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Mediation analysis in the presence of continuous exposure measurement error

Chao Cheng[1,2], **Donna Spiegelman**[1,2], **Fan Li**[1,2]

[1]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut, USA

[2]Center for Methods in Implementation and Prevention Science, Yale School of Public Health, New Haven, Connecticut, USA

Abstract

The difference method is used in mediation analysis to quantify the extent to which a mediator explains the mechanisms underlying the pathway between an exposure and an outcome. In many health science studies, the exposures are almost never measured without error, which can result in biased effect estimates. This article investigates methods for mediation analysis when a continuous exposure is mismeasured. Under a linear exposure measurement error model, we prove that the bias of indirect effect and mediation proportion can go in either direction but the mediation proportion is usually be less biased when the associations between the exposure and its error-prone counterpart are similar with and without adjustment for the mediator. We further propose methods to adjust for exposure measurement error with continuous and binary outcomes. The proposed approaches require a main study/validation study design where in the validation study, data are available for characterizing the relationship between the true exposure and its error-prone counterpart. The proposed approaches are then applied to the Health Professional Follow-up Study, 1986–2016, to investigate the impact of body mass index (BMI) as a mediator for mediating the effect of physical activity on the risk of cardiovascular diseases. Our results reveal that physical activity is significantly associated with a lower risk of cardiovascular disease incidence, and approximately half of the total effect of physical activity is mediated by BMI after accounting for exposure measurement error. Extensive simulation studies are conducted to demonstrate the validity and efficiency of the proposed approaches in finite samples.

Keywords

mediation analysis; mediation proportion; mismeasured continuous exposure; natural indirect effect; regression calibration; validation study

1 | INTRODUCTION

Mediation analysis[1–3] is widely-used in public health research. In mediation analysis, the primary focus lies in the decomposition of the total effect (TE) of the exposure on the

Correspondence: Chao Cheng, Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA. c.cheng@yale.edu.

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outcome into the natural indirect effect (NIE) through the mediator and the natural direct effect (NDE) whose impact is due solely to the exposure and possibly other mediators. In addition, the mediation proportion (MP; sometimes also referred as the proportion mediated or attributable risk percent) has been defined as the ratio of the NIE and the TE to quantify the relative importance of the mediator in explaining the exposure-outcome mechanism. Throughout, we shall refer to NIE, NDE, and MP as mediation measures of potential interest. The product method and difference method are two regression-based approaches to estimate the mediation measures, which were first developed outside of the counterfactual outcome framework commonly used for causal inference;[1] under certain assumptions, regression-based mediation analyses have since been shown to have causal interpretations under the counterfactual outcome framework.[3–5] The product method fits one regression for the outcome and another regression for the mediator, whereas the difference method evaluates two regression models for the outcome, one with and the other without adjusting for the mediator. A detailed comparison of both methods and their pros and cons are provided in Cheng et al.[6]

Measurement error is a common problem in mediation analysis from observational studies, and standard mediation estimators can be biased if the measurement error is not appropriately addressed. Table 1 provides a full summary of the existing literature addressing measurement error/misclassification issues in mediation analysis (typically measurement error refers to an error-prone continuous variable, whereas misclassification refers to an error-prone binary or categorical variable, and we follow that tradition here). There have been a few previous efforts to investigate the estimation bias in NIE and NDE due to an error-prone binary or continuous mediator and to develop bias correction approaches for mediation analysis. Others have studied the impact of misclassification of a binary exposure or a binary outcome on estimation of the NIE and NDE. However, there are no methods currently available to address measurement error with a continuous exposure, although exposure measurement error in continuous variables is a major source of bias in epidemiologic studies.[7]

The objective of this article is to develop statistical approaches for valid estimation and inference of mediation measures in the presence of an error-prone continuous exposure. Specifically, we develop strategies to correct for the bias in estimation and inference when using the difference method. In contrast to most of the existing literature on measurement error and misclassification in mediation analysis which consider the product method (Table 1), we focus on the difference method as it is the method of choice in most epidemiologic studies, simple to implement, and robust to misspecification of the exposure-mediator relationship.[6] Moreover, almost all prior work in Table 1 (except for Ssenkusu[12]) considered mediation analysis with a known measurement error process or conducted sensitivity analysis over a range of assumed parameter values that characterize the degree of measurement error. In this article, instead of assuming known measurement error model parameters, as is often done in sensitivity analysis, we work under the main study/validation study design,[19] where a gold standard measurement of the exposure is obtained in a validation study that allows us to estimate the parameters of interest in the measurement error model. The main study/validation study design is commonly used in epidemiology. For instance, our motivating example investigates the effect of physical activity on the

risk of cardiovascular diseases among participants in the Health Professionals Follow-up Study (HPFS)[20] The exposure, physical activity, was assessed through questionnaires on frequency of common types of leisure-time physical activities during the previous year. The accuracy of the questionnaire responses were then validated with physical activity diaries in a validation study involving 238 participants.[21] In the validation study, the correlation between the questionnaire-based and diary-based physical activity scores was estimated to be 0.28, indicating the questionnaire-based activity data in the main study were subject to measurement error.

To reliably assess mediation with an error-prone continuous exposure in a main study/validation study design, we develop two bias correction approaches, one based on the regression calibration[22] and the other based on the expected estimating equations.[23] We first explicitly derive a new set of bias formulas for estimating NIE and MP due to exposure measurement error, based on which a computationally convenient regression calibration approach is motivated. In addition, we also generalize the formulation of the expected estimation equation approach to potentially make more efficient use of the available main and validation study data. For both approaches, we also derive consistent sandwich variance estimators to quantify the uncertainty in the estimators and compare their operating characteristics through extensive simulations.

The remainder of this article is organized as follows. In Section 2, we review the difference method for mediation analysis without exposure measurement error. Section 3 introduces the measurement error model. Next, the proposed correction approaches are developed in Sections 4 and 5, where a brief discussion for the connections between the proposed approached are provided in Section 6. In Section 7, we provide extensive simulations to evaluate the empirical performance of the proposed approaches. In Section 8, we apply the proposed approaches to evaluate the extent to which the effect of vigorous physical activity on the risk of cardiovascular diseases is mediated by body mass index in the HPFS, followed by a brief discussion in Section 9.

2 | MEDIATION ANALYSIS WITHOUT EXPOSURE MEASUREMENT ERROR: A RECAP

2.1 | Mediation measures and assumptions

Let A be an exposure, M be a mediator, Y be an outcome, and $\boldsymbol{C}$ be a vector of covariates. A directed acyclic graph describing the causal relationship between those variables is shown in Figure 1, where the exposure exerts an effect on the outcome either through its impact on the mediator or by affecting the outcome directly. The mediation measures have been previously defined under the counterfactual framework.[24,25] Specifically, let $M(a)$ be the potential values of the mediator when setting the exposure, possibly contrary to fact, to the value a. We let $Y(a, m)$ be the potential value of the outcome when the exposure and mediator are set to a and m, respectively. Following Nevo et al,[5] the NIE can be defined as: $\text{NIE} = g(E[Y(a, M(a)) \mid \boldsymbol{C} = \boldsymbol{c}]) - g(E[Y(a, M(\widetilde{a})) \mid \boldsymbol{C} = \boldsymbol{c}])$, where $g(.)$ is the link function given by the outcome regression model. Common choices of $g(.)$ include the identity and log functions when the outcome is continuous and binary,

leading to the NIE defined on an identity scale and log risk ratio scale, respectively. The NIE measures the extent to which the conditional mean of the outcome on the scale of the g-function would change if the mediator were changed from the level that would be observed under $\tilde{a}$ vs a but exposure is fixed at level a. The NDE, defined as $g(E[Y(a, M(\tilde{a})) \mid \boldsymbol{C} = \boldsymbol{c}]) - g(E[Y(\tilde{a}, M(\tilde{a})) \mid \boldsymbol{C} = \boldsymbol{c}])$, measures how much the mean of the outcome on the scale of the g-function would change if the exposure is set at level a vs $\tilde{a}$ but the mediator remaining fixed at the value it would have if the exposure was set to $\tilde{a}$. The TE, defined by $g(E[Y(a, M(a)) \mid \boldsymbol{C} = \boldsymbol{c}]) - g(E[Y(\tilde{a}, M(\tilde{a})) \mid \boldsymbol{C} = \boldsymbol{c}])$, is the total of NIE and NDE. Finally, the MP is given by the ratio of NIE and TE, and measure the relative importance of the mediator in explaining the observed exposure-outcome relationship. Throughout, we requires several standard assumptions applied to mediation analysis, including the consistency assumption, the composition assumption, and the following four no unmeasured confounding assumptions: (i) $Y(a,\ m) \perp A \mid \boldsymbol{C}$, (ii)$Y(a, m) \perp M \mid A, \boldsymbol{C}$, (iii)$M(a) \perp A \mid \boldsymbol{C}$, and (iv)$Y(a,\ m) \perp M(\tilde{a}) \mid \boldsymbol{C}$. Detail explanations of these assumptions are shown in VanderWeele and Vansteelandt.[26]

2.2 | The difference method

The difference method[1,5] is a commonly used approach to evaluate mediation, which considers the following two generalized linear models for the conditional mean of outcome, both without and with inclusion of the mediator in the model:

$$g(\mathbb{E}[Y \mid A,\ \boldsymbol{C}]) = \alpha_0 + \alpha_1 A + \boldsymbol{\alpha}_3^T \boldsymbol{C}, \tag{1}$$

$$g(\mathbb{E}[Y \mid A, M, \boldsymbol{C}]) = \beta_0 + \beta_1 A + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{C}, \tag{2}$$

where $g(.)$ is the link function. These two models may be technically incompatible as they target a same response variable, Y. Jiang and VanderWeele[27] and Nevo et al[5] show that (1) is compatible with (2) under the following scenarios: (A) Scenario I: Y is continuous and is linear on the identity link scale (ie, $g(x) = x$); (B) Scenario II: Y is binary and its conditional mean is linear on the log scale (ie, $g(x) = \log(x)$), and (1) is a good approximation of the marginal mean induced from (2) under the following scenario, (C) Scenario III: Y is a rare binary outcome and its conditional mean is linear on the logistic link scale (ie, $g(x) = \log(x/(1-x))$). The mediation measures, including NIE (originally called the *indirect effect*), NDE (originally called the *direct effect*), TE, and MP, were originally defined outside of the counterfactual framework given in Section 2.1. Specifically, the NIE and NDE defined for A in changing from $\tilde{a}$ to a can be represented as functions of the regression parameters α_1 and β_1 in (1) and (2): $\text{NIE} = (\alpha_1 - \beta_1)(a - \tilde{a})$ and $\text{NDE} = \beta_1(a - \tilde{a})$, as shown in Baron and Kenny.[1] It follows that $\text{TE} = \alpha_1(a - \tilde{a})$ and $\text{MP} = 1 - \beta_1/\alpha_1$. In this article, and without loss of generality and unless otherwise specified, we set $a - \tilde{a} = 1$ such that the mediation measures are defined for one unit increase of A. More recently, Jiang and

VanderWeele[27] and Nevo et al[5] prove that, for either Scenario I, II, or III, the expressions of mediation measures shown above coincide with the mediation measures defined under the counterfactual framework described in Section 2.1, if the consistency, composition, and no unmeasured confounding assumptions hold. In other words, the results given by the difference method have a well-defined causal interpretation under these structural assumptions. Here and throughout, we shall focus on Scenarios I and II, where Scenario III can be seen as a special case of Scenario II by noticing that the logistic link function is a good approximation to the log link function when the outcome is rare.

In a study where the exposure, A, is perfectly measured, the observed data consists of n_1 independent observations $\{Y_i, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i\}, i = 1, \ldots, n_1$. Henceforth, we shall refer to this study as the main study (MS), in contrast to the validation study introduced below. As shown in Nevo et al,[5] the regression coefficients $\boldsymbol{\alpha} = \left[\alpha_0, \alpha_1, \boldsymbol{\alpha}_3^T\right]^T$ in model (1) and $\boldsymbol{\beta} = \left[\beta_0, \beta_1, \beta_2, \boldsymbol{\beta}_3^T\right]^T$ in model (2) can be estimated by separately solving the estimating equations $\sum_{i=1}^{n_1} \mathbb{U}_{\boldsymbol{\alpha}}(Y_i, A_i, \boldsymbol{C}_i) = 0$ and $\sum_{i=1}^{n_1} \mathbb{U}_{\boldsymbol{\beta}}(Y_i, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i) = 0$, where

$$\mathbb{U}_{\boldsymbol{\alpha}}(Y_i, A_i, \boldsymbol{C}_i) = \boldsymbol{U}_{i1} V_{i1}^{-1} \left\{ Y_i - g^{-1}\left(\left[1, A_i, \boldsymbol{C}_i^T\right]\boldsymbol{\alpha}\right)\right\}, \tag{3}$$

$$\mathbb{U}_{\boldsymbol{\beta}}(Y_i, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i) = \boldsymbol{U}_{i2} V_{i2}^{-1} \left\{ Y_i - g^{-1}\left(\left[1, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i^T\right]\boldsymbol{\beta}\right)\right\}, \tag{4}$$

$\boldsymbol{U}_{i1} = \partial g^{-1}\left(\left[1, A_i, \boldsymbol{C}_i^T\right]\boldsymbol{\alpha}\right)/\partial\boldsymbol{\alpha}$, $\boldsymbol{U}_{i2} = \partial g^{-1}\left(\left[1, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i^T\right]\boldsymbol{\beta}\right)/\partial\boldsymbol{\beta}$, V_{i1} and V_{i2} are working variances for the error terms, $\epsilon_{1i} = Y_i - g^{-1}\left(\left[1, A_i, \boldsymbol{C}_i^T\right]\boldsymbol{\alpha}\right)$, and $\epsilon_{2i} = Y_i - g^{-1}\left(\left[1, A_i, \boldsymbol{M}_i, \boldsymbol{C}_i^T\right]\boldsymbol{\beta}\right)$, respectively. In Scenario I, we set $V_{i1} = V_{i2} = 1$ such that (3) and (4) provide the ordinary least squares estimators. In Scenario II, we set $V_{i1} = e^{\left[1, A_i, C_i^T\right]\boldsymbol{\alpha}} \times \left(1 - e^{\left[1, A_i, M_i C_i^T\right]\boldsymbol{\beta}}\right)$ and $V_{i2} = e^{\left[1, A_i, C_i^T\right]\boldsymbol{\alpha}} \times \left(1 - e^{\left[1, A_i, M_i C_i^T\right]\boldsymbol{\beta}}\right)$ such that (3) and (4) will be the likelihood scores for $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$. Once $\hat{\boldsymbol{\alpha}}$ and $\hat{\boldsymbol{\beta}}$ are obtained, one can substitute $\hat{\alpha}_1$ and $\hat{\beta}_1$ into the expressions for the mediation measures to obtain their corresponding estimators, that is, $\widehat{\mathrm{NIE}} = \left(\hat{\alpha}_1 - \hat{\beta}_1\right)\left(a - \tilde{a}\right)$, $\widehat{\mathrm{NDE}} = \hat{\beta}_1\left(a - \tilde{a}\right)$, $\widehat{\mathrm{TE}} = \hat{\alpha}_1\left(a - \tilde{a}\right)$, and $\widehat{\mathrm{MP}} = 1 - \hat{\beta}_1/\hat{\alpha}_1$. The variance-covariance matrix of $\hat{\boldsymbol{\phi}} = \left[\hat{\alpha}_1, \hat{\beta}_1\right]^T$ can be estimated by the sandwich variance approach, denoted by $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}}$. Then, the estimated asymptotic variance of the mediation measure estimators can be obtained by the multivariate delta method: $\widehat{\mathrm{Var}}\left(\widehat{\mathrm{NIE}}\right) = \boldsymbol{\theta}_1 \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}} \boldsymbol{\theta}_1^T$, $\widehat{\mathrm{Var}}\left(\widehat{\mathrm{NDE}}\right) = \boldsymbol{\theta}_2 \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}} \boldsymbol{\theta}_2^T$, $\widehat{\mathrm{Var}}\left(\widehat{\mathrm{TE}}\right) = \boldsymbol{\theta}_3 \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}} \boldsymbol{\theta}_3^T$, and $\widehat{\mathrm{Var}}\left(\widehat{\mathrm{MP}}\right) = \boldsymbol{\theta}_4 \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}} \boldsymbol{\theta}_4^T$, where $\boldsymbol{\theta}_1 = [a - \tilde{a}, \tilde{a} - a]^T$, $\boldsymbol{\theta}_2 = [0, a - \tilde{a}]^T$, $\boldsymbol{\theta}_3 = [a - \tilde{a}, 0]^T$, and $\boldsymbol{\theta}_4 = \left[\hat{\beta}_1/\hat{\alpha}_1^2, -1/\hat{\alpha}_1\right]^T$. Finally, a $(1 - \alpha)$-level asymptotic confidence interval for τ can be obtained as $\left(\hat{\tau} - z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}\left(\hat{\tau}\right)}, \hat{\tau} + z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}\left(\hat{\tau}\right)}\right)$, where τ can be NIE, NDE, TE, and MP, and $z_{1-\alpha/2}$ is the $(1 - \alpha/2)$th quantile for a standard normal distribution.

3 | DEMYSTIFY THE IMPACT OF EXPOSURE MEASUREMENT ERROR

3.1 | Measurement error methods

In practice, the true exposure, A, may be mismeasured in the main study and, instead, an error-prone surrogate A^* is observed; that is, only $\{Y_i, A_i^*, M_i, \boldsymbol{C}_i\}, i = 1, \ldots, n_1$, is available. Meanwhile, there is often a validation study for us to characterize the relationship between the true exposure A and its surrogate A^*. If the validation study is part of the primary study sample and includes outcome data Y_i, we refer to it as an internal validation study (IVS); otherwise, if the validation study is taken from a different set of participants, we refer to it as an external validation study (EVS).[19] Specifically, an IVS consists of data $\{Y_i, A_i, A_i^*, M_i, \boldsymbol{C}_i\}, i = n_1 + 1, \ldots, n$, whereas an EVS consists of data $\{A_i, A_i^*, M_i, \boldsymbol{C}_i\}, i = n_1 + 1, \ldots, n$. We make the *surrogacy* assumption such that $P(Y_i \mid A_i, A_i^*, \boldsymbol{C}_i) = P(Y_i \mid A_i, \boldsymbol{C}_i)$ and $P(Y_i \mid A_i, A_i^*, M_i, \boldsymbol{C}_i) = P(Y_i \mid A_i, M_i, \boldsymbol{C}_i)$ to ensure that the surrogate value A_i^* is not informative for predicting Y_i once we know the true exposure A_i. With a MS/EVS design, we further assume transportability such that the conditional distribution of A_i, A_i^*, M_i given $\boldsymbol{C}_i$ in the validation samples is same as which would have been observed in the main study to allow that key parameters estimation in the EVS can be validly transported to identify and obtain consistent estimates of the mediation measures.[28] This empirically unverifiable assumption is usually reasonable for scenarios when the method of exposure assessment is similar in both study samples. To summarize, in either a MS/IVS or MS/EVS design, we have a total of n participants where the first n_1 participants are from the main study. Typically, the validation study size, $n_2 = n - n_1$, is much smaller than the main study size, n_1, because the true exposure is much more expensive to measure.

To utilize the validation study data for exposure measurement error correction, the next step is to fit an appropriate measurement error model connecting the true exposure, A, with its surrogate, A^*. We assume that the measurement error process can be characterized by the following two models for the true exposure, $f_1(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma})$ and $f_2(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\eta})$, where $\widetilde{\boldsymbol{C}}$ is a subset of $\boldsymbol{C}$ that are predictive of the exposure error process. Here, $f_1(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma})$ describes the distribution of A conditional on the surrogate exposure A^* and covariates $\widetilde{\boldsymbol{C}}$ and $f_2(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma})$ describes the distribution of A conditional on the surrogate exposure A^*, mediator M, and covariates $\widetilde{\boldsymbol{C}}$. We use $f_1(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma})$ and $f_2(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\eta})$ to account for the measurement error-induced bias in (1) and (2), respectively. The unknown parameters, $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$, can be estimated by solving $\sum_{i=n_1+1}^{n} \mathbb{U}_{\gamma}(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i) = 0$ and $\sum_{i=n_1+1}^{n} \mathbb{U}_{\boldsymbol{\eta}}(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i) = 0$, which are assumed to satisfy the conditions for unbiased estimating equations, $\mathbb{E}[\mathbb{U}_{\gamma}(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i)] = 0$ and $\mathbb{E}[\mathbb{U}_{\boldsymbol{\eta}}(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i)] = 0$. A convenient choice is using the likelihood scores $\mathbb{U}_{\gamma}(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i) = \partial \log f_1(A_i \mid A_i^*, \widetilde{\boldsymbol{C}}_i; \boldsymbol{\gamma}) / \partial \boldsymbol{\gamma}$ and $\mathbb{U}_{\boldsymbol{\eta}}(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i) = \partial \log f_2(A_i \mid A_i^*, M_i, \widetilde{\boldsymbol{C}}_i; \boldsymbol{\eta}) / \partial \boldsymbol{\eta}$.

For example, we first consider $f_1(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma})$ and $f_2(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\eta})$ follow the linear measurement error models

$$f_1\left(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma}\right) \sim N\left(\gamma_0 + \gamma_1 A^* + \boldsymbol{\gamma}_3^T \widetilde{\boldsymbol{C}}, \sigma_\gamma^2\right), \tag{5}$$

$$f_2\left(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\eta}\right) \sim N\left(\eta_0 + \eta_1 A^* + \eta_2 M + \boldsymbol{\eta}_3^T \widetilde{\boldsymbol{C}}, \sigma_\eta^2\right), \tag{6}$$

where γ_1 and η_1 are so called calibration coefficients,[29] which measure the associations between A and A^* without and with adjustment for the mediator M. We may expect $\gamma_1 > 0$ and $\eta_1 > 0$ such that the true exposure and its measurement are positively associated. Spiegelman et al[19] have shown that the linear measurement error models provide a good fit for the measurement error process of dietary intake data. In Section 8, we observe that the linear measurement error models also provide an adequate fit for the measurement error process for physical activity. The regression coefficients, $\tilde{\boldsymbol{\gamma}} = \left[\gamma_0, \gamma_1, \boldsymbol{\gamma}_3^T\right]^T$ and $\tilde{\boldsymbol{\eta}} = \left[\eta_0, \eta_1, \eta_2, \boldsymbol{\eta}_3^T\right]^T$ can be estimated using the following likelihood scores,

$$\mathbb{U}_{\tilde{\gamma}}\left(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i\right) = \left[1, A_i^*, \widetilde{\boldsymbol{C}}_i^T\right]^T \left\{A_i - \left(\left[1, A_i^*, \widetilde{\boldsymbol{C}}_i^T\right]\tilde{\boldsymbol{\gamma}}\right)\right\},$$

$$\mathbb{U}_{\tilde{\eta}}\left(A_i, A_i^*, M_i, \boldsymbol{C}_i\right) = \left[1, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i^T\right]^T \left\{A_i - \left(\left[1, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i^T\right]\tilde{\boldsymbol{\eta}}\right)\right\}.$$

Comparing the above two equations to (3) and (4), we find that the construction of the estimating scores for $\tilde{\gamma}$ and $\tilde{\boldsymbol{\eta}}$ are identical to that for outcome regression coefficients $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ with an identity link function. Therefore, we use the difference method under Scenario I with the outcome and mediator variable replaced by A and A^*, respectively, to estimate the regression coefficients, $\tilde{\boldsymbol{\gamma}}$ and $\tilde{\boldsymbol{\eta}}$, in the linear measurement error model. The variance terms, σ_γ^2 and σ_η^2, can be estimated by the sample variances of the regression residuals. Note that (5) and (6) require that the the measurement error is normally distributed. One can fit measurement error models in the validation study and empirically assess the aspects of the distribution of estimated residuals to explore whether there is evidence suggesting violation of the normality assumption.

3.2 | Bias of the mediation measure estimators under linear measurement error models

When outcome models (1) and (2) are fit with A^* in place of A, then the corresponding mediation measure estimators will be biased and inconsistent. Here, we derive the limiting values of naive mediation measure estimators when the exposure follows linear measurement error models (5) and (6). Let $\widehat{\alpha}_1^*$ and $\widehat{\beta}_1^*$ be naive estimators of the regression coefficients α_1 and β_1 in (1) and (2) when A^* is used in place of A. We define $\widehat{\mathrm{NIE}}^*$ as the naive estimator of NIE, and $\widehat{\mathrm{NDE}}^*$, $\widehat{\mathrm{TE}}^*$, and $\widehat{\mathrm{MP}}^*$ are similarly defined. The following theorem presents the asymptotic relative bias (*RelBias*) of the naive mediation measure estimators, defined as the ratio of the asymptotic bias and the true mediation measure value:

Theorem 1. *For an outcome modeled with either an identity or a log link function (Scenario I or II),* $\widehat{\alpha}_1^* \xrightarrow{p} \alpha_1\gamma_1$ *and* $\widehat{\beta}_1^* \xrightarrow{p} \beta_1\eta_1$ *if measurement error models* (5) *and* (6) *hold, where* '$\xrightarrow{p}$' *denotes convergence in probability. In addition, the relative bias for each mediation measure has an analytical representation given by*

$$RelBias\left(\widehat{NIE}^*\right) = \gamma_1 - 1 + \left(\frac{1}{MP} - 1\right)(\gamma_1 - \eta_1),$$

$$RelBias\left(\widehat{NDE}^*\right) = \eta_1 - 1,$$

$$RelBias\left(\widehat{TE}^*\right) = \gamma_1 - 1,$$

$$RelBias\left(\widehat{MP}^*\right) = \left(\frac{1}{MP} - 1\right)\left(1 - \frac{\eta_1}{\gamma_1}\right).$$

Proof of this theorem is given in Appendix A in the Supplementary Material. Clearly, the naive estimators will be unbiased when the calibration coefficients (γ_1 and η_1) are both 1. The biases in the naive estimators have a particular direction when γ_1 and/or η_1 do not equal to 1. Specifically, the naive NIE estimator will converge to a negative relative bias when $\gamma_1 < 1$ and $\gamma_1 < \eta_1$, and converge to a positive relative bias when $\gamma_1 > 1$ and $\gamma_1 > \eta_1$. The naive NDE and TE estimators will be biased towards the null if $\eta_1 < 1$ and $\gamma_1 < 1$, respectively, and will be biased away from the null if $\eta_1 > 1$ and $\gamma_1 > 1$, respectively. The naive MP estimator will have a negative relative bias when $\eta_1 > \gamma_1$ and have a positive relative bias when $\eta_1 < \gamma_1$. Interestingly, the naive MP estimator will also present small relative bias when $\eta_1 \approx \gamma_1$ and MP is close to 1, regardless of the magnitudes of η_1 and γ_1.

Remark 1. In some cases, the normality assumption in measurement error models (5) and (6) may not hold even though the conditional means given by (5) and (6) are correct. If only the conditional means in (5) and (6) are correct, we show in Appendix B that the probability limits for $\widehat{\alpha}_1^*$ and $\widehat{\beta}_1^*$ and the asymptotic relative bias formulas for mediation measures shown in Theorem 1 still hold exactly under Scenario I and hold approximately under Scenario II when both $\left\{\mathrm{Var}\left(A \mid A^*, \widetilde{\boldsymbol{C}}\right), \mathrm{Var}\left(A \mid A^*, M, \widetilde{\boldsymbol{C}}\right)\right\}$ are small and/or both $\{|\beta_1|, |\alpha_1|\}$ in the outcome models are small. In other words, when the conditional means in (5) and (6) are true, Theorem 1 still hold in Scenario I regardless of whether the measurement error is normally distributed and Theorem 1 still approximately hold in Scenario II when the measurement error is small and/or the exposure effect on the outcome is not large.

4 | USING REGRESSION CALIBRATION TO ADDRESS EXPOSURE MEASUREMENT ERROR

We can leverage the idea of regression calibration (more specifically the Rosner-Spiegelman-Willett-type or RSW-type regression calibration[30,31]) to correct for the measurement error induced bias. As suggested by Rosner, Willett, and Spiegelman,[30] we can fit outcome models (1) and (2) based on the surrogate exposure and then bias-corrects the regression coefficients based on the bias formulas in Theorem 1. Specifically, one can construct consistent estimators of α_1 and β_1 by the following three steps under a MS/EVS design. In step 1, we implement the standard difference method in the main study with $Y, A^*, M, \boldsymbol{C}$ as the outcome, exposure, mediator, and a vector of confounders, respectively, to obtain naive estimators of $\boldsymbol{\phi} = [\alpha_1, \beta_1]$, denoted by $\widehat{\boldsymbol{\phi}}^* = \left[\widehat{\alpha}_1^*, \widehat{\beta}_1^*\right]$. In step 2, we implement a standard difference method in the validation study with $A, A^*, M, \widetilde{\boldsymbol{C}}$ as the outcome, exposure, mediator, and a vector of confounders in the outcome model, respectively, to estimate $[\gamma_1, \eta_1]$ in the measurement error models, denoted by $[\hat{\gamma}_1, \hat{\eta}_1]$. In step 3, following Theorem 1, a consistent estimator for $\boldsymbol{\phi} = [\alpha_1, \beta_1]^T$ can be constructed by $\hat{\boldsymbol{\phi}}_{RC} = \left[\widehat{\alpha}_{1,RC}, \widehat{\beta}_{1,RC}\right]^T$, where $\widehat{\alpha}_{1,RC} = \frac{\widehat{\alpha}_1^*}{\widehat{\gamma}_1}$ and $\widehat{\beta}_{1,RC} = \frac{\widehat{\beta}_1^*}{\widehat{\eta}_1}$. The following theorem clarifies the asymptotic properties of $\widehat{\boldsymbol{\phi}}_{RC}$, where the proof is deferred in Appendix C of the Supplementary Material.

Theorem 2. *Suppose that measurement error models* (5) *and* (6) *hold, then* $\hat{\boldsymbol{\phi}}_{RC}$ *is a consistent and asymptotically normal estimator of* $\boldsymbol{\phi}$, *under the regularity conditions outlined in* Appendix C.1 *of the* Supplementary Material.

The variance-covariance matrix for $\widehat{\boldsymbol{\phi}}_{RC}$ consists of two components: the first is the contribution to the variance due to estimating $\left[\widehat{\alpha}_1^*, \widehat{\beta}_1^*\right]$ in the main study and the second is the contribution to the variance due to estimating $[\hat{\gamma}_1, \hat{\eta}_1]$ in the validation study. As shown at the end of Appendix C.1 in the Supplementary Material, the variance-covariance matrix of $\widehat{\phi}_{RC}$ can be consistently estimated by

$$\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}RC} = \begin{bmatrix} \frac{\widehat{\mathrm{Var}}\left(\widehat{\alpha}_1^*\right)}{\hat{\gamma}_1^2} + \frac{\hat{\alpha}_1^{*2}\widehat{\mathrm{Var}}(\hat{\gamma}_1)}{\hat{\gamma}_1^4} & \frac{\widehat{\mathrm{Cov}}\left(\widehat{\alpha}_1^*, \widehat{\beta}_1^*\right)}{\hat{\gamma}_1\hat{\eta}_1} + \frac{\hat{\alpha}_1^*\hat{\beta}_1^*\widehat{\mathrm{Cov}}(\hat{\gamma}_1, \hat{\eta}_1)}{\hat{\gamma}_1^2\hat{\eta}_1^2} \\ \frac{\widehat{\mathrm{cov}}\left(\widehat{\alpha}_1^*, \widehat{\beta}_1^*\right)}{\hat{\gamma}_1\hat{\eta}_1} + \frac{\hat{\alpha}_1^*\hat{\beta}_1^*\widehat{\mathrm{cov}}(\hat{\gamma}_1, \hat{\eta}_1)}{\hat{\gamma}_1^2\hat{\eta}_1^2} & \frac{\widehat{\mathrm{Var}}\left(\widehat{\beta}_1^*\right)}{\hat{\eta}_1^2} + \frac{\hat{\beta}_1^{*2}\widehat{\mathrm{Var}}(\hat{\eta}_1)}{\hat{\eta}_1^4} \end{bmatrix},$$

where $\widehat{\mathrm{Var}}(\cdot)$ and $\widehat{\mathrm{Cov}}(\cdot, \cdot)$ are the variance and covariance estimators for $\left[\widehat{\alpha}_1^*, \widehat{\beta}_1^*\right]$ and $[\hat{\gamma}_1, \hat{\eta}_1]$, which can be obtained from the output from fitting models (3) and (4), and (5) and (6) in a standard software supporting difference method (for example, the `R` package `GEEmediate`). Once we obtain $\hat{\boldsymbol{\phi}}_{RC} = \left[\widehat{\alpha}_{1,RC}, \widehat{\beta}_{1,RC}\right]^T$ with its variance-covariance matrix $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\phi}_{RC}}$, we can substitute $\widehat{\boldsymbol{\phi}}_{RC}$ into the mediation measure expressions to obtain their corresponding point estimators, and finally, we can apply the multivariate delta method introduced at the end of Section 2.2 in $\widehat{\boldsymbol{\Sigma}}_{\phi_{RC}}$ to calculate the variance and interval estimators.

In a MS/IVS design, we can further improve the efficiency in estimating $\phi = [\alpha_1, \beta_1]$ by using information on the outcome in the validation study. Similar to Spiegelman et al[22] and Shu and Yi,[32] we propose a more efficient estimator for $\boldsymbol{\phi}$ through a weighted combination of the two estimators, that is, $\widehat{\boldsymbol{\phi}}_{RC,I} = W_{RC}\widehat{\boldsymbol{\phi}}_{RC} + W_I\widehat{\boldsymbol{\phi}}_I$, where $\widehat{\boldsymbol{\phi}}_{RC}$ is the estimator for $\boldsymbol{\phi}$ given in Step 3, $\widehat{\phi}_I$ is the estimator for $\boldsymbol{\phi}$ from applying the difference method on the validation study alone, W_{RC} and W_I are the weights. The following theorem shows that $\widehat{\boldsymbol{\phi}}_{RC,I}$ is consistent for any choice of W_{RC} and W_I satisfying the constraint $W_{RC} + W_I = I$, where I is a 2×2 identity matrix.

Theorem 3. *Suppose that measurement error models* (5) *and* (6) *hold and* $W_{RC} + W_I = I$, *then* $\hat{\boldsymbol{\phi}}_{RC,I}$ *is a consistent and asymptotically normal estimator of* $\boldsymbol{\phi}$, *under the regularity conditions outlined in* Appendix C.2 *of the* Supplementary Material.

Proof of Theorem 3 is given in Appendix C.2 of the Supplementary Material. Spiegelman et al[22] suggested weighting $\hat{\boldsymbol{\phi}}_{RC}$ and $\hat{\boldsymbol{\phi}}_I$ by the inverse of their variance matrix, that is, $W_{RC} = \left(\widehat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}RC} + \widehat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}I}\right)^{-1}\widehat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}RC}$ and $W_I = \left(\widehat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}RC} + \widehat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}I}\right)^{-1}\hat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}I}$, where $\widehat{\boldsymbol{\Sigma}}_{\hat{\phi}RC}$ and $\widehat{\boldsymbol{\Sigma}}_{\hat{\phi}I}$ are the estimated variance-covariance matrices for $\hat{\boldsymbol{\phi}}_{RC}$ and $\hat{\boldsymbol{\phi}}_I$, respectively. Since $\hat{\boldsymbol{\phi}}_{RC}$ and $\hat{\boldsymbol{\phi}}_I$ are asymptotically uncorrelated (see Appendix C.3 in the Supplementary Material), the variance-covariance matrix for this inverse-variance weighted estimator, $\hat{\boldsymbol{\phi}}_{RC}$, can be given approximately by $\hat{\boldsymbol{\Sigma}}_{\hat{\phi}RC,I} = \left(\hat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}RC} + \hat{\boldsymbol{\Sigma}}^{-1}_{\hat{\phi}I}\right)^{-1}$. Once we have $\hat{\boldsymbol{\phi}}_{RC,I}$ with its variance-covariance matrix $\hat{\boldsymbol{\Sigma}}_{\hat{\phi}RC,I}$, we can obtain the point, variance, and interval estimators of the mediation measures by the multivariate delta method, as described above. The inverse-variance weight used in $\hat{\boldsymbol{\phi}}_{RC,I}$ leads to the asymptotically most efficient estimator for $\boldsymbol{\phi}$ among all linear combinations of $\widehat{\boldsymbol{\phi}}_{RC}$ and $\hat{\boldsymbol{\phi}}_I$, as proven in Spiegelmant et al.[22] Therefore, $\widehat{\boldsymbol{\phi}}_{RC,I}$ is at least as efficient as $\widehat{\boldsymbol{\phi}}_{RC}$ under a MS/IVS design. An empirical efficiency comparison between $\hat{\boldsymbol{\phi}}_{RC,I}$ and $\hat{\boldsymbol{\phi}}_{RC}$ is provided in Appendix C.4 in the Supplementary Material, which suggests that the efficiency loss of $\hat{\boldsymbol{\phi}}_{RC}$ is usually non-negligible. Since $\widehat{\boldsymbol{\phi}}_{RC,I}$ more efficiently use the information from both the main study and validation study, in this article we shall always use $\hat{\boldsymbol{\phi}}_{RC,I}$ to calculate the mediation measures under a MS/IVS design.

5 | USING ESTIMATING EQUATIONS TO ADDRESS EXPOSURE MEASUREMENT ERROR

5.1 | Expected estimating equations

In addition to regression calibration that relies upon the simple results in Theorem 1, we propose an additional method to correct for exposure measurement error using the expected estimating equations, which might improve the efficiency of the mediation measure estimators by making additional distributional assumptions such as in Scenario I we additionally assume the error terms in the outcome models following a common normal distribution. Because we observe A_i^* in place of A_i in the main study, we cannot compute the complete-data estimating estimation components (1) and (2) from the main study. Instead, Wang and Pepe[23] suggested to construct the estimating estimation as the expectation of the

complete-data estimating equation conditional on the observed data, referred to as expected estimating equation (EEE), which is unbiased by iterated expectation and depends only upon the observed data. In a MS/IVS design, we use the EEEs for the main study and the complete-data estimating equations for the validation study. Specifically, consider the following estimating equations for $\widehat{\boldsymbol{\alpha}}$ and $\widehat{\boldsymbol{\beta}}$, respectively,

$$\sum_{i=1}^{n}(1-R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\alpha}(Y_i,A_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,\boldsymbol{C}_i\right]+R_i\mathbb{U}_{\alpha}(Y_i,A_i,\boldsymbol{C}_i)=\mathbf{0}, \tag{7}$$

$$\sum_{i=1}^{n}(1-R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\beta}(Y_i,A_i,M_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,M_i,\boldsymbol{C}_i\right]+R_i\mathbb{U}_{\beta}(Y_i,A_i,M_i,\boldsymbol{C}_i)=\mathbf{0}, \tag{8}$$

where $R_i=1$ if the participants is in the validation study (ie, $i>n_1$), $R_i=0$ if the participants is in the main study (ie, $i\le n_1$), and the expectation $\mathbb{E}_X[\cdot\mid Z]$ is taken with respect to the distribution of X conditional on Z. Evaluation of the above observed-data estimating equations involves calculation of expectations of the forms, $\mathbb{E}_{A_i}\left[g(Y_i,A_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,\boldsymbol{C}_i\right]$ and $\mathbb{E}_{A_i}\left[g(Y_i,A_i,M_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,M_i,\boldsymbol{C}_i\right]$, for some functions $g(Y_i,A_i,\boldsymbol{C}_i)$ and $g(Y_i,A_i,M_i,\boldsymbol{C}_i)$. Using the Bayes' rules and the surrogacy assumption, we can rewrite the expectations as

$$\mathbb{E}_{A_i}\left[g(Y_i,A_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,\boldsymbol{C}_i\right]=\frac{\int_a g(Y_i,a,\boldsymbol{C}_i)P(Y_i\mid a,\boldsymbol{C}_i)f_1\left(a\mid A_i^*,\widetilde{\boldsymbol{C}}_i;\boldsymbol{\gamma}\right)da}{\int_a P(Y_i\mid a,\boldsymbol{C}_i)f_1\left(a\mid A_i^*,\widetilde{\boldsymbol{C}}_i;\boldsymbol{\gamma}\right)da}, \tag{9}$$

$$\mathbb{E}_{A_i}\left[g(Y_i,A_i,M_i,\boldsymbol{C}_i)\mid Y_i,A_i^*,M_i,\boldsymbol{C}_i\right]=\frac{\int_a g(Y_i,a,M_i,\boldsymbol{C}_i)P(Y_i\mid a,M_i,\boldsymbol{C}_i)f_2\left(a\mid A_i^*,M_i,\widetilde{\boldsymbol{C}}_i;\boldsymbol{\eta}\right)da}{\int_a P(Y_i\mid a,M_i,\boldsymbol{C}_i)f_2\left(a\mid A_i^*,M_i,\widetilde{\boldsymbol{C}}_i;\boldsymbol{\eta}\right)da}, \tag{10}$$

which are functions of the measurement error models (5) and (6), and the outcome distributions $P(Y\mid A,\boldsymbol{C})$ and $P(Y\mid A,M,C)$. Generally, the above expectations do not have explicit solutions but can be numerically calculated by standard method of numerical integration. However, when A follows the measurement error models (5) and (6), the above expectations have explicit expressions, which are derived in Appendix D.1 in the Supplementary Material. To calculate (9) and (10), we must fully specify $P(Y\mid A,\boldsymbol{C})$ and $P(Y\mid A,M,\boldsymbol{C})$. With binary data, as in Scenario II, the conditional mean models (1) and (2) fully determine $P(Y\mid A,\boldsymbol{C})$ and $P(Y\mid A,M,\boldsymbol{C})$, as can be seen by noting that $P(Y=1\mid A,\boldsymbol{C})=\mathbb{E}[Y\mid A,\boldsymbol{C}]$ and $P(Y=1\mid A,M,\boldsymbol{C})=\mathbb{E}[Y\mid A,M,\boldsymbol{C}]$. In Scenario I, however, additional assumptions are needed to specify $P(Y\mid A,\boldsymbol{C})$ and $P(Y\mid A,M,\boldsymbol{C})$. When empirically verifiable, we can set $Y\mid A,\boldsymbol{C}\sim N\left(\mathbb{E}\left[Y\mid A,\boldsymbol{C}\right],\sigma_{\alpha}^2\right)$ and

$Y \mid A, M, \boldsymbol{C} \sim N\left(\mathbb{E}\left[Y \mid A, M, \boldsymbol{C}\right], \sigma_\beta^2\right)$, where $\mathbb{E}[Y \mid A, \boldsymbol{C}]$ and $\mathbb{E}[Y \mid A, M, \boldsymbol{C}]$ are given by (1) and (2), and σ_α^2 and σ_β^2 denote the conditional variances for the outcome in the two models.

Notice that Equation (7) for estimating $\boldsymbol{\alpha}$ also depends on $\boldsymbol{\gamma}$ (and σ_α^2 if Scenario I) and the Equation (8) for estimating $\boldsymbol{\beta}$ also depends on $\boldsymbol{\eta}$ (and σ_β^2 if Scenario I). Motivated by the formulation of the estimating equations for estimating $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$, we propose the following estimating equations for $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$,

$$\sum_{i=1}^{n} (1 - R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\boldsymbol{\gamma}}\left(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i\right) \mid Y_i, A_i^*, \boldsymbol{C}_i\right] + R_i \mathbb{U}_{\boldsymbol{\gamma}}\left(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i\right) = \mathbf{0}, \tag{11}$$

$$\sum_{i=1}^{n} (1 - R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\boldsymbol{\eta}}\left(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i\right) \mid Y_i, A_i^*, M_i, \boldsymbol{C}_i\right] + R_i \mathbb{U}_{\boldsymbol{\eta}}\left(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i\right) = \mathbf{0}, \tag{12}$$

where $\mathbb{U}_{\boldsymbol{\gamma}}\left(A_i, A^*, \widetilde{\boldsymbol{C}}_i\right)$ and $\mathbb{U}_{\boldsymbol{\eta}}\left(A_i, A^*, M_i, \widetilde{\boldsymbol{C}}_i\right)$ are the components for the complete-data estimating equations for $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$, respectively. Similarly, the additional parameters σ_α^2 and σ_β^2 used in Scenario I can be estimated by solving

$$\sum_{i=1}^{n} (1 - R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\sigma_\alpha^2}(Y_i, A_i, \boldsymbol{C}_i) \mid Y_i, A_i^*, \boldsymbol{C}_i\right] + R_i \mathbb{U}_{\sigma_\alpha^2}(Y_i, A_i, \boldsymbol{C}_i) = \mathbf{0}, \tag{13}$$

$$\sum_{i=1}^{n} (1 - R_i)\mathbb{E}_{A_i}\left[\mathbb{U}_{\sigma_\beta^2}(Y_i, A_i, M_i, \boldsymbol{C}_i) \mid Y_i, A_i^*, M_i, \boldsymbol{C}_i\right] + R_i \mathbb{U}_{\sigma_\beta^2}(Y_i, A_i, M_i, \boldsymbol{C}_i) = \mathbf{0}, \tag{14}$$

where $\mathbb{U}_{\sigma_\alpha^2}(Y_i, A_i, \boldsymbol{C}_i) = \sigma_\alpha^2 - \left\{Y_i - \left[1, A_i, \boldsymbol{C}_i^T\right]\boldsymbol{\alpha}\right\}^2$ and $\mathbb{U}_{\sigma_\beta^2}(Y_i, A_i, M_i, \boldsymbol{C}_i) = \sigma_\beta^2 - \left\{Y_i - \left[1, A_i, M_i, \boldsymbol{C}_i^T\right]\boldsymbol{\beta}\right\}^2$ are the complete-data likelihood scores for σ_α^2 and σ_β^2, respectively. Calculation of the expected scores in (11) and (13) follow (9) and calculation of the expected scores in (12) and (14) follow (10).

Denote all the unknown parameters as $\boldsymbol{\Theta}$, which includes $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ for the outcome models (1) and (2), $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$ for the measurement error models $f_1\left(A \mid A^*, \widetilde{\boldsymbol{C}}; \boldsymbol{\gamma}\right)$ and $f_2\left(A \mid A^*, M, \widetilde{\boldsymbol{C}}; \boldsymbol{\eta}\right)$, and the parameters σ_α^2 and σ_β^2 when relevant (Scenario I). Write all the estimating Equations (7), (8), (11)–(14) as $\sum_{i=1}^{n} g_i(\boldsymbol{\Theta}) = 0$, then $\widehat{\boldsymbol{\Theta}}$ can be obtained by solving $\sum_{i=1}^{n} g_i(\boldsymbol{\Theta}) = 0$. We note that $\sum_{i=1}^{n} g_i(\boldsymbol{\Theta}) = 0$ can be divided into two groups of estimating equations with no common parameters, where the first group includes (7), (11), and (13) which depend on $\left[\boldsymbol{\alpha}, \boldsymbol{\gamma}, \sigma_\alpha^2\right]$ and

the second group includes (8), (12), and (14) which depend on $[\boldsymbol{\beta}, \boldsymbol{\eta}, \sigma_\beta^2]$. Therefore, $\boldsymbol{\Theta}$ can be consistently estimated by first solving (7), (11), and (13) simultaneously for $[\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\gamma}}, \hat{\sigma}_\alpha^2]$ and then solving (8), (12), and (14) simultaneously for $[\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\eta}}, \hat{\sigma}_\beta^2]$. Typically, each group of estimating equations does not have explicit solutions. In the application and simulation studies, we employed the Newton-Raphson method to numerically find their roots. The following theorem summarizes the asymptotic properties of $\widehat{\boldsymbol{\Theta}}$.

Theorem 4. *Assuming that measurement error models* (5) *and* (6) *are correctly specified, and for a continuous outcome (Scenario I), further assuming that error terms in outcome models* (1) *and* (2) *are normally distributed and homoskedastic, then,* $\widehat{\boldsymbol{\Theta}}$ *is a consistent and asymptotically normal estimator of* $\boldsymbol{\Theta}$, *under the regularity conditions outlined in* Appendix D.2 *of the* Supplementary Material.

Proof of Theorem 2 is provided in Appendix D.2. The variance-covariance matrix $\widehat{\boldsymbol{\Theta}}$ can be consistently estimated by

$$\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\Theta}} = \frac{1}{n} G_n^{-1}\left(\widehat{\boldsymbol{\Theta}}\right) V_n\left(\widehat{\boldsymbol{\Theta}}\right) G_n^{-1}\left(\widehat{\boldsymbol{\Theta}}\right),$$

where $G_n\left(\widehat{\boldsymbol{\Theta}}\right) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\partial g_i(\boldsymbol{\Theta})}{\partial \boldsymbol{\Theta}^T}\Big|_{\boldsymbol{\Theta}=\widehat{\boldsymbol{\Theta}}}\right]$ and $V_n\left(\widehat{\boldsymbol{\Theta}}\right) = \frac{1}{n}\sum_{i=1}^{n} g_i\left(\widehat{\boldsymbol{\Theta}}\right) g_i^T\left(\widehat{\boldsymbol{\Theta}}\right)$. Once we obtain $\widehat{\boldsymbol{\Theta}}$ and $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\Theta}}$, we can extract $\widehat{\boldsymbol{\phi}} = \left[\widehat{\alpha}_1, \widehat{\beta}_1\right]^T$ from $\widehat{\boldsymbol{\Theta}}$ and calculate the variance-covariance matrix of $\widehat{\boldsymbol{\phi}}$ based on $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\Theta}}$. Then, the point, variance, and interval estimators of the mediation measures can be obtained by the multivariate delta method shown at the end of Section 2.2.

5.2 | Reduced expected estimating equations

The EEE approach uses the main and validation studies together to estimate the unknown parameters of the measurement error models, $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$, as shown in (11) and (8). Alternatively, we could estimate $\boldsymbol{\gamma}$ and $\boldsymbol{\eta}$ based on the validation study only, that is, finding $\hat{\boldsymbol{\gamma}}$ and $\hat{\boldsymbol{\eta}}$ by solving the following reduced estimating equations

$$\sum_{i=1}^{n} R_i \mathbb{U}_{\boldsymbol{\gamma}}\left(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i\right) = \mathbf{0}, \tag{15}$$

$$\sum_{i=1}^{n} R_i \mathbb{U}_{\boldsymbol{\eta}}\left(A_i, A_i^*, M_i, \widetilde{\boldsymbol{C}}_i\right) = \mathbf{0}, \tag{16}$$

respectively and separately. Then, the other parameters in $\boldsymbol{\Theta}$ can be estimated by solving their corresponding estimating equations evaluated at $\boldsymbol{\gamma} = \hat{\boldsymbol{\gamma}}$ and $\boldsymbol{\eta} = \hat{\boldsymbol{\eta}}$. Specifically, we can obtain $[\hat{\boldsymbol{\alpha}}, \hat{\sigma}_\alpha^2]$ by solving (7) and (13), simultaneously, at $\boldsymbol{\gamma} = \hat{\boldsymbol{\gamma}}$ and obtain $[\hat{\boldsymbol{\beta}}, \hat{\sigma}_\beta^2]$ by solving

(8) and (14), simultaneously, at $\boldsymbol{\eta} = \hat{\boldsymbol{\eta}}$. We will denote this as the reduced EEE approach, in order to distinguish it with the full EEE approach introduced previous Section 5.1. Under the assumptions outlined in Theorem 4, one can also show that the reduced EEE is also a consistent and asymptotically normal estimator, following similar arguments in Appendix D.2 to prove Theorem 4. Then, the point, variance, and interval estimates of the mediation measures are similar to what we introduced in the previous subsection.

Compared with the full EEE, the reduced EEE can be substantially more computationally convenient, since now we estimate the measurement error model parameters and outcome model parameters separately, in contrast to the full EEE approach, which estimates them simultaneously. However, the statistical efficiency in estimating $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ might be compromised as we only use the validation study to estimate the measurement error model parameters. In fact, if the $A - Y$ associations conditional on (A^*, C) and $(A, \boldsymbol{M}, \boldsymbol{C})$ are weak (ie, $P(A \mid Y, A^*, \boldsymbol{C}) \approx P(A \mid A^*, \boldsymbol{C})$ and $P(A \mid Y, A^*, \boldsymbol{M}, \boldsymbol{C}) \approx P(A \mid A^*, \boldsymbol{M}, \boldsymbol{C})$), then the expected scores in (11) and (12), that is, $\mathbb{E}_{A_i}\left[\mathbb{U}_{\gamma}\left(A_i, A_i^*, \widetilde{\boldsymbol{C}}_i\right) \mid Y_i, A_i^*, \boldsymbol{C}_i\right]$ and $\mathbb{E}_{A_i}\left[\mathbb{U}_{\eta}\left(A_i, A_i^*, \boldsymbol{M}_i, \widetilde{\boldsymbol{C}}_i\right) \mid Y_i, A_i^*, \boldsymbol{M}_i, \boldsymbol{C}_i\right]$, are approximately equal to 0 (Appendix D.3 in the Supplementary Material). It follows that (11) and (15) are approximately the same, so are (12) and (16). Therefore, under these circumstances, it is likely that the efficiency loss is minimal. Our simulation studies also confirm that the reduced EEE approach has very similar finite-sample efficiency as compared to the full EEE, and therefore can be considered as a computationally convenient alternative for exposure measurement error correction in mediation analysis.

5.3 | Extension to the MS/EVS design

The full EEE and reduced EEE can be easily adapted for the a MS/EVS design. In this design, the outcome variable is typically not available in the validation study. Therefore, the components of the complete-data estimating equations $\mathbb{U}_{\boldsymbol{\alpha}}(Y_i, \boldsymbol{A}_i, \boldsymbol{C}_i)$, $\mathbb{U}_{\boldsymbol{\beta}}(Y_i, \boldsymbol{A}_i, \boldsymbol{M}_i, \boldsymbol{C}_i)$, $\mathbb{U}_{\sigma_{\alpha}^2}(Y_i, \boldsymbol{A}_i, \boldsymbol{C}_i)$, and $\mathbb{U}_{\sigma_{\beta}^2}(Y_i, \boldsymbol{A}_i, \boldsymbol{M}_i, \boldsymbol{C}_i)$, which correspond to $\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma_{\alpha}^2$, and σ_{β}^2, cannot be evaluated in the validation study. Thus, we must remove the components contributed by the validation study from the proposed estimating equations. Specifically, for both the full and reduced EEE approaches, we remove the $R_i\mathbb{U}_{\boldsymbol{\alpha}}(Y_i, \boldsymbol{A}_i, \boldsymbol{C}_i)$ term in (7), the $R_i\mathbb{U}_{\boldsymbol{\beta}}(Y_i, \boldsymbol{A}_i, \boldsymbol{M}_i, \boldsymbol{C}_i)$ term in (8), the $R_i\mathbb{U}_{\sigma_{\alpha}^2}(Y_i, \boldsymbol{A}_i, \boldsymbol{C}_i)$ term in (13), and the $R_i\mathbb{U}_{\sigma_{\beta}^2}(Y_i, \boldsymbol{A}_i, \boldsymbol{M}_i, \boldsymbol{C}_i)$ term in (14). Because these resulting estimating equations are still unbiased, we can still use the same procedure described in the previous two sections to calculate the point, variance, and interval estimators of the mediation measures.

6 | CONNECTIONS BETWEEN REGRESSION CALIBRATION AND EEE

Using the outcome regression (1) and its associated measurement error model (5) as an example, we show in Appendix E the connections among the full EEE, reduced EEE and regression calibration. Specifically, we show that the full EEE is the maximum likelihood estimation for parameters in (1), $\boldsymbol{\alpha}$, and therefore maximizes the efficiency. The reduced EEE does not consider information from the main study for estimating the measurement error model parameters and thus compromises the statistical efficiency. The estimating

equations of the regression calibration approach are approximately equal to the estimating equations of the reduced EEE approach when the measurement error is small ($\sigma_\gamma^2 \approx 0$) and/or the exposure effect on the outcome is small ($\alpha_1 \approx 0$). Therefore, we can treat regression calibration as an alternative to the reduced EEE that gives approximately the same estimator to the reduced EEE whenever the measurement error is small and the exposure effect is not large.

7 | SIMULATION STUDIES

We conducted extensive simulations to evaluate the finite-sample performance of the full and reduced EEE, regression calibration, the naive approach, and a gold standard approach, when the outcome is continuous (Scenario I) and binary (Scenario II). The naive approach follows the difference method in the main study treating A^* as the true exposure. The gold standard approach assumes A is available in the main study and follows the difference method in the absence of exposure measurement errors. By comparing this estimator to those given by the correction approaches proposed, we can learn how much additional variance and bias are induced from the measurement error on estimation and how close the correction methods get to the situation where this no error at all. The study focuses on the NIE and MP estimators, as these are the most commonly using mediation measures in epidemiology.[33] We denote $\hat{\tau}^{(\mathrm{N})}, \hat{\tau}^{(\mathrm{G})}, \hat{\tau}^{(\mathrm{EI})}$, and $\hat{\tau}^{(\mathrm{E2})}$ to refer to the estimates obtained from the naive approach, the gold standard approach, the full EEE approach, and the reduced EEE approach, respectively, where τ can be NIE and MP. Also, let $\hat{\tau}^{(\mathrm{RC})}$ be the regression calibration estimator based on $\hat{\boldsymbol{\phi}}_{RC}$ and $\hat{\tau}^{(\mathrm{RC,\,I})}$ be the regression calibration estimator based on $\hat{\boldsymbol{\phi}}_{RC,\,I}$ with the inverse-variance weight.

The data generation process is summarized as follows. Throughout, we considered a continuous confounder C. The mediator M, true exposure A, and confounder C were generated from a multivariate normal distribution with mean $[0,\ 0,\ 0]^T$ and variance-covariate matrix $\begin{bmatrix} 1 & \rho_{MA} & 0.2 \\ \rho_{MA} & 1 & 0.2 \\ 0.2 & 0.2 & 1 \end{bmatrix}$, where the correlation between the mediator and exposure (ie, ρ_{MA}) was chosen from 0.3 to 0.6. The correlation between the confounder and mediator and between the confounder and exposure were fixed to 0.2, which were slightly stronger than the observed correlation coefficients in our illustrative example of HPFS. Given A, the surrogate exposure, A^*, was generated from $N\left(A, 1/\rho_{AA^*}^2 - 1\right)$ to fix the correlation between the true and surrogate exposure to ρ_{AA^*}. We selected $\rho_{AA^*} \in (0.75,\ 0.5,\ 0.25)$ to represent weak, moderate, and strong measurement error. In Scenarios I and II, we generated Y from the following linear and log-binomial regression models,

$$Y \mid A, M, C \sim N(\beta_0 + \beta_1 A + \beta_2 M + \beta_3 C, 1),$$
$$\log(P(Y = 1 \mid A, M, C)) = \beta_0 + \beta_1 A + \beta_2 M + \beta_3 C,$$

respectively, where the coefficient for the confounder, β_3, was set to 0.2, and β_1 and β_2 were chosen as follows. First, we fixed TE, on the identity and log risk ratio scale for

Scenarios I and II, to 0.5 and log(1.5), respectively. Then, we chose MP $\in (0.2,\ 0.5)$ to represent a moderate and high mediation proportion. Finally, by definition we have $\beta_1 = (1 - \text{MP}) \times \text{TE}$ and $\beta_2 = 0.96 \times \text{TE} \times \text{MP}/(\rho_{MA}^2 - 0.04)$, where derivations of both formulas are given in Appendix F in the Supplementary Material. The intercept β_0 was set to 0 for Scenario I and was chosen such that the marginal outcome prevalence $P(Y = 1)$ equaled 10% in Scenario II. We assumed the main study contained 5000 samples ($n_1 = 5000$); and the validation study sample size (ie, n_2) was chosen from 200 and 1000 to represent a moderate and large validation study. For each Scenario, MP, n_2, ρ_{MA}, and ρ_{AA^*} considered, we conducted 1000 simulations and compared the mean percent bias, Monte Carlo standard error, and 95% confidence interval coverage rate among the proposed approaches.

We first consider a MS/EVS design, which is also the study design for our data application. The simulation results for the $\widehat{\text{NIE}}$ with a continuous (Scenario I) and a binary outcome (Scenario II) are illustrated in Tables 2 and 3, respectively. As expected, the naive approach performs poorly, where the percent bias of $\widehat{\text{NIE}}^{(\text{N})}$ is over 59% on average over all combinations of parameters in both Scenarios I and II. The gold standard approach provides approximately unbiased point estimates with confidence interval coverage rates close to the nominal 95%. Comparing across the measurement error correction methods, the full EEE approach usually has the smallest Monte Carlo standard errors, followed by the reduced EEE approach and then regression calibration. All of the proposed methods for measurement error correction substantially reduce bias compared to the naive approach. The reduced EEE and regression calibration achieve negligible bias with nominal confidence interval coverage among all combinations of parameters considered in the simulation. The full EEE approach also leads to minimal bias for a binary outcome (Scenario II), but it tends to provide biased estimates for a continuous outcome (Scenario I) when the validation study was small and measurement error is large ($n_2 = 200$ and $\rho_{AA^*} = 0.25$). This result may be driven by the fact that the full EEE approach involves greater computational complexity than the other approaches, thereby requiring larger validation study sizes to provide estimates with small finite-sample bias. We further compare the performance of $\widehat{\text{NIE}}^{(E1)}$ to other estimators with increased validation study size from 200 to 10 000 in Figure S1 of the Supplementary Material, in the scenario with a continues outcome (Scenario I) and large exposure measurement error ($\rho_{AA^*} = 0.25$). As expected, when the validation study size increases, the percent bias of $\widehat{\text{NIE}}^{(E1)}$ decreases toward 0 but it does so much more slowly compared to $\widehat{\text{NIE}}^{(E2)}$ and $\widehat{\text{NIE}}^{(RC)}$. For example, the absolute value of the percent bias of $\widehat{\text{NIE}}^{(E1)}$ at MP = 0.2 and $\rho_{MA} = 0.3$ decreases from 24% at $n_2 = 200$ to 11% at $n_2 = 1000$ and then further drops to 5% at $n_2 = 5000$. In contrast, the reduced EEE and regression calibration already produce a percent bias below 5% at $n_2 = 200$. Varying the MP and mediator-exposure association (ρ_{MA}) had relatively smaller influence on the bias of proposed correction approaches, but a larger MP and ρ_{MA} appears to be associated with a higher bias of NIE estimates. The simulation results of MP estimates for a continuous and binary outcome are provided in Tables S1 and S2 in the Supplementary Material, respectively. The simulation results of MP estimates are generally similar to those for the NIE estimates, but

the Monte Carlo standard error for the MP estimate is generally larger as MP is defined as a ratio effect measure.

Then, we investigate the proposed approaches under a MS/IVS design. The data generation process is almost identical to that under a MS/EVS design, but we assumed the outcome information was available in the validation study. Since $\hat{\tau}^{(RC,\,I)}$ is more efficient than $\hat{\tau}^{(RC)}$ under a MS/IVS design as we demonstrate in Section 4 and Appendix C.4, we only present the results of $\hat{\tau}^{(RC,\,I)}$ here. The results are shown in Tables S3 and S4 in the Supplementary Material for a continuous and binary outcome, respectively. All of the full EEE, the reduced EEE and the regression calibration provide small bias with nominal coverage, even with a small validation study size ($n_2 = 200$).

The previous simulation studies consider measurement error models (5) and (6) with homoscedastic normal error terms. Additional simulation studies show that all of the proposed measurement error correction approaches have relatively robust performance when either the normality assumption or homoscedasticity assumption in the measurement error models are moderately violated. Full details of these additional simulations can be found in Appendix G in the Supplementary Material.

Theorems 2–4 require that, for the full and reduced EEE approaches, the error terms of the outcome model in Scenario I are normally distributed and homoskedastic, whereas regression calibration does not place any distributional assumptions on these error terms. Additional simulations described in Appendix H of the Supplementary Material suggest that the EEE approaches are relatively insensitive to the violation of either the normality or homoskedasticity assumptions in the outcome models in Scenario I, although these assumptions are required to construct the expected estimating equations.

8 | APPLICATION TO THE THE HEALTH PROFESSIONALS FOLLOW-UP STUDY (HPFS) DATA

We applied the proposed approaches to an analysis of a large prospective cohort of US men, the HPFS.[34] The HPFS began in 1986, when 51 529 male health professionals, aged 40 to 75 years, completed a baseline questionnaire providing information about physical activity, diet, lifestyle, and medical history. Biannual follow-up questionnaires have been retrieved by more than 90% of the participants. Chomistek et al[20] showed that physical activity was associated with decreased risk of cardiovascular diseases (CVD) in HPFS. Here, we investigated the extent to which the effect of physical activity on CVD risk is direct and to what extent that effect is mediated by body mass index (BMI).

Starting from 1986, physical activity was assessed in biannual questionnaires on average time per week spent on 10 common activities, including walking, jogging, bicycling and so forth during the past year. Then, the total MET-hours per week (MET h wk^{-1})) was calculated to measure total physical activity, which is defined as the time spent at each activity in hours per week multiplied by its MET score and then summed over the 10 activities.[21] In our analysis, the exposure and mediator were defined as physical activity (MET h wk^{-1})) and BMI (kg/m^2) at baseline, where both were treated as continuous.

After excluding men with a history of CVD or whose physical activity or BMI data were missing at baseline, a total 43 547 individuals were included in this analysis, among whom 6330 (14.5%) of them developed CVD between 1986 to 2016. We adjusted for all baseline covariates considered by Chomistek et al[20] as potential confounders, where a list of confounders are shown in Table 4.

The questionnaire measured physical activity with some degree of error and was validated by physical activity diaries. In the HPFS validation study,[21] physical activity data from 238 participants were measured using both the questionnaires and the more accurate diaries, which served as an EVS in this example. We considered using measurement error models (5) and (6) to describe the physical activity measurement error process. As a preliminary step, we assessed the validity of the measurement error models by fitting them in the validation study, adjusting for the aforementioned covariates. An empirical check on QQ-plots (Figure S2 in the Supplementary Material) for the regression residuals indicated little evidence for violation of the normality assumption. The calibration coefficients were $\hat{\gamma}_1 = 0.27$ and $\hat{\eta}_1 = 0.30$. Since $\hat{\gamma}_1 < \hat{\eta}_1 < 1$, we expect that the naive NIE, NDE, and TE estimates will be biased toward the null, given the results in Section 3.2. In addition, because $\hat{\gamma}_1$ and $\hat{\eta}_1$ are similar, bias in the MP naive estimator may be small.

Next, we proceed to the mediation analysis. Tables S5 and S6 in the Supplementary Material present the point estimates with their standard errors of the outcome regression coefficients given by the full and reduced EEE, regression calibration, and the naive approach as a benchmark, which implemented the difference method in the HPFS main study treating the questionnaire-based physical activity variable as the true exposure. Table 4 presents results of $\widehat{\text{NIE}}$, $\widehat{\text{TE}}$, and $\widehat{\text{MP}}$. The $\widehat{\text{NIE}}$ and $\widehat{\text{TE}}$ were given in a log risk ratio scale for 10 METs h wk^{-1}) increase. All methods indicated that physical activity exerted a protective effect against CVD incidence, but the $\widehat{\text{NIE}}$ and $\widehat{\text{TE}}$ given by the naive approach appeared to be severely attenuated towards null. For example, the $\widehat{\text{NIE}}$ given by the naive approach was −0.007, corresponding to a risk ratio of 0.993 for 10 MET h wk^{-1}) increase in physical activity. In the full and reduced EEE approaches and regression calibration approach, stronger NIEs were observed, with risk ratios at 0.956, 0.972, and 0.973, respectively. The MP given by the naive approach was also found to be slightly underestimated. The naive approach indicated that about 41% of the effect of physical activity on CVD risk was mediated by BMI. The proposed correction approaches provided slightly higher $\widehat{MP}$; the full EEE, reduced EEE, and regression calibration approaches show that $\widehat{\text{MP}} = 52\,\%, 45\,\%$, and 45%, respectively.

9 | DISCUSSION

In this article, we propose approaches to correct for exposure measurement error for estimating mediation measures using the difference method, a commonly used regression-based approach for mediation analysis that also bears a causal interpretation under the structural assumptions outlined in Section 2.1. We assume a main study/validation study framework where the validation study enables us to estimate, rather than assuming model parameter values, for the relationships between the true exposure and mismeasured

measurements. Under measurement error models (5) and (6), we derive formulas for the bias of naive estimators of the mediation measures in the presence of exposure measurement error. The formulas show that the bias of naive estimators depends on the calibration coefficients γ_1 and η_1, where γ_1 and η_1 are associations between the true exposure and its error-prone counterpart without and with conditional on the mediator level, respectively. We show that NIE, NDE, and TE estimators are typically biased when $\gamma_1 \neq 1$ and $\eta_1 \neq 1$ but the MP estimator can provide minimal relative bias when $\gamma_1 \approx \eta_1$ and MP is not small regardless of the extent of the measurement error.

Measurement error models (5) and (6) describe the distributions of the true exposure A conditional on its surrogate A^* and other variables, which is a Berkson-type measurement error model.[35] Another class of measurement error model is the classic measurement error models (see, for example, Chapter 2 in Carroll[35]), which includes the commonly-used classic additive measurement error model as a special case. Below we show that the Berkson-type measurement error model used in this article is equivalent to the classic additive measurement error model under certain parametric assumptions. Specifically, the classic additive measurement error model assumes $A^* = A + \epsilon$, where ϵ is a zero-mean error term due to imperfect measurement. If we assume that ϵ follows a normal distribution with a common variance and the mediator-exposure relationship follows a linear regression with a normal error term such that $M \mid A, \boldsymbol{C} \sim N\left(\xi_0 + \xi_1 A + \xi_2^T \boldsymbol{C}, \sigma_M^2\right)$, then one can verify that measurement error models (5) and (6) still hold. Thus, under the aforementioned assumptions, the proposed correction methods are still valid even if the true data generating mechanism follows the classic additive measurement error model.

Among the proposed approaches, the full EEE is most efficient but is computationally more intensive as the parameters in the outcome model and measurement error models are estimated simultaneously. The proposed reduced EEE approach improves the computational efficiency by solving for the outcome model parameters and measurement error model parameters, separately. In practice, alternative reduced EEE approaches can be developed to reduce the computational complexity. For example, in the outcome model EEEs, (7) and (8), one can take the expectations of A_i over $\left(A_i^*, \boldsymbol{C}_i\right)$ and $\left(A_i^*, M_i, \boldsymbol{C}_i\right)$, respectively, without conditional on the outcome variable Y_i. The resulting estimating equations are still unbiased but we will simplify calculation for the conditional expectations in (9) and (10) since now the outcome densities are no longer included in the integrals. We shall evaluate the performance of this new reduced EEE approach in the future. Example R code for implementing the proposed approaches is available at https://github.com/chaochengstat/mediate_error.

We evaluated the empirical performance of the proposed methods via Monte Carlo simulations. We found that the full EEE approach maximized efficiency compared to the reduced EEE and regression calibration methods, but the efficiency difference was usually moderate to minimal when the measurement error was not too large. The reduced EEE and regression calibration approaches provide small bias and nominal coverage among all scenarios considered in the simulation study. The full EEE also provides asymptotically unbiased estimates under a MS/IVS design; however, under a MS/EVS design with a

continuous outcome, the full EEE approach can require unrealistic large validation study sizes ($n_2 > 2000$ if measurement error is large) to ensure small finite-sample bias. This is somewhat expected because prior work in measurement error correction (developed for association analysis rather mediation analysis) indicated that more sophisticated approaches may lead to larger finite-sample bias or variance compared to simpler approach such like regression calibration under a MS/EVS design. For example, simulations in Spiegelman et al[19] showed that the maximum likelihood estimator performed poorly with large bias under a MS/EVS design and therefore suggested regression calibration as a computationally simpler alternative under the MS/EVS design. Our simulation results reinforced that recommendation for mediation analysis, where the reduced EEE and regression calibration methods are preferable under a MS/EVS design and when the measurement error is expected to be non-trivial. For the MP estimates, we observed that regression calibration, reduced EEE, and full EEE approaches sometimes provide large Monte Carlo standard errors when the measurement error was large ($\rho_{AA^*} = 0.25$). This is because the MP is defined as the ratio of NIE and TE and therefore can have more uncertainty as compared to other mediation measures estimated on the additive or difference scale. When the measurement error was large, we observed that the $\widehat{\text{TE}}$ occasionally had very close to 0 values in several Monte Carlo replicates, leading to large Monte Carlo variances for estimating MP since $\widehat{\text{MP}} \approx \frac{\widehat{\text{NIE}}}{\widehat{\text{TE}}} \approx \frac{\widehat{\text{ME}}}{0} \approx \infty$ in those replicates. Therefore, the large Monte Carlo standard error was driven by several extreme simulation replicates. Therefore, we interpret the large empirical variance for estimating MP with caution.

We introduced two assumptions in Section 3.1 regarding the measurement error process, including (i) the transportability assumption in a MS/EVS design such that relevant parameters in the validation study and used for bias correction can reasonably be assumed to be the same as those that produced the surrogate exposure in the main study, and (ii) surrogacy assumption such that the A^* is independent of the outcome Y conditional on the true exposure A and covariates. In our analysis of the HPFS, the transportability assumption is considered plausible because validation study participants are members draw from the same target population with HPFS and both studies shared the same method of physical activity assessment. The surrogacy assumption cannot be empirically verified in the HPFS dataset, although this is a common assumption in the measurement error correction literature. If the surrogacy assumption is violated, then one may need to conduct sensitivity analysis and assess the impact under certain departures from surrogacy assumption. Developing such sensitivity analysis strategy under the context of mediation analysis is beyond the scope of this article but remains a fruitful direction for future research.

Regression calibration can be easily implemented, where its point estimators can be obtained by any standard software supporting a difference method. This article provides closed-form formulas on how to calculate consistent variance estimators for the regression calibration in Section 4. Comparing to EEE approaches that requires full distribution assumptions in the outcome models and measurement error models, the regression calibration requires fewer parametric assumptions (not requiring the full distributional assumptions in the outcome

models) and appears to be fairly robust; furthermore it is also approximately consistent even if the the normality assumptions in the measurement error models are violated (see Remark 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The HPFS is not publicly available due to ethical restrictions. Data requests may be directed to the first author.

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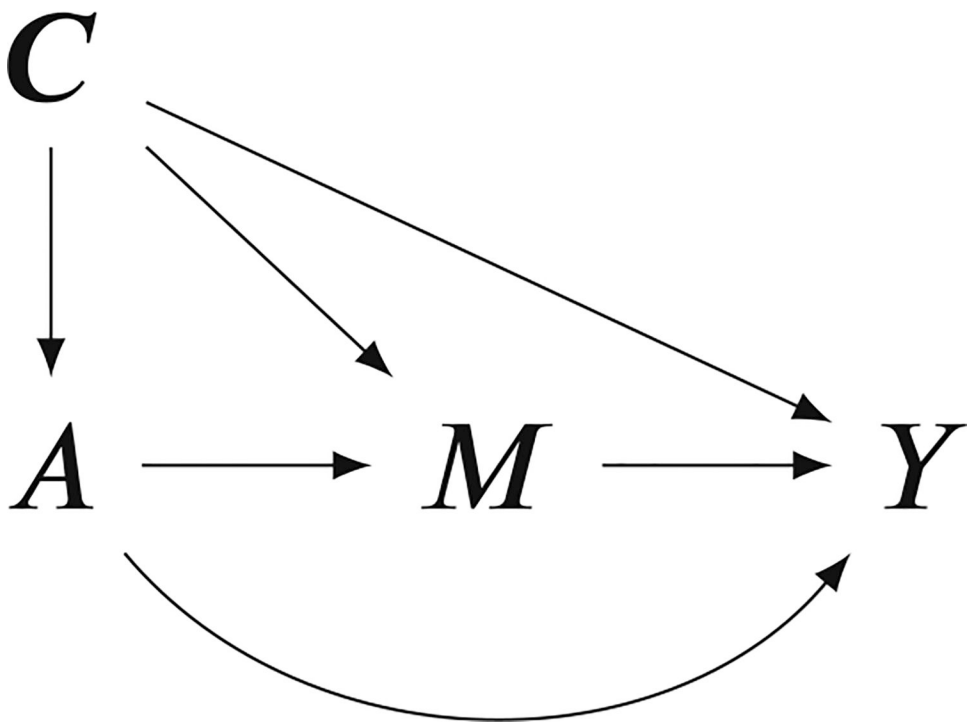

FIGURE 1.

Mediation directed acyclic graph, where A, M, Y, and $\boldsymbol{C}$ denote the exposure, mediator, outcome, and a vector of covariates that may confound the exposure-outcome, exposure-mediator, and mediator-outcome relationships. The $A \rightarrow M \rightarrow Y$ pathway denotes the natural indirect and the $A \rightarrow Y$ pathways denotes the natural direct effect

TABLE 1

A summary of the existing literature addressing mediation analysis in the presence of mismeasured or misclassified variables, classified by the variable subject to measurement error (outcome, mediator, exposure) and the variable type (continuous, binary)

Variable	Type	Reference
Outcome	Continuous	*Null. There is no bias in standard statistical inference when outcome follows classic additive measurement error model.*
	Binary	Jiang and VanderWeele.[4]
Mediator	Continuous	Cessie et al;[8] VanderWeele et al;[9] Valeri et al;[10] Zhao and Prentice;[11] Ssenkusu;[12] Fulcher et al;[13] Gaynor et al[14]
	Binary	Ogburn and VanderWeele;[15] Valeri and VanderWeele.[16]
Exposure	Continuous	*Null (primary focus of this article).*
	Binary	Valeri et al;[17] Jiang and VanderWeele.[18]

Note: All publications shown in this table assumed that the measurement error or misclassification process is known, except for Ssenkusu,[12] who considered that repeated measurements on the mediator are available to describe the measurement error process of a mismeasured mediator. Zhao and Prentice[11] also mentioned an external dataset can be used to estimate the measurement error model parameters, but they did not consider the variability of estimating measurement error models in drawing statistical inference. Zhao and Prentice[11] and Valeri et al[17] considered the difference method in the presence of measurement error; all other publications considered the product method when addressing measurement error/misclassification.

TABLE 2

Simulation results of $\widehat{\text{NIE}}$ for a continuous outcome (Scenario I) with a MS/EVS design

				Percent bias					SE×100					Empirical coverage rate				
n_2	**MP**	ρ_{MA}	ρ_{AA^*}	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$
200	0.2	0.3	0.75	−0.5	−0.1	−0.1	−37.4	−0.3	2.61	2.71	2.71	0.90	1.08	94.6	94.4	94.4	0.0	95.2
			0.50	−8.6	−0.2	−0.5	−70.5	−0.4	3.32	5.15	5.23	0.67	1.06	95.1	95.1	95.5	0.0	95.5
			0.25	−24.3	−5.4	5.5	−92.4	−0.1	3.51	6.81	21.30	0.32	1.07	94.6	96.5	96.5	0.0	96.0
		0.6	0.75	−3.5	−0.7	−0.7	−3.4	−0.1	3.98	4.13	4.14	0.78	1.07	97.5	97.4	97.4	86.0	97.3
			0.50	−21.7	−1.6	−2.5	−48.6	−0.2	5.61	8.77	9.25	0.54	1.08	95.6	96.7	97.1	0.0	95.3
			0.25	−40.0	−6.3	7.1	−86.1	0.0	6.15	11.17	48.90	0.28	1.17	92.6	99.5	99.9	0.0	93.7
	0.5	0.6	0.75	−0.9	0.2	0.3	−34.3	0.1	4.57	4.71	4.71	1.11	1.39	93.8	94.6	94.7	0.0	95.6
			0.50	−11.6	1.1	1.2	−69.0	−0.0	6.05	8.81	8.92	0.73	1.39	89.8	94.9	95.0	0.0	95.5
			0.25	−31.8	−6.8	−1.3	−92.0	0.0	7.43	12.79	46.71	0.39	1.44	66.2	94.3	94.9	0.0	94.4
1000	0.2	0.3	0.75	0.8	0.9	0.9	−36.9	0.3	1.85	1.86	1.86	0.89	1.07	95.2	95.0	95.1	0.0	95.3
			0.50	−0.4	−0.1	−0.3	−70.4	0.0	3.02	3.17	3.17	0.64	1.10	94.7	94.1	94.0	0.0	94.3
			0.25	−10.7	−2.9	0.4	−92.3	0.1	4.15	5.53	7.05	0.34	1.15	97.3	96.8	96.1	0.0	93.2
		0.6	0.75	−0.3	0.0	0.0	−3.4	0.2	2.53	2.54	2.54	0.85	1.15	94.6	94.5	94.4	84.4	94.8
			0.50	−2.6	0.3	0.0	−48.4	−0.1	4.19	4.42	4.45	0.54	1.11	95.9	95.3	95.2	0.0	95.0
			0.25	−22.2	−5.3	−2.7	−86.1	−0.1	5.64	7.25	10.66	0.29	1.11	96.0	98.5	97.3	0.0	94.7
	0.5	0.6	0.75	−0.2	0.0	0.0	−34.3	0.1	2.85	2.86	2.86	1.10	1.46	95.1	95.1	95.1	0.0	94.3
			0.50	−0.9	−0.0	0.0	−69.0	−0.1	4.81	5.03	5.04	0.79	1.39	94.6	94.5	94.4	0.0	95.8
			0.25	−15.5	−4.6	1.6	−92.0	0.1	7.14	8.60	11.41	0.40	1.42	88.2	95.7	95.6	0.0	95.7

Note: Here, $\widehat{\text{NIE}}^{(E1)}$, $\widehat{\text{NIE}}^{(E2)}$, $\widehat{\text{NIE}}^{(RC)}$, $\widehat{\text{NIE}}^{(N)}$, and $\widehat{\text{NIE}}^{(G)}$ denote the NIE estimators given by the full EEE approach, reduced EEE approach, regression calibration approach based on $\hat{\boldsymbol{\phi}}_{RC}$ naive approach, and gold standard approach, respectively. n_2, MP, ρ_{MA}, and ρ_{AA^*} denote the validation study size, mediation proportion, the correlation between the mediator and exposure, and the correlation between the exposure and its surrogate value, respectively. The percent bias was calculated as the median of the ratio of bias to the true value over 1000 replications, that is, $\boldsymbol{median}\left(\frac{\widehat{\text{NIE}} - \text{NIE}}{\text{NIE}}\right) \times 100\%$. The standard error (SE) is defined as the square root of empirical variance of mediation measure estimates from the 1000 replications.

TABLE 3

Simulation results of $\widehat{\text{NIE}}$ for a binary outcome (Scenario II) with a MS/EVS design

				Percent bias					SE×100					Empirical coverage rate				
n_2	MP	ρ_{MA}	ρ_{AA^*}	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$	$\widehat{\text{NIE}}^{(E1)}$	$\widehat{\text{NIE}}^{(E2)}$	$\widehat{\text{NIE}}^{(RC)}$	$\widehat{\text{NIE}}^{(N)}$	$\widehat{\text{NIE}}^{(G)}$
200	0.2	0.3	0.75	−0.5	−0.3	−0.4	−38.0	−0.2	1.73	1.72	1.73	0.79	1.34	95.1	95.1	94.8	3.6	94.1
			0.50	−2.3	−2.2	−2.1	−70.7	−0.2	2.57	2.53	2.55	0.41	1.30	96.8	96.9	96.8	0.0	94.8
			0.25	−2.9	−1.8	−2.2	−92.4	−0.7	5.24	14.81	9.14	0.16	1.29	97.5	97.2	97.4	0.0	95.7
		0.6	0.75	−1.8	−1.4	−1.6	−2.9	−0.6	4.07	4.07	4.07	1.51	2.97	95.8	95.8	95.8	94.6	95.3
			0.50	3.0	3.1	4.4	−48.4	1.0	6.27	6.27	6.34	0.68	3.00	96.8	96.9	97.0	0.0	95.9
			0.25	−2.2	−0.8	5.6	−86.4	−2.6	13.07	30.46	100.22	0.19	3.09	95.3	96.0	99.9	0.0	93.7
	0.5	0.6	0.75	−0.3	−0.4	−0.2	−34.4	−1.1	4.10	4.11	4.12	1.59	3.04	95.5	95.4	95.5	0.7	95.0
			0.50	2.1	1.7	1.7	−68.9	−0.2	6.19	6.18	6.22	0.69	2.98	97.1	96.8	96.7	0.0	95.7
			0.25	−1.9	0.2	3.1	−92.0	−0.1	14.65	21.64	28.35	0.23	3.12	95.2	95.9	98.5	0.0	94.1
1000	0.2	0.3	0.75	1.8	1.9	1.4	−36.6	1.0	1.44	1.44	1.44	0.75	1.28	95.4	95.3	95.5	4.8	94.8
			0.50	−1.5	−1.5	−1.9	−70.6	−1.3	1.91	1.91	1.90	0.39	1.27	95.1	94.9	94.9	0.0	95.5
			0.25	1.8	1.8	−0.5	−92.4	0.9	3.58	3.55	3.68	0.16	1.29	97.8	97.4	97.1	0.0	95.6
		0.6	0.75	−1.0	−1.0	−1.0	−4.4	−2.4	3.81	3.81	3.81	1.53	3.04	94.0	93.9	93.8	94.1	95.3
			0.50	−1.0	−1.0	−1.0	−49.2	−1.8	5.41	5.40	5.40	0.67	3.08	94.3	94.4	94.5	0.0	95.1
			0.25	1.9	1.9	4.4	−86.2	−1.8	9.54	9.55	10.34	0.20	3.17	93.0	93.2	97.7	0.0	93.8
	0.5	0.6	0.75	−0.6	−0.7	−0.7	−34.8	−0.5	3.82	3.83	3.83	1.58	3.13	95.1	95.0	95.1	1.0	94.7
			0.50	1.6	1.6	1.4	−68.9	1.4	5.50	5.50	5.53	0.72	2.98	95.4	95.3	94.9	0.0	95.5
			0.25	2.5	2.5	2.9	−92.0	−0.2	10.55	10.49	11.24	0.23	3.10	94.8	95.2	97.6	0.0	95.3

Note: Here, $\widehat{\text{NIE}}^{(E1)}$, $\widehat{\text{NIE}}^{(E2)}$, $\widehat{\text{NIE}}^{(RC)}$, $\widehat{\text{NIE}}^{(N)}$, and $\widehat{\text{NIE}}^{(G)}$ denote the MP estimators given by the full EEE approach, reduced EEE approach, regression calibration approach based on $\hat{\boldsymbol{\phi}}_{RC}$, naive approach, and gold standard approach, respectively. n_2, MP, ρ_{MA}, and ρ_{AA^*} denote the validation study size, mediation proportion, the correlation between the mediator and exposure, and the correlation between the exposure and its surrogate value, respectively. The percent bias was calculated as the median of the ratio of bias to the true value over 1000 replications, that is, $\boldsymbol{median}\left(\frac{\text{MP}-\text{MP}}{\text{MP}}\right) \times 100\%$. The standard error (SE) is defined as the square root of empirical variance of mediation measure estimates from the 1000 replications.

TABLE 4

The extent to which the effect of physical activity on cardiovascular diseases incidence is mediated by body mass index, HPFS($n_1 = 43\ 547, n_2 = 238$), 1986–2016

Method	TE	NIE	MP
Naive	−0.018 (0.005)	−0.007 (0.001)	0.408 (0.099)
Full EEE	−0.084 (0.013)	−0.044 (0.017)	0.520 (0.273)
Reduced EEE	−0.062 (0.026)	−0.028 (0.009)	0.450 (0.125)
Regression calibration	−0.062 (0.025)	−0.027 (0.009)	0.448 (0.121)

Note: The NIE and TE were defined in a log risk ratio scale for a 10 METs h wk^{-1} increase. The numbers in the brackets denote the standard errors of the point estimator. The confounders considered in the mediation analysis include age (years), smoking status (current/past/never), parental history of myocardial infarction and cancer at or before 60 years old (yes/no), aspirin use (yes/no), vitamin E supplement use (yes/no), intake of polyunsaturated fat, trans fat, eicosapentaenoic acid and docosahexaenoic acid (g/day), alcohol intake (yes/no), and diabetes (yes/no), and hypertension (yes/no).