \( f_y' \) denote the false positive probability of the measurement \( A^* \) for \( A \) conditional on \( Y=y \) and \( C=c \), that is, the probability, conditional on \( Y=y \) and \( C=c \) that when in fact \( A=0 \), we have the measurement that \( A^*=1 \). In terms of probabilities, \( f_y' = P(A^*=1|Y=y,A=0,C=c) \).

Consider now the ratio of the sensitivity parameter for the exposure conditional on the outcome being present versus absent i.e.
\( s_1'/s_0' = P(A^*=1|Y=1,A=1,C=c)/P(A^*=1|Y=0,A=1,C=c) \). This ratio is essentially the risk ratio for the effect of the outcome \( Y \) on the exposure measurement \( A^* \) conditional on \( A=1 \) and \( C=c \). It corresponds to the effect represented by arrow from \( Y \) to \( A^* \) in Figure 2b when \( A=1 \). It assesses how much more likely the measurement of \( A^* \) is reported to be present, \( A^*=1 \), when the outcome is present versus absent, in settings in which the true exposure is in fact present. Likewise, consider the ratio of the false positive probabilities for the exposure \( f_1'/f_0' = P(A^*=1|Y=1,A=0,C=c)/P(A^*=1|Y=0,A=0,C=c) \). This is essentially the risk ratio for the effect of the outcome \( Y \) on the exposure measurement \( A^* \) conditional on \( A=0 \) and \( C=c \). It corresponds to the effect represented by arrow from \( Y \) to \( A^* \) in Figure 2b when \( A=1 \). It assesses how much more likely the measurement of \( A^* \) is reported to be present, \( A^*=1 \), when the outcome is present versus absent, in settings in which the true exposure is in fact absent.

We can now state our second sensitivity analysis result. It essentially says that for an observed association between exposure measurement \( A^* \) and outcome \( Y \) the true effect of \( A \) on \( Y \) on the risk ratio scale must be at least as large as the observed association between \( A^* \) and \( Y \) divided by the maximum strength of differential measurement error,
assessed as the risk ratio of the effect of outcome Y on exposure measurement A* conditional on true exposure A. In terms of probabilities we have the following result.

Theorem 2. Under differential measurement error of the outcome, if \( p_1/p_0 \geq 1 \) then
\[
p_1/p_0 \geq (p_1'/p_0') / \max(s_1'/s_0', f_1'/f_0');
\] and if \( p_1/p_0 \leq 1 \) then
\[
p_1/p_0 \leq (p_1'/p_0') / \min(s_1'/s_0', f_1'/f_0').
\]

Consider the case of a causative exposure so that the true risk ratio is greater than or equal to 1. The theorem states that the true effect of the exposure on the outcome on the risk ratio scale, \( p_1/p_0 \), must be at least as large as the observed association between exposure A and measurement Y* on the risk ratio scale, \( p_1'/p_0' \), divided by the maximum of the effect of Y on A* conditional on A i.e. the maximum of the sensitivity risk ratio for Y on A*, \( s_1'/s_0' \), and the false positive probability ratio for the effect of Y on A*, \( f_1'/f_0' \). This also implies that for the observed association between A* and Y to be completely explained away by differential measurement error so there is no true causative effect, then the strength of the differential measurement error, assessed as the risk ratio for the effect of Y on A* conditional on A must be at least as large as the observed association between A* and Y for either when A=1, which is \( s_1'/s_0' \), or when A=0, which is \( f_1'/f_0' \). This is stated formally is Corollary 2.

Corollary 2. Under differential measurement error of the exposure, if the observed association between the mis-measured exposure and the outcome is to be due solely to differential measurement error, rather than a true effect, then if \( p_1/p_0 > 1 \) it must be the case that either \( s_1'/s_0' \geq p_1'/p_0' \) or that \( f_1'/f_0' \geq p_1'/p_0' \); and if \( p_1/p_0 < 1 \) it must be the case that either \( s_1'/s_0' \leq p_1'/p_0' \) or that \( f_1'/f_0' \leq p_1'/p_0' \).

The result is again perhaps relatively intuitive graphically insofar as if the A-Y arrow in Figure 2b is to be absent and we observe an association between A* and Y then the direct effect arrow from Y to A* must be at least as large as our observed association between A* and Y. Similar logic can of course be used to assess the extent of measurement error needed to shift the estimate to any other value.

A very simple sensitivity analysis thus consists of specifying the maximum effect that the investigator believes is possible for Y to have on A* conditional on A, i.e. how much more likely is the exposure reported to be present, A*=1, comparing when the outcome is present versus absent, when the true exposure is present, or how much more likely when the true exposure is absent. Once this is specified one simply divides the observed association between A* and Y by this parameter corresponding to the maximum direct effect of Y on A* conditional on A; the true effect of A on Y must be at least this large. Alternatively, one might just report that for differential measurement error to completely explain away the effect of the observed association between exposure measurement A* and outcome Y, the magnitude of differential measurement error, assessed by the maximum effect on the risk ratio scale of Y on A* conditional on A, must be at least as large as the observed association between A* and Y. We will now illustrate this result with an example.
5. Example

Zhong et al.\(^{16}\) use data from 2,279 mothers in Peru to examine the effects of social support during pregnancy on antepartum depression. Social support was assessed in these studies either by satisfaction with social support or with self-report of the number of support providers available. We will focus here on the analyses in which social support was operationalized by satisfaction. Conditional on various social, demographic, and health characteristics, and having high social support at baseline prior to pregnancy, those who had low social support during pregnancy were at 1.51 higher odds (95% CI: 1.03, 2.22) of antepartum depression than those with high social support during pregnancy. The social support exposure in this study was assessed by self-report with reference to the period during early pregnancy or since becoming pregnant; however self-reported social support was itself assessed at the same time as antepartum depression. If depression itself alters self-reported social support, then this could potentially account for the whole of the association. In other words, differential measurement error of the social support exposure might potentially explain away the association. Assuming the antepartum depression outcome is relatively rare in this study so that odds ratios approximate risk ratios, then we can apply Corollary 2. We would then have that for differential measurement error to be responsible for the whole of the observed association between social support and antepartum depression, the presence of antepartum depression would have to increase the probability of self-reporting high social support by at least 1.51-fold, either for the group that did in fact have high social support or for the group that in fact had low social support. This would constitute moderately strong differential measurement error but is perhaps not entirely implausible. We could of course examine other potential values as well; if we thought the effect would only be meaningful if it were at least as large as 1.1, we could state that to reduce the estimated odds ratio from 1.51 to 1.1, the presence of antepartum depression would have to increase the probability of self-reporting high social support by at least 1.37-fold (\(=1.51/1.1\)), either for the group that did in fact have high social support or for the group that in fact had low social support.

If instead we thought the maximum effect of antepartum depression on self-reported social support conditional on true social support was a risk ratio of at most 1.2-fold then, by applying Theorem 2, the most such differential measurement error could alter the observed odds ratio of 1.51 (95% CI: 1.03, 2.22) can be obtained by dividing this estimate and confidence interval by 1.2 to obtain an effect estimate of 1.26 (95% CI: 0.86, 1.85). While differential measurement error of this magnitude would not suffice to explain away the point estimate, it would suffice to shift the confidence interval to include 1. We can thus see that while moderately strong differential measurement error would be needed to explain away the effect estimate only relatively modest differential measurement error would be needed for the confidence interval to include 1.
6. Discussion

In this paper we have provided a relatively straightforward sensitivity analysis approach to evaluate the robustness or sensitivity of results to potential differential measurement error of the exposure or the outcome. The results led to the conclusion that the magnitude of the differential measurement error, quantified on the risk ratio scale for the direct effect of the exposure on the mis-measured outcome, or as the effect of the outcome on the mis-measured exposure, must be at least as large as the observed risk ratio relating the exposure and outcome measurements. Like all sensitivity analysis techniques the results do not necessarily yield definite conclusions but can be helpful in establishing a general sense as to the robustness of results.

Of course, if data are available on the necessary sensitivity and specificities concerning the differentially mis-measured exposure or outcome then such data could be used to obtain more precise inferences about the magnitude of the true effect. However, data from such validation studies are often absent; it can be difficult to obtain such data even for a non-differentially mis-measured exposure or outcome, and for a differentially mis-measured exposure or outcome, it will be more challenging still. The results in this paper can be of use when such data are not available.

The results given here are particularly easy to use, and can furthermore be employed, without specifying the magnitude of the effects of differential measurement error simply by reporting (i) how strong the differential measurement error would need to be to completely explain away the estimate of the exposure-outcome association with the mis-measured variables and (ii) the minimum strength of differential measurement error needed to shift the confidence interval to include 1. An analogous approach, referred to as the “E-value”, has recently been put forward to address the minimum strength of unmeasured confounding necessary to explain away an observed exposure-outcome association. The E-value is defined as the “minimum strength of association on the risk ratio scale that an unmeasured confounder(s) would have to have with both the exposure and the outcome to explain away an observed exposure-outcome relationship.” The E-value is always larger in magnitude than the magnitude of the risk ratio to be explained away. For example, a risk ratio of 1.1 yields an E-value of 1.43. In contrast, the magnitude of the minimum strength of differential measurement on the risk scale needed to explain away an observed association is simply equal to the observed exposure-outcome measurement risk ratio. Thus, to explain away an observed risk ratio of 1.1 one only needs a differential measurement error risk ratio of 1.1.

It may seem from this analysis that measurement error is perhaps a stronger threat to the validity of etiologic studies than is unmeasured confounding. In the context of differential measurement error, that conclusion might often be warranted. We might then wonder why questions of measurement error seem to be addressed with somewhat less frequency than those of unmeasured confounding. The answer perhaps lies in part in the fact that, as noted in the introduction, non-differential measurement error often, though not always, biases estimates towards the null making them conservative. It is thus principally differential, rather than non-differential, measurement error, that typically has the potential for such large biases and substantial differential measurement error may be less common,
at least outside of contexts in which exposures are reported retrospectively after the outcome occurs. Moreover, for many exposure and outcomes, measurement error, either differential or non-differential, may be minimal when more objective measurements are used. This will of course vary across contexts and areas of research but with certain objective measurements, such as with mortality, measurement error is hardly a concern at all. In contrast in nearly any observational study, unmeasured confounding will likely be a concern. Exceptions can occur with natural experiments (and confounding for the exposure is of course eliminated on average in randomized trial) but these settings may be less frequent than those with measurements that are highly accurate and/or objective. The relatively greater emphasis on assessing the implications of unmeasured confounding over measurement error thus may not be entirely unreasonable, though both should arguably more often be assessed. And moreover, as shown here, when measurement error is differential it can be particularly problematic insofar as the magnitude of effects needed to explain away an observed exposure-outcome association are considerably more modest for differential measurement error than they are for unmeasured confounding.

We have focused here on differential measurement error of either a binary exposure or a binary outcome. However, analogous results are also possible for continuous exposure and/or outcome and can be obtained by adapting existing results in the literature. We state these formally in the Appendix. It is hoped that the results in this paper will allow for a more straightforward and more frequent assessment of the potential of differential measurement to explain away, or substantially alter, effect estimates.

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Appendix

Simple Sensitivity Analysis for Differential Measurement Error of Continuous Outcomes and Exposures

We first consider the case of differential measurement error of a continuous outcome in the context of linear regression.

Theorem 3. If the measure $Y^*$ of outcome $Y$ is subject to differential measurement error with respect to exposure $A$ and if $E[Y^*|a,y,c]=g_0 + g_1 a + g_2 y + g_3 c$ and $E[Y|a,c]=b_0 + b_1 a + b_2 c$ and $E[Y^*|a,c]=b_0^* + b_1^* a + b_2^* c$ then $\beta_1 = (\beta_1^* - \gamma_1)/\gamma_2$.

From Theorem 3 we have that if the outcome is subject to differential measurement error and we fit the regression model, $E[Y^*|a,c]=b_0^* + b_1^* a + b_2^* c$ with the mis-measured outcome data then we can obtain a corrected estimate of the effect of $A$ on the true outcome $Y$ by $\beta_1 = (\beta_1^* - \gamma_1)/\gamma_2$ where $\gamma_1$ corresponds to the differential measurement error direct effect of $A$ on $Y^*$ not through $Y$ and where $\gamma_2$ corresponds to the effect of $Y$ on $Y^*$. If $\gamma_2=1$ so that $Y^*$ scales with $Y$, then we have that $\beta_1 = \beta_1^*$ so that we obtain the corrected estimate of the effect of $A$ on $Y$ simply by taking the estimate $\beta_1^*$ obtained using the observed data and subtracting from it $\gamma_1$, the differential measurement error direct effect of $A$ on $Y^*$ not through $Y$.

We now consider an analogous result for differential measurement error of a continuous exposure.

Theorem 4. Suppose the measure $A^*$ of exposure $A$ is subject to differential measurement error with respect to outcome $Y$ and that $E[A^*|a,y,c]=g_0 + a + g_1 y + g_2 c$. Let $\sigma^2_u$ denote the error variance in this regression, let $\sigma^2_a=\text{Var}(A|C)$ and let $\lambda = \text{Var}(A|C) / \text{Var}(A^*|C,Y) = \sigma^2_a/(\sigma^2_a+\sigma^2_u)$. For a continuous outcome $Y$ with linear regressions $E[Y|a,c]=b_0 + b_1 a + b_2 c$ and $E[Y^*|a,c]=b_0^* + b_1^* a + b_2^* c$, we have $\beta_1 = (\beta_1^* - \gamma_1/(\sigma^2_a+\sigma^2_u)) / \lambda$.

For a rare binary outcome with logistic regression $\logit(Y=1|a,c)=\theta_0 + \theta_1 a + \theta_2 c$ and $\logit(Y^*=1|a,c)=\theta_0^* + \theta_1^* a + \theta_2^* c$, we have $\theta_1 \approx (\theta_1^* - \gamma_1/(\sigma^2_a+\sigma^2_u)) / \lambda$.

From Theorem 4 we have that if the exposure is subject to differential measurement error and we fit the regression model $E[Y^*|a,c]=b_0^* + b_1^* a + b_2^* c$ with the mis-measured exposure data then we can obtain a corrected estimate of the effect of true exposure $A$ on outcome $Y$ by $\beta_1 = (\beta_1^* - \gamma_1/(\sigma^2_a+\sigma^2_u)) / \lambda$, where we essentially subtract off a scaled version, $\gamma_1/(\sigma^2_a+\sigma^2_u)$, of the differential measurement error effect of $Y$ on $A^*$, from our estimate, $\beta_1^*$, of the mis-measured effect of $A$ on $Y$, and then we rescale this again by diving by $\lambda$. The $\gamma_1/(\sigma^2_a+\sigma^2_u)$ that we subtract off from our the observed estimate, $\beta_1^*$, is essentially measured in standard deviations of $A^*$ (conditional on $Y,C$).

We now give the proofs of each of the results.

Proof of Theorem 1. First consider the case with $p_1/p_0 \geq 1$. We have that
\[
\frac{p_1^*}{p_0^*} = \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)}
\]

Suppose first that \(s_1/s_0 > f_1/f_0\). We want to show
\[
\frac{p_1}{p_0} > \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)} \cdot \frac{s_1}{s_0}
\]
which can be rewritten as \(p_1 s_0 p_0 + f_0 s_0 p_0 s_0 - f_0 p_0 s_0 s_0 > p_1 s_1 s_0 p_0 + f_1 p_0 s_0 - f_1 p_0 s_0 s_0\) and simplified to \(s_1 f_0 (p_1 - p_0 p_1) > s_0 f_1 (p_0 - p_0 p_1)\) and this holds because \(s_1 f_0 > s_0 f_1\) and \(p_1 \geq p_0\).

If instead we had \(f_1/f_0 > s_1/s_0\) then we want to show
\[
\frac{p_1}{p_0} > \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)} \cdot \frac{s_1}{s_0}
\]
which can be rewritten as \(p_1 f_0 s_0 (p_1 - p_0 p_1) < s_0 f_1 (p_0 - p_0 p_1)\) and this holds because \(s_1 f_0 < s_0 f_1\) and \(p_1 \leq p_0\). If instead we had \(f_1/f_0 < s_1/s_0\) then we want to show
\[
\frac{p_1}{p_0} < \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)} \cdot \frac{s_1}{s_0}
\]
which can be simplified to \(p_1 p_0 (f_1 s_0 - f_0 s_1) + f_0 f_1 (p_1 - p_0) > 0\) and this holds because \(f_1 s_0 > f_0 s_1\) and \(p_1 \geq p_0\).

Now consider the case with \(p_1/p_0 \leq 1\). Suppose first \(s_1/s_0 < f_1/f_0\). We want to show
\[
\frac{p_1}{p_0} < \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)} \cdot \frac{s_1}{s_0}
\]
which can be simplified to \(s_1 f_0 (p_1 - p_0 p_1) < s_0 f_1 (p_0 - p_0 p_1)\) and this holds because \(s_1 f_0 < s_0 f_1\) and \(p_1 \leq p_0\). If instead we had \(f_1/f_0 < s_1/s_0\) then we want to show
\[
\frac{p_1}{p_0} < \frac{s_1 p_1 + f_1 (1 - p_1)}{s_0 p_0 + f_0 (1 - p_0)} \cdot \frac{s_1}{s_0}
\]
which can be simplified to \(p_1 p_0 (f_1 s_0 - f_0 s_1) + f_0 f_1 (p_1 - p_0) < 0\) and this holds because \(f_1 s_0 < f_0 s_1\) and \(p_1 \leq p_0\).

**Proof of Theorem 2.** If we apply Theorem 1 with the roles of \(A\) and \(Y\) reversed then we have that if \(P(A=1|Y=1,c)=P(A=1|Y=0,c)=1\) then \(P(A=1|Y=1,c)/P(A=1|Y=0,c) = P(A^*=1|Y=1,c)/P(A^*=1|Y=0,c) \geq \max(s_1/s_0', f_1/f_0')\); and if 
\[
P(A=1|Y=1,c)/P(A=1|Y=0,c) \leq 1\ then P(A=1|Y=1,c)/P(A=1|Y=0,c) \leq P(A^*=1|Y=1,c)/P(A^*=1|Y=0,c) \text{ / min}(s_1/s_0', f_1/f_0').
\]
Now,
\[
\frac{P(A=1|Y=1,c)}{P(A=1|Y=0,c)} = \frac{P(Y=1|A=1,c)P(A=1|c)}{P(Y=0|A=1,c)} \quad \text{and} \quad \frac{P(A^*=1|Y=1,c)}{P(A^*=1|Y=0,c)} = \frac{P(Y=1|A^*=1,c)P(A^*=1|c)}{P(Y=0|A^*=1,c)}
\]
from which it then follows if \(P(A=1|Y=1,c)/P(A=1|Y=0,c) \geq 1\ then \(p_1/p_0 \geq (p_1'/p_0') / \max(s_1/s_0', f_1/f_0')\) and if \(P(A=1|Y=1,c)/P(A=1|Y=0,c) \leq 1\ then \(p_1/p_0 \leq (p_1'/p_0') / \min(s_1/s_0', f_1/f_0')\). The condition \(P(A=1|Y=1,c)/P(A=1|Y=0,c) \geq 1\ holds if and only if \(p_1/p_0 \geq 1\ and the condition \(P(A=1|Y=1,c)/P(A=1|Y=0,c) \leq 1\ holds if and only if \(p_1/p_0 \leq 1\, and from this the result follows.

**Proof of Theorem 3.** We have that \(E[Y^*|a,c] = E[E[Y^*|a,Y,c]|a,c] = \gamma_0 + \gamma_1 a + \gamma_2 E[Y|a,c] + \gamma_3 c = \gamma_0 + \gamma_1 a + \gamma_2 (\beta_0 + \beta_1 a + \beta_2 c) + \gamma_3 c = (\gamma_0 + \gamma_2 \beta_0) + (\gamma_1 + \gamma_2 \beta_1) a + (\gamma_3 + \gamma_2 \beta_2) c\). Since we also have that \(E[Y^*|a,c] = \beta_0^* + \beta_1^* a + \beta_2^* c\) it follows, by comparing coefficients for \(A\), that \(\beta_1^*=(\gamma_1 + \gamma_2 \beta_1)\) and thus that \(\beta_1 = (\beta_1^* - \gamma_1)/\gamma_2\).


Proof of Theorem 4. This result can be derived using the proof given in the eAppendix of le Cessie et al.\textsuperscript{17} for situation 6 by relabeling “M” in the proof of le Cessie et al.\textsuperscript{17} by “A”, and by relabeling both “(X,C)” jointly as “C.”