# Reverse attenuation in interaction terms due to covariate measurement error

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Covariate measurement error may cause biases in parameters of regression coefficients in generalized linear models. The influence of measurement error on interaction parameters has, however, only rarely been investigated in depth, and if so, attenuation effects were reported. In this paper, we show that also reverse attenuation of interaction effects may emerge, namely when heteroscedastic measurement error or sampling variances of a mismeasured covariate are present, which are not unrealistic scenarios in practice. Theoretical findings are illustrated with simulations. A Bayesian approach employing integrated nested Laplace approximations is suggested to model the heteroscedastic measurement error and covariate variances, and an application shows that the method is able to reveal approximately correct parameter estimates.

*Keywords:* Attenuation; Bayesian analysis; Berkson error; Classical error; Heteroscedastic error.

Additional supporting information including source code to reproduce the results may be found in the online version of this article at the publisher's web-site

## 1 Introduction

The effects of measurement error (ME) in covariates of statistical analyses have been recognized and discussed for a long time, see for example Pearson (1902), Wald (1940), Berkson (1950), Fuller (1987), Carroll et al. (2006). Ignoring ME in regression models may lead to serious biases in parameter estimates and confidence intervals (Fuller, 1987). Importantly, ME not only affects estimates associated with mismeasured covariates, but also estimates associated with error-free covariates, if the covariates are correlated and the error is not accounted for (Carroll et al., 1985; Gleser et al., 1987; Freckleton, 2011). The ME-induced biases in parameters can roughly be classified into attenuation (bias toward zero) and reverse attenuation (bias away from zero) effects. The application of suitable ME modeling approaches can remove the biases in estimates of parameters and confidence intervals (Fuller, 1987; Carroll et al., 2006; Buonaccorsi, 2010). Various ways of ME modeling have been proposed, such as likelihood approaches (Carroll et al., 1984; Schafer, 1987, 1993), score function methods (Stefanski, 1989; Nakamura, 1990), method-of-moments correction (Fuller, 1987), simulation extrapolation (SIMEX) (Cook and Stefanski, 1994), regression calibration (Carroll and Stefanski, 1990; Gleser, 1990), or Bayesian analyses (Lindley and El-Sayyad, 1968; Clayton, 1992; Stephens and Dellaportas, 1992; Richardson and Gilks, 1993; Dellaportas and Stephens, 1995; Gustafson, 2004; Muff et al., 2015).

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While the effects of ME on parameter estimates of covariates have received considerable attention (Fuller, 1987; Carroll et al., 2006; Buonaccorsi, 2010), the effects on multiplicative interaction parameters are less well studied. The few cases that have addressed it explicitly have mainly dealt with cases leading to attenuated interaction coefficients (Jaccard and Wan, 1995; Lobach et al., 2011). In the work presented here, we focus on the influence of ME on multiplicative interaction parameters in generalized linear regression models (GLMs). Many interesting hypotheses in biology or medicine are specifically about interactions (Ruxton and Colegrave, 2010, p. 132), as, for example, gene–environment interactions in the etiology of human diseases (Hunter, 2005). In other contexts the interest may not be in the interactions themselves, but it is vital to detect them, for instance in the evaluation of intervention strategies in epidemiology (Greenland, 2009). The occurrence of significant interactions that are unexpected or difficult to explain suggest that reverse attenuation may be an issue in some situations (Vandewater et al., 2004; Hagen et al., 2006; Reid et al., 2007; Bailey et al., 2014). Here, we discuss two specific situations where ME in covariates can induce reversely attenuated interaction parameters, namely when the error variance or the sampling variance of a mismeasured covariate involved in the interaction has a heteroscedastic structure. While attenuation leads to an increased rate of type II errors in standard testing procedures that evaluate the influence of regression terms, reverse attenuation increases the rate of type I errors and may thus lead to spurious interaction effects.

With this paper we pursue three objectives. First, we intend to raise awareness that parameter estimates of interaction effects in GLMs may be reversely attenuated due to ME in covariates, particularly when heteroscedasticities in the error or sampling variance of a mismeasured covariate are present. Second, we would like to give an easy-to-digest theoretical background to understand this phenomenon. And third, we give guidance on how to appropriately model such ME by employing a Bayesian approach. The modeling is done by using integrated nested Laplace approximations (INLA) (Rue et al., 2009), a valid alternative to time-consuming Markov chain Monte Carlo sampling to obtain posterior marginals for the subclass of latent Gaussian models, and it is suitable to fit the most common regression models, such as generalized linear-mixed models (GLMMs) (Fong et al., 2010). Moreover, INLA was shown to be useful for error modeling in GLMMs when there is Gaussian error in a continuous covariate (Muff et al., 2015). The INLA methodology is implemented in `C` and runs under Linux, Windows, and Macintosh via a freely available `R`-interface (R Core Team, 2013). The `R`-package `r-inla` can be downloaded from `www.r-inla.org`. Data and `r-inla` code of a selected example presented in this paper are provided as Supporting Information.

This paper is organized as follows. Section 2 gives an overview of the regression and error models discussed here. In Section 3, we will review some ME theory and present cases that lead to attenuation or reverse attenuation of interaction parameters in linear regression. Section 4 illustrates the theory with simulation examples. Bayesian measurement analysis with INLA is presented in Section 5 and applied in Section 6. Finally, Section 7 provides a discussion.

## 2 Regression and error models

### 2.1 The generalized linear regression model

Assume we have $n$ observations in a GLM. The data are given as $(\boldsymbol{y}, \boldsymbol{x}, \boldsymbol{s}, z)$, with $\boldsymbol{y} = (y_1, \ldots, y_n)^\top$ denoting the response, $\boldsymbol{x} = (x_1, \ldots, x_n)^\top$ a single continuous error-prone covariate whose true values are unobserved, $\boldsymbol{s} = (s_1, \ldots, s_n)^\top$ an error-free covariate that is independent of $\boldsymbol{x}$, and $z = (\boldsymbol{z}_1, \ldots, \boldsymbol{z}_p)$ a covariate matrix of dimension $n \times p$ for another $p$ error-free covariates.

Suppose $\boldsymbol{y}$ is of exponential family form with mean $\mu_i = \mathsf{E}(y_i \mid x_i, s_i, \boldsymbol{z}_{[i,]}, \boldsymbol{\beta})$, linked to the linear predictor $\eta_i$ via

$$
\begin{aligned}
\mu_i &= h(\eta_i) \\
\eta_i &= \beta_0 + \beta_x x_i + \beta_s s_i + \beta_{sx} s_i x_i + \boldsymbol{z}_{[i,]}\boldsymbol{\beta}_z,
\end{aligned}
\tag{1}
$$

 

where $h(\cdot)$ is a known monotonic inverse link function, and $\boldsymbol{\beta} = (\beta_0, \beta_x, \beta_s, \beta_{sx}, \boldsymbol{\beta}_z^\top)^\top$ denotes the vector of *true* regression coefficients. Note that the interaction between $\boldsymbol{s}$ and $\boldsymbol{x}$ is explicitly considered here. Let $\boldsymbol{w} = (w_1, \ldots, w_n)^\top$ be the observed version of the true, but unobservable covariate $\boldsymbol{x}$. When $\boldsymbol{w}$ instead of $\boldsymbol{x}$ is included in the regression, the linear predictor is given as

$$\eta_i^\star = \beta_0^\star + \beta_x^\star w_i + \beta_s^\star s_i + \beta_{sx}^\star s_i w_i + \boldsymbol{z}_{[i,]}\boldsymbol{\beta}_z^\star.$$

The vector $\boldsymbol{\beta}^\star = (\beta_0^\star, \beta_x^\star, \beta_s^\star, \beta_{sx}^\star, \boldsymbol{\beta}_z^{\star\top})^\top$ then contains as elements the *naive* regression coefficients.

### 2.2 Classical measurement error model

In the classical ME model it is assumed that the covariate $\boldsymbol{x}$ can be observed only via a proxy $\boldsymbol{w}$, such that, in vector notation,

$$\boldsymbol{w} = \boldsymbol{x} + \boldsymbol{u},$$

with $\boldsymbol{u} = (u_1, \ldots, u_n)^\top$. Throughout the paper, the components of the error vector $\boldsymbol{u}$ are assumed to be independent and normally distributed with mean zero. We assume that the ME is nondifferential, meaning that $\boldsymbol{y}$ and $\boldsymbol{w}$ are conditionally independent given $(\boldsymbol{x}, \boldsymbol{s}, z)$. In most applications, this assumption is plausible as it implies that, given the true covariate $\boldsymbol{x}$ and covariates $\boldsymbol{s}$ and $z$, no additional information about the response variable $\boldsymbol{y}$ is gained through $\boldsymbol{w}$ (Carroll et al., 2006). Ideally, repeated measurements $w_{ij}$, $j = 1, \ldots, J_i$, of the true value $x_i$ are available, so that

$$w_{ij} \mid x_i \sim \mathcal{N}\left(x_i, \sigma_u^2\right),$$

with error variance $\sigma_u^2$. The repeated measurements $w_{ij}$ are usually assumed to be conditionally independent and may be unbalanced. However, for notational convenience we assume in the following that no repeated measurements are available, that is $J_1 = \cdots = J_n = 1$, and thus omit the index $j$.

The above formulation implies that the covariate $x_i$ can be measured with constant error variance for all individuals $i$ (homoscedastic ME). However, this assumption is often unjustified. A heteroscedastic ME model is required when different components of $\boldsymbol{x}$ are measured with different accuracies. Both the homo- and heteroscedastic cases are relevant in practice (see, e.g. Subar et al., 2001). Here, we concentrate on a special type of heteroscedasticity, namely when the measurement accuracy of $x_i$ depends on the value of another covariate $s_i$, and thus

$$w_i \mid x_i, s_i \sim \mathcal{N}\left(x_i, \sigma_{u^{(s_i)}}^2\right). \tag{2}$$

The covariate $\boldsymbol{s}$ is assumed to be independent of $\boldsymbol{x}$ and error free. If $\boldsymbol{s}$ is binary with values $\{0, 1\}$, indicating group membership for instance, sampling effort or sampling precision for $\boldsymbol{x}$ could be different in the two groups. Such circumstances lead to error variances depending on $\boldsymbol{s}$ with $\sigma_{u^{(0)}}^2 \neq \sigma_{u^{(1)}}^2$.

### 2.3 Berkson measurement error model

Berkson-type error can be observed in experimental settings where the value of a covariate may correspond to, for example, a predefined fixed dose, temperature or time interval, but the true values $\boldsymbol{x}$ may deviate from these planned values $\boldsymbol{w}$ due to imprecision in the realization. The second setting where Berkson-type error occurs is in epidemiological or biological studies, where, for example, exposure measurements are assigned to individuals in the same area. Examples are the application of fixed doses of herbicides in bioassay experiments (Rudemo et al., 1989) or the radiation epidemiology study described in Kerber et al. (1993) and Simon et al. (1995). These situations lead to the Berkson ME model (Berkson, 1950)

$$\boldsymbol{x} = \boldsymbol{w} + \boldsymbol{u},$$

where $\boldsymbol{u}$ and $\boldsymbol{w}$ are independent. As for classical ME, the Berkson error is assumed to be nondifferential throughout the paper. We again allow for heteroscedasticity in the error model

$$x_i \mid w_i, s_i \sim \mathcal{N}\big(w_i, \sigma^2_{u^{(s_i)}}\big), \tag{3}$$

where the error variance may depend on some independent covariate $\boldsymbol{s}$, which is known exactly. In epidemiology, for instance, $\boldsymbol{s}$ might indicate different regions, where the density of measurement stations determines the Berkson error variances within regions.

## 3 The effects of measurement error on interaction terms

It is well known that ME in covariates can induce bias in regression coefficients if erroneous covariates are naively regressed against the response (Pearson, 1902; Wald, 1940; Berkson, 1950; Fuller, 1987; Carroll et al., 2006; Buonaccorsi, 2010). Moreover, Carroll et al. (1985) and Gleser et al. (1987) have shown that even parameters $\beta_z$ of other covariates $z$ measured without error may be biased by the error in $\boldsymbol{x}$ if the two covariates are not independent. Carroll et al. (2006, Section 3.3) showed that naive least-squares does not estimate $\beta_z$, but

$$\beta_z^\star = \beta_z + \beta_x(1-\lambda)\Gamma_z,$$

where $\Gamma_z$ is the slope of $z$ when $\boldsymbol{x}$ is regressed on $z$, that is, $\mathsf{E}(\boldsymbol{x} \mid z) = \Gamma_0\mathbf{1} + \Gamma_z z$, and $\lambda$ is a value in the interval [0, 1] (see below). The bias in $\beta_z^\star$ may be in both directions, thus depending on the relation between $\boldsymbol{x}$ and $z$, the error in $\boldsymbol{x}$ may attenuate *or* reversely attenuate the slope parameter $\beta_z$. As pointed out by Carroll et al. (1985) and Carroll (1989), a specific implication of this result is that in a two-group analysis of covariance, where $\boldsymbol{s}$ is a treatment variable and $\boldsymbol{x}$ an error-prone covariate, inconsistent estimates of the treatment effect $\beta_s$ must be expected if the two groups have heterogeneous means, that is, when the assignment of the treatment depends on $\boldsymbol{x}$. Here, we will show that not only different means but also different variances lead to biased results: within-group variances or ME variances of $\boldsymbol{x}$ that depend on $\boldsymbol{s}$ lead to inconsistent estimates of $\beta_{sx}$. To understand the origin of such effects, a basic result about ME-induced biases in parameters is recalled first. If in simple linear regression

$$y_i = \beta_0 + \beta_x x_i + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}\big(0, \sigma_\varepsilon^2\big),$$

the covariate $\boldsymbol{x}$ is subject to classical, homoscedastic ME ($w_i \sim \mathcal{N}(x_i, \sigma_u^2)$), it is well known that if the error in $\boldsymbol{x}$ is ignored and the naive model including $\boldsymbol{w}$ is fitted instead, the magnitude of the least-squares slope estimate is attenuated by a factor $\lambda = \sigma_x^2/(\sigma_x^2 + \sigma_u^2)$, with $\sigma_x^2$ denoting the sampling variance of $\boldsymbol{x}$ (Fuller, 1987). The coefficient $\lambda$ is known as the *coefficient of attenuation* or *reliability ratio*. For a given reliability ratio, a naive regression estimates $\beta_x^\star = \lambda\beta_x$ instead of $\beta_x$. In practical applications, $\lambda$ is usually not known, but can be consistently estimated as $\hat{\lambda} = (\hat{\sigma}_w^2 - \hat{\sigma}_u^2)/\hat{\sigma}_w^2$, where $\hat{\sigma}_w^2$ is the sampling variance of $\boldsymbol{w}$ (Carroll et al., 2006). An unbiased estimate of $\beta_x$ is then obtained by $\hat{\beta}_x^\star/\hat{\lambda}$.

Consider now the simple linear regression model with linear predictor (1) including a binary covariate $\boldsymbol{s}$ taking values in {0, 1}, and an interaction term $\boldsymbol{sx}$, but without other covariates $z$. Two separate linear regression models can then be formulated for the two groups with $s_i = 0$ and $s_i = 1$, namely

$$y_i = \beta_0^{(0)} + \beta_x^{(0)} x_i + \varepsilon_i, \text{ if } \quad s_i = 0,$$

 

$$y_i = \beta_0^{(1)} + \beta_x^{(1)} x_i + \varepsilon_i, \text{ if } \quad s_i = 1,$$

with $\beta_0^{(0)}$, $\beta_x^{(0)}$, $\beta_0^{(1)}$, and $\beta_x^{(1)}$ denoting the respective regression parameters. The interaction coefficient $\beta_{sx}$ can then be interpreted as the difference in the slope coefficients $\beta_{sx} = \beta_x^{(1)} - \beta_x^{(0)}$. Assume that $\boldsymbol{x}$ is subject to classical ME as in equation (2), with error variances $\sigma^2_{u^{(0)}}$ and $\sigma^2_{u^{(1)}}$ potentially depending on group membership $\boldsymbol{s}$. The naive least-squares method then does not estimate $\beta_x^{(0)}$ and $\beta_x^{(1)}$, but rather $\lambda_0\beta_x^{(0)}$ and $\lambda_1\beta_x^{(1)}$, with group-specific attenuation factors

$$\lambda_0 = \frac{\sigma^2_{x^{(0)}}}{\sigma^2_{x^{(0)}} + \sigma^2_{u^{(0)}}} \quad \text{and} \quad \lambda_1 = \frac{\sigma^2_{x^{(1)}}}{\sigma^2_{x^{(1)}} + \sigma^2_{u^{(1)}}}.$$

The variance terms $\sigma^2_{x^{(0)}}$ and $\sigma^2_{x^{(1)}}$ denote group-specific sampling variances with $\boldsymbol{x}^{(0)}$ and $\boldsymbol{x}^{(1)}$ being the respective subsets of $\boldsymbol{x}$, with $x_i \in \boldsymbol{x}^{(0)}$ if $s_i = 0$ and $x_i \in \boldsymbol{x}^{(1)}$ if $s_i = 1$. Note that such heteroscedastic sampling variances are not implausible. If $s_i$ indicates the sex of study participants, for instance, such a situation may arise when physical indicators, such as weight or height, have larger variability in males than in females. Naive least-squares then estimate

$$\beta^{\star}_{sx} = \lambda_1\beta_x^{(1)} - \lambda_0\beta_x^{(0)}, \tag{4}$$

which implies that $\beta^{\star}_{sx}$ may be an attenuated *or* reversely attenuated version of $\beta_{sx}$, depending on the combination of true slope coefficients and attenuation factors. Three special cases are of particular interest:

(i) When the error and sampling variances are both homoscedastic, the attenuation factors are $\lambda_0 = \lambda_1 = \lambda$, and thus $\beta^{\star}_{sx} = \lambda(\beta_x^{(1)} - \beta_x^{(0)}) = \lambda\beta_{sx}$. The interaction coefficient is then attenuated to the same degree as the slope, whose naive version estimates $\beta^{\star}_x = \lambda\beta_x$. This case has been previously addressed (Jaccard and Wan, 1995; Lobach et al., 2011).

(ii) With heteroscedastic error variances ($\sigma^2_{u^{(0)}} \neq \sigma^2_{u^{(1)}}$), but constant sampling variance, the attenuation factors are $\lambda_0 \neq \lambda_1$. When the two groups have equal true slopes $\beta_x^{(0)} = \beta_x^{(1)} = \beta_x$, the true interaction coefficient is $\beta_{sx} = 0$. The naive interaction then estimates $\beta^{\star}_{sx} = (\lambda_1 - \lambda_0)\beta_x$, which implies $|\beta^{\star}_{sx}| > 0$, unless $\beta_x = 0$. This situation gives raise to reverse attenuation.

(iii) Reverse attenuation may also arise when the error is homoscedastic, but the sampling variance of the true covariate is heteroscedastic ($\sigma^2_{x^{(0)}} \neq \sigma^2_{x^{(1)}}$), and the true interaction coefficient is $\beta_{sx} = 0$. As above, this case leads to $\lambda_0 \neq \lambda_1$ and thus $|\beta^{\star}_{sx}| > 0$, unless $\beta_x = 0$.

Cases (ii) and (iii) with reverse attenuation are the main focus of this work. The top panel of Fig. 1 illustrates the effect of case (ii), that is, for heteroscedastic error and homoscedastic sampling variance of $\boldsymbol{x}$, and a true interaction effect that is zero. We set $\sigma^2_{u^{(0)}} < \sigma^2_{u^{(1)}}$, thus the subset $\boldsymbol{w}^{(1)}$ spreads more around the true distribution than $\boldsymbol{w}^{(0)}$. When the error-free covariate $\boldsymbol{x}$ is used in the linear regression, the slopes for $\boldsymbol{x}$ are identical in both groups (Fig. 1A). However, when the mismeasured $\boldsymbol{w}$ is regressed against $\boldsymbol{y}$, the slope parameter $\beta_x^{(1)}$ is attenuated more than $\beta_x^{(0)}$, which leads to a spurious interaction $\beta^{\star}_{sx} < 0$, indicated by nonparallel regression lines (Fig. 1B).

The bottom panel of Fig. 1 illustrates the effect of case (iii) with homoscedastic ME, heteroscedastic sampling variance of $\boldsymbol{x}$, and $\beta_{sx} = 0$. When the error-free covariate $\boldsymbol{x}$ is used in the regression, the slopes for $\boldsymbol{x}$ are parallel for groups 0 and 1, thus no interaction (Fig. 1C). When $\sigma^2_{x^{(0)}} < \sigma^2_{x^{(1)}}$ and ME with constant $\sigma^2_u > 0$ is added to $\boldsymbol{x}$, the regression parameter $\beta_x^{(0)}$ is attenuated more than $\beta_x^{(1)}$ in the naive analysis, leading to a spurious interaction $\beta^{\star}_{sx} > 0$ (Fig. 1D), that is, nonparallel regression lines for the two groups. Note that the bias in the interaction effect is exactly in the opposite direction as in the previous case, although the sampling variance of $\boldsymbol{w}^{(1)}$ is larger than the sampling variance of $\boldsymbol{w}^{(0)}$

 

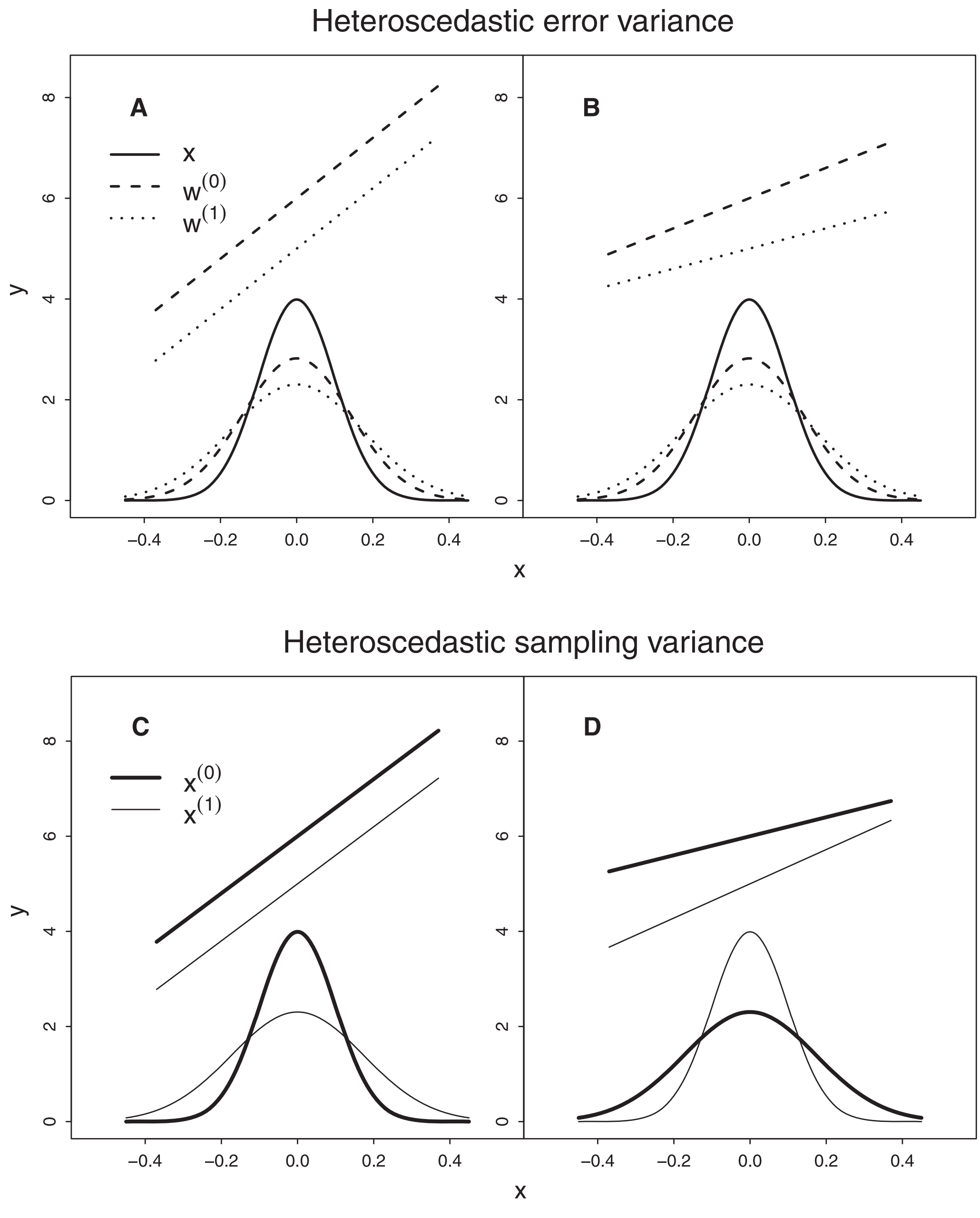


**Figure 1** Illustration of how heteroscedastic error variances or heteroscedastic sampling variances may lead to spurious interaction effects in the presence of ME in linear regression. (Top panel) The error in $\boldsymbol{x}$ is heteroscedastic with variances $\sigma^2_{u^{(0)}} < \sigma^2_{u^{(1)}}$. The distribution of $\boldsymbol{x}$ is shown with solid lines, and the measured covariate $\boldsymbol{w}$ is subdivided into subsets $\boldsymbol{w}^{(0)}$ and $\boldsymbol{w}^{(1)}$. The corresponding distributions are shown with dashed and dotted lines. (A) Parallel regression slopes indicate no interaction effect when the true covariate $\boldsymbol{x}$ is included in the linear regression. (B) The lines are no longer parallel when $\boldsymbol{w}$ is included in the regression. (Bottom panel) The error in $\boldsymbol{x}$ is homoscedastic, but the sampling variance is heteroscedastic with $\sigma^2_{x^{(0)}} < \sigma^2_{x^{(1)}}$. (C) No interaction is present when $\boldsymbol{x}$ is included in the regression. (D) A spurious interaction occurs when $\boldsymbol{w}$ is used instead.

 

in both examples. In practice, of course, any combination of heteroscedastic error and heteroscedastic sampling variances may occur.

Equation (4) gives an analytical expression of the bias in the naive interaction coefficient $\beta^{\star}_{sx}$ in a simple linear regression when $\boldsymbol{x}$ suffers from classical heteroscedastic ME and/or sampling variance, and when the covariate $\boldsymbol{s}$ is binary. The central aspect of Eq. (4) is that the attenuation factors $\lambda_0$ and $\lambda_1$ depend on the error variance and the sampling variance of $\boldsymbol{x}$. For this reason alone, group-specific error variances or sampling variances lead to group-specific slope estimates with different biases, and this absolute difference is then absorbed by the interaction term.

It is not straightforward to generalize these analytical results to GLMs, as there is no general theory predicting the size and the direction of bias in GLMs induced by ME in covariates. However, as long as covariate error leads to an error/sampling-variance-dependent bias in the parameter estimates, the origin of bias in interaction terms remains conceptually the same as that for linear regression. For classical covariate error in logistic regression, for instance, Stefanski and Carroll (1985) found that the magnitude of the bias in the slope parameter depends on the ME variance. For Berkson ME, Tosteson et al. (1989) have shown how the error variance influences the bias in the parameters of probit regression, and the results approximately hold for logistic regression. A similar bias as in the linear model is thus expected in the interaction term when heteroscedastic classical or Berkson error variances (or heteroscedastic sampling variances) are present in logistic regression (see also the simulation results of Sections 4.1 and 4.4). On the other hand, Berkson ME in linear or log-linear regression does not lead to biased slopes (Carroll, 1989). Consequently, no biases in the interaction terms are expected in these cases, neither in the presence of homoscedastic, nor heteroscedastic error or sampling variances.

## 4 Simulations

The following simulation examples illustrate the effects on the interaction parameter of GLMs when covariate $\boldsymbol{x}$ suffers from classical heteroscedastic ME or sampling variance. R-code for all simulations of this section is available as Supporting Information. The reference model is given by Eq. (1), but all simulations presented here have as true linear predictor

$$\eta_i = 1 + x_i,$$

for $i = 1, \ldots, n$, with $n = 1000$ being the number of data points in all simulations. The reference regression parameters are thus always given as $\beta_0 = \beta_x = 1$ and $\beta_s = \beta_{sx} = 0$. For simplicity, no additional error-free covariates $z$ were added. The true covariate $\boldsymbol{x}$ was Gaussian with $x_i \sim \mathcal{N}(0, \sigma^2_{x^{(s_i)}})$ and potentially heteroscedastic sampling variance depending on $s_i$. The error models were either classical or Berkson as in Eqs. (2) or (3). In simulations 1, 2, and 4, $\boldsymbol{s}$ was a binary covariate with $s_i = 0$ for $i = 1, \ldots, \frac{n}{2}$ and $s_i = 1$ otherwise.

In each of the following simulations 10,000 datasets including erroneous proxies $\boldsymbol{w}$ of $\boldsymbol{x}$ were generated according to different error models. The regression parameters were then estimated with a likelihood approach for both the correct data including $\boldsymbol{x}$, and when their distorted versions $\boldsymbol{w}$ were used instead. Means and intervals ranging from the 2.5% to the 97.5% quantile obtained from the 10,000 data sets are summarized in Fig. 2, and an overview of the models is given in Table 1.

### 4.1 Simulation 1

In this simulation the model was logistic with

$$\eta_i = \text{logit}\left[\Pr(y_i = 1 \mid x_i)\right]. \tag{5}$$

 

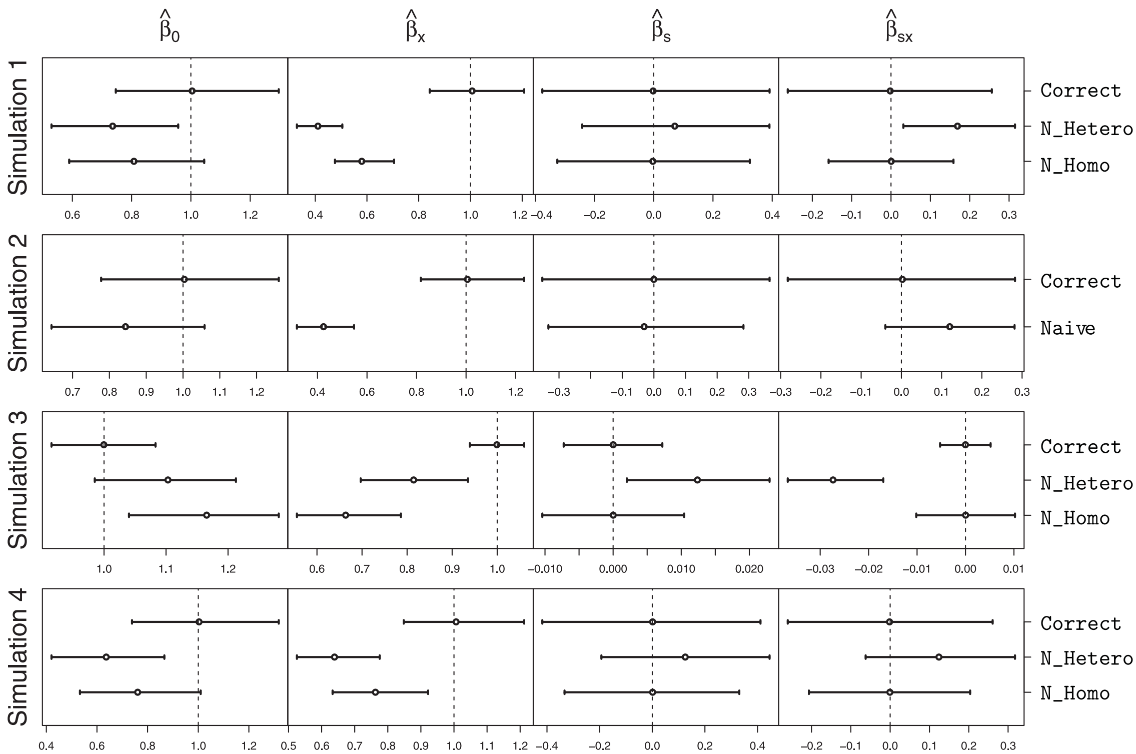


**Figure 2** Means and 2.5% to 97.5% quantile intervals of the iteratively estimated parameters for the regression and error models including $\boldsymbol{x}$ (`Correct`) or $\boldsymbol{w}$ (`Naive`) as covariates in simulations 1–4, as described in the text. `N_Hetero` and `N_Homo` denote the results from the naive analyses with heteroscedastic and homoscedastic error or sampling variance, respectively. The dashed lines indicate the true values from the data-generating process.

**Table 1** Overview of the setup for simulations 1–4.

| Example | Regr. model | $\boldsymbol{s}$ | $\sigma_x^2$ or $\sigma_w^2$ | $\sigma_u^2$ | Error type |
|---|---|---|---|---|---|
| 1 | Logistic | Binary<br>$s_i \in \{0, 1\}$ | Homoscedastic<br>$\sigma_x^2 = 5$ | Heteroscedastic<br>$\sigma_{u^{(0)}}^2 = 4, \sigma_{u^{(1)}}^2 = 2$<br>Homoscedastic<br>$\sigma_u^2 = 2$ | Classical |
| 2 | Logistic | Binary<br>$s_i \in \{0, 1\}$ | Heteroscedastic<br>$\sigma_{x^{(0)}}^2 = 2, \sigma_{x^{(1)}}^2 = 4$ | Homoscedastic<br>$\sigma_u^2 = 2$ | Classical |
| 3 | Poisson | Continuous<br>$s_i \in [0, 20]$ | Homoscedastic<br>$\sigma_x^2 = 1$ | Heteroscedastic<br>$\sigma_{u_i}^2 = s_i \cdot 0.1$<br>Homoscedastic<br>$\sigma_u^2 = 0.5$ | Classical |
| 4 | Logistic | Binary<br>$s_i \in \{0, 1\}$ | Homoscedastic<br>$\sigma_w^2 = 5$ | Heteroscedastic<br>$\sigma_{u^{(0)}}^2 = 4, \sigma_{u^{(1)}}^2 = 2$<br>Homoscedastic<br>$\sigma_u^2 = 2$ | Berkson |

 

The true covariate was distributed as $x_i \sim \mathcal{N}(0, 5)$, and the error model was classical with heteroscedastic error variances depending on the binary covariate $\boldsymbol{s}$ as $w_i \sim \mathcal{N}(x_i, \sigma^2_{u^{(s_i)}})$ with $\sigma^2_{u^{(0)}} = 4$ and $\sigma^2_{u^{(1)}} = 2$. For comparison, we also simulated the respective homoscedastic case with constant error variance $\sigma^2_u = 2$. The first panel of Fig. 2 shows the results of simulation 1. In the presence of heteroscedastic error, all four parameters are biased. In particular, the interaction estimate $\hat{\beta}_{sx}$ is reversely attenuated, which is in agreement with the theory of Section 3, and the interval covering the range between the 2.5% and the 97.5% quantile does not overlap 0. Notably, also $\hat{\beta}_s$ is biased, which can be explained as follows: in the presence of homoscedastic ME, both $\hat{\beta}_0$ and $\hat{\beta}_x$ are affected, as can also be seen in the first panel of Fig. 2. Consequently, when ME differs for the two groups determined by $s_i = 0$ and $s_i = 1$, both the biases in $\hat{\beta}_0$ and $\hat{\beta}_x$ depend on group membership, and their differences are absorbed in $\hat{\beta}_s$ and $\hat{\beta}_{sx}$, respectively.

### 4.2 Simulation 2

The model was as in Eq. (5) with binary covariate $\boldsymbol{s}$, but with constant error variance $\sigma^2_u = 2$ (homoscedastic ME), while the variance of $\boldsymbol{x}$ depended on group membership with $\sigma^2_{x^{(0)}} = 2$ and $\sigma^2_{x^{(1)}} = 4$, respectively. The results in panel 2 of Fig. 2 show that the bias in $\hat{\beta}_{sx}$ emerges as predicted. As in Simulation 1, all four regression coefficients are affected.

### 4.3 Simulation 3

The regression model was Poisson with

$$\eta_i = \log\left[\mathsf{E}(y_i \mid x_i)\right].$$

Covariate $\boldsymbol{s}$ was distributed in the interval [0, 20] with $s_1 = 0$, $s_n = 20$, and equal distances $(s_{i+1} - s_i) = 20/(n-1)$, emulating a continuous covariate. The true covariate $\boldsymbol{x}$ was simulated independently as $x_i \sim \mathcal{N}(0, 1)$, and the classical error model was heteroscedastic with $\sigma^2_{u^{(i)}} = s_i \cdot 0.1$, taking increasing values in the range between 0 and 2 depending on $s_i$. The constant error variance case with $\sigma^2_u = 0.5$ was also simulated for comparison. The results are summarized in panel 3 of Fig. 2. A similar picture as for logistic regression emerges, with biased estimates $\hat{\beta}_0$ and $\hat{\beta}_x$, but unbiased estimates $\hat{\beta}_s$ and $\hat{\beta}_{sx}$ for homoscedastic ME. With heteroscedastic ME all four regression coefficients are biased. Again, the interval for $\hat{\beta}_{sx}$ does not cover 0, and also the coefficient $\hat{\beta}_s$ is severely biased.

### 4.4 Simulation 4

Except in linear and log-linear regression, the presence of Berkson error may also bias regression coefficients (Burr, 1988; Bateson and Wright, 2010). To illustrate how interaction terms are affected, we repeated Simulation 1 of model (5), but with the continuous covariate $\boldsymbol{x}$ suffering from heteroscedastic Berkson ME. We simulated independent $w_i \sim \mathcal{N}(0, 5)$ and used the heteroscedastic error model $x_i \sim \mathcal{N}(w_i, \sigma^2_{u^{(s_i)}})$ with $\sigma^2_{u^{(0)}} = 4$ and $\sigma^2_{u^{(1)}} = 2$. Note that with this simulation setup, the sampling variance of $\boldsymbol{x}$ is also expected to be heteroscedastic with $\sigma^2_{x^{(0)}} = \sigma^2_w + \sigma^2_{u^{(0)}} = 9$ and $\sigma^2_{x^{(1)}} = \sigma^2_w + \sigma^2_{u^{(1)}} = 7$. A comparative dataset with constant error variance $\sigma^2_u = 2$ was also simulated. The results in panel 4 of Fig. 2 show that the bias induced by Berkson error is very similar to that of classical error. Again, heteroscedastic ME biases all coefficients, although the effects on $\hat{\beta}_s$ and $\hat{\beta}_{sx}$ are somewhat less pronounced than for classical ME. Homoscedastic ME attenuates $\hat{\beta}_0$ and $\hat{\beta}_x$, but not $\hat{\beta}_s$ and $\hat{\beta}_{sx}$.

 

## 5 Bayesian measurement error modeling

Both theory (Section 3) and simulations (Section 4) have shown that interaction parameters of GLMs may be seriously biased, and in particular reversely attenuated, when one of the covariates involved in the interaction has been mismeasured. Even if the simulation examples in Section 4 used more pronounced errors and heteroscedasticities than what one would expect in practice, error estimation, and error modeling might be beneficial or even crucial in many applications.

To account for heteroscedastic error or sampling variance in a covariate $\boldsymbol{x}$ that appears also in an interaction term $\boldsymbol{sx}$ as in model (1), we employ a Bayesian approach using INLA (Rue et al., 2009). INLA has been shown to be suitable for error modeling in GLMMs when there is Gaussian classical or Berkson ME in a continuous covariate $\boldsymbol{x}$ (Muff et al., 2015). The Bayesian ME modeling approach is based on a hierarchical model that encompasses the following levels:

(i) The *regression model*, which is here

$$\mathsf{E}(\boldsymbol{y} \mid \boldsymbol{x}, \boldsymbol{\theta}_1) = h(\beta_0 \mathbf{1} + \beta_x \boldsymbol{x} + \beta_s \boldsymbol{s} + \beta_{sx} \boldsymbol{sx} + z\boldsymbol{\beta}_z), \tag{6}$$

where $\boldsymbol{\theta}_1$ is a vector of potential additional hyperparameters of the likelihood. Note that, thanks to the modular framework of INLA, it is straightforward to extend model (6) to a GLMM by adding normally distributed random effects on the linear predictor scale.

(ii) The *error model*, either classical (C) or Berkson (B),

$$\begin{aligned} &(\mathrm{C}) \quad \boldsymbol{w} = \boldsymbol{x} + \boldsymbol{u}, \\ &(\mathrm{B}) \quad \boldsymbol{x} = \boldsymbol{w} + \boldsymbol{u}, \end{aligned}$$

with $\boldsymbol{u} \sim \mathcal{N}(0, \sigma_u^2 \mathbf{D}_u)$, and $\mathbf{D}_u$ denoting a diagonal matrix, where the specification of unequal entries in $\mathbf{D}_u$ allows for heteroscedastic ME. In this paper we are interested in the particular case where error variances depend on $\boldsymbol{s}$ according to Eqs. (2) or (3). However, any types of heteroscedasticities can be modelled, see, for example, Muff et al. (2015, Section 5.1).

(iii) If the error model is classical, an additional level is needed to specify the distribution of $\boldsymbol{x}$, the so-called *exposure model*

$$\boldsymbol{x} \mid \boldsymbol{s}, z = \alpha_0 \mathbf{1} + \alpha_s \boldsymbol{s} + z\boldsymbol{\alpha}_z + \boldsymbol{\varepsilon}_x, \quad \boldsymbol{\varepsilon}_x \sim \mathcal{N}\left(0, \sigma_x^2 \mathrm{D}_x\right),$$

accounting for a potential linear dependency of $\boldsymbol{x}$ on $\boldsymbol{s}$ and other covariates $z$. An important prerequisite for applying INLA is the normality of $\boldsymbol{x} \mid \boldsymbol{s}, z$, although recent extensions of INLA might relax this restriction in the future (Martins and Rue, 2014). The matrix $\mathrm{D}_x$ is such that $\boldsymbol{x}$ fits into a Gaussian Markov random field (GMRF) structure to account for temporal and/or spatial dependencies (Rue and Held, 2005). Here, we consider only the case where the components of $\boldsymbol{x}$ are independent, but we allow for heteroscedasticity, that is, diagonal entries that depend on $\boldsymbol{s}$. Note that if $\boldsymbol{x}$ is assumed to be independent of the other covariates, all coefficients in the exposure model except $\alpha_0$ can be fixed at zero.

(iv) Independent normal priors with low precisions are specified for the regression parameters $\boldsymbol{\beta} = (\beta_0, \beta_x, \beta_s, \beta_{sx}, \boldsymbol{\beta}_z^\top)^\top$ and $\boldsymbol{\alpha} = (\alpha_0, \alpha_s, \boldsymbol{\alpha}_z^\top)^\top$, and *hyperpriors* are defined for the hyperparameters $\boldsymbol{\theta}_1$, $\sigma_u^2$, and $\sigma_x^2$. Note that, technically, $\beta_x$ and $\beta_{sx}$ are also treated as hyperparameters in the INLA framework. As a convention in Bayesian statistics, variances are parameterized as precisions. For $\tau_x = 1/\sigma_x^2$ and $\tau_u = 1/\sigma_u^2$ we assume gamma distributions, where the corresponding shape and rate parameters are chosen based on expert knowledge.

For details of the INLA approach we refer to the original paper of Rue et al. (2009), and Muff et al. (2015) describe how the hierarchical model including (i)–(iv) fits into the INLA framework.

 

## 6 Example: The Framingham heart study

The Framingham heart study is a large cohort study that aims to understand the factors leading to coronary heart disease and, in particular, the role of systolic blood pressure (SBP) (Kannel et al., 1986). The outcome $y_i \in \{0, 1\}$ is an indicator for presence or absence of the disease, and is modelled via a logistic regression.

The dataset that encompasses measurements from $n = 641$ males was originally presented in MacMahon et al. (1990), and later in Carroll et al. (2006, Section 9.10). The continuous, error-prone covariate is $x_i = \log(\text{SBP}_i - 50)$, a transformation of SBP that was originally proposed by Cornfield (1962). The second predictor is binary, indicating smoking status with $s_i = 0$ for nonsmokers and $s_i = 1$ for smokers. Since it is impossible to measure the long-term SBP, measurements at clinical visits had to be used as proxies. These might considerably differ from the long-term blood pressure, making them error-prone covariates (Carroll et al., 2006). Importantly, the SBP had been measured twice at different examinations. These proxy measures for $x_i$ are denoted as $w_{i1}$ and $w_{i2}$, and they were centered around zero in our analyses. The dataset is identical to the one used in Muff et al. (2015, Section 5.2), where error modeling with INLA was presented for the case of homoscedastic error variances. However, here we created additional error in the measurements $w_{i1}$ and $w_{i2}$ if the person was a smoker ($s_i = 1$) to emulate heteroscedastic ME. The hierarchical levels of the model for this modified dataset can be specified as follows:

(i) The outcome $\boldsymbol{y}$ is assumed to be Bernoulli distributed, and the regression model is logistic with linear predictor

$$\text{logit}\,[\mathsf{E}(\boldsymbol{y} \mid \boldsymbol{x})] = \beta_0 + \beta_x \boldsymbol{x} + \beta_s \boldsymbol{s} + \beta_{sx} \boldsymbol{s}\boldsymbol{x}.$$

The interaction between $\boldsymbol{x}$ and $\boldsymbol{s}$ in the regression was included here to study the effect of heteroscedastic error and to illustrate that it is possible to correctly model such an error structure using INLA.

(ii) In the specification of the error model we assumed that the (transformed) repeated measurements $\boldsymbol{w}_1 = (w_{11}, \ldots, w_{n1})^\top$ and $\boldsymbol{w}_2 = (w_{12}, \ldots, w_{n2})^\top$ at examinations 1 and 2, respectively, were independent and normally distributed with mean $\boldsymbol{x}$. We artificially increased the ME for the smoking group. To this end, the measurement error variance in the actual data points $w_{ij}$ was assumed to be homoscedastic and approximately equal to the posterior mean estimate from the analysis in Muff et al. (2015), namely $\sigma_u^2 = 0.013$. We then added error independently as

$$w_{ij}^\star = w_{ij} + u_{ij}, \quad u_{ij} \sim \mathcal{N}(0, 0.117), \quad \text{if } s_i = 1,$$

and $w_{ij}^\star = w_{ij}$ if $s_i = 0$, so that $\boldsymbol{w}_1^\star = (w_{11}^\star, \ldots, w_{n1}^\star)^\top$ and $\boldsymbol{w}_2^\star = (w_{12}^\star, \ldots, w_{n2}^\star)^\top$ denote the naive measurements at examinations 1 and 2 with heteroscedastic ME. Measurements for smokers then suffer from error with ten times larger variance than for nonsmokers. This leads to the classical heteroscedastic error model

$$\boldsymbol{w}_j^\star \mid \boldsymbol{x} \sim \mathcal{N}\left(\boldsymbol{x}, \sigma_u^2 \mathrm{D}_u\right), \quad j = 1, 2, \tag{7}$$

where the entries in the diagonal matrix can be used to scale the error variance.

(iii) The exposure model depended on the smoking status

$$\boldsymbol{x} \mid \boldsymbol{s} \sim \mathcal{N}\left(\alpha_0 \mathbf{1} + \alpha_s \boldsymbol{s}, \sigma_x^2 \mathrm{I}\right), \tag{8}$$

where the variance of $\boldsymbol{x}$ was assumed to be independent of $\boldsymbol{s}$ and thus homoscedastic, with $\mathbf{I}$ denoting the identity matrix of appropriate dimension.

**Table 2** Posterior means and 95% credible intervals given by INLA for cases 1–5 in the analysis of the (modified) Framingham data for different ME types, ME models, and sampling variance (SV) models for $\boldsymbol{x}$. Homoscedastic (homosc.) error type means that the error variance is approximately constant $\sigma_u^2 = 0.013$, while for heteroscedastic (heterosc.) error the variance for individual $i$ is either $\sigma_{u^{(0)}}^2 = 0.013$ or $\sigma_{u^{(1)}}^2 = 0.130$, depending on its smoking status $s_i \in \{0, 1\}$.

| Case | ME type | ME model | SV model | $\hat{\beta}_x$ | $\hat{\beta}_s$ | $\hat{\beta}_{sx}$ |
|---|---|---|---|---|---|---|
| 1 | homosc. | homosc. | homosc. | 3.10 [0.72,5.51] | 0.55 [−0.09,1.28] | −1.54 [−4.24,1.12] |
| 2 | heterosc. | heterosc. | homosc. | 3.05 [0.71,5.39] | 0.55 [ −0.10,1.27] | −1.70 [−4.62,1.22] |
| 3 | heterosc. | homosc. | homosc. | 4.47 [ 0.98,8.23] | 0.73 [−0.02,1.65] | −3.46 [−7.42,0.33] |
| 4 | heterosc. | homosc. | heterosc. | 5.11 [1.20,9.16] | 0.75 [−0.02,1.69] | −4.15 [−8.53,0.03] |
| 5 | heterosc. | none | homosc. | 2.49 [1.71,3.25] | 0.53 [−0.10,1.22] | −1.86 [−2.73,−1.04] |

(iv) Prior distributions were taken as in Muff et al. (2015), namely $(\beta_0, \beta_x, \beta_s, \beta_{sx})^\top \sim \mathcal{N}(\mathbf{0}, 100 \cdot \mathrm{I})$, $(\alpha_0, \alpha_s)^\top \sim \mathcal{N}(\mathbf{0}, \mathrm{I})$, $\tau_x = 1/\sigma_x^2 \sim \mathrm{G}(10, 1)$, and $\tau_u = 1/\sigma_u^2 \sim \mathrm{G}(100, 1)$, where parameters of the gamma distribution are the shape and rate parameters, respectively.

To assess the capability of the INLA approach in modeling heteroscedastic ME, we ran five analyses (cases) with different combinations of error types and error models (see Table 2 for an overview). All calculations were done using the `r-inla` version updated on January 27, 2015. In case 1, we included $\boldsymbol{w}_1$ and $\boldsymbol{w}_2$ without additional error, and correctly modelled the ME as homoscedastic. The covariance matrix $\mathrm{D}_u$ of error model (7) was set to the identity matrix I. Case 2 included $\boldsymbol{w}_1^\star$ and $\boldsymbol{w}_2^\star$ with heteroscedastic error, and the error was appropriately accounted for by fixing the entries of the diagonal matrix $\mathrm{D}_u$ to be 1 or 10, depending on smoking status $\boldsymbol{s}$. The `r-inla` code and data for this example are provided as Supporting Information. In case 3 we also included $\boldsymbol{w}_1^\star$ and $\boldsymbol{w}_2^\star$ as proxies for $\boldsymbol{x}$, but the error model was erroneously assumed to be homoscedastic, using $\mathrm{D}_u = \mathrm{I}$ in (7). This setup aimed to illustrate the bias that is induced in the parameter estimates when the error model is not appropriately specified. Posterior distributions of case 1 served as references to quantify this bias. Case 4 again included $\boldsymbol{w}_1^\star$ and $\boldsymbol{w}_2^\star$ with heteroscedastic error, but now it was erroneously assumed that the unequal variances between the nonsmoking ($s_i = 0$) and the smoking ($s_i = 1$) group were due to different sampling variances in the covariate $\boldsymbol{x}$, and not due to heteroscedastic ME. Thus we used $\mathrm{D}_u = \mathrm{I}$, but replaced I in the exposure model (8) by the diagonal matrix $\mathrm{D}_x$ with entries equal to 1 or 2, depending on smoking status $\boldsymbol{s}$, assuming that smokers had twice the variance of nonsmokers. Finally, in case 5, we carried out a naive analysis, including $\boldsymbol{w}_1^\star$ and $\boldsymbol{w}_2^\star$ as proxies for $\boldsymbol{x}$, but neglecting the error by fixing its variance at $\sigma_u^2 = 10^{-12}$, using otherwise the same framework.

Posterior means and 95% credible intervals of the posterior marginals for $\hat{\beta}_x$, $\hat{\beta}_s$ , and $\hat{\beta}_{sx}$ are summarized in Table 2. Case 1 serves as the reference case. The error type and the used error model were both homoscedastic. In case 2 with heteroscedastic ME in the covariate and appropriate error modeling, approximately correct parameter estimates could be recovered with INLA. This is true in particular for the interaction term $\hat{\beta}_{sx}$, the focus of interest, but also for the estimates of the main effects. As expected, the estimated coefficients of case 3, where error modeling did not account for heteroscedasticity, are biased with respect to the reference case 1. The posterior mean estimate of the interaction coefficient $\hat{\beta}_{sx}$ is significantly more negative in case 3 ($\hat{\beta}_{sx} = -1.54$ in case 1 versus $\hat{\beta}_{sx} = -3.46$ in case 3), thus suffering from reverse attenuation. Notably, $\hat{\beta}_x$ and $\hat{\beta}_s$ are also reversely attenuated. The results of case 4 show that if the heteroscedasticity in the covariate measurements $\boldsymbol{w}_1^\star$ and $\boldsymbol{w}_2^\star$ is erroneously assigned to the covariate $\boldsymbol{x}$ instead to the error $\boldsymbol{u}$, the bias in the parameter estimates is not corrected, but aggravated. This result is not surprising, see also the illustrative example of Section 3. Finally, the posterior means for $\hat{\beta}_x$ and $\hat{\beta}_{sx}$ of case 5, where a naive analysis without error modeling was carried out, lie between those of the correct model of case 2 and the misspecified model of case 3 (assuming homoscedastic error and sampling variances). Cases 3–5 illustrate the importance of detailed knowledge of the ME structure for appropriate error modeling, as it may be worse to use a misspecified error model than to do a simple naive analysis that does not take the error into account.

## 7 Discussion

It is well known that the presence of measurement error (ME) in covariates may seriously bias estimates of parameters and confidence intervals of statistical models when the error is not accounted for. Many approaches to quantify the bias and to model the ME to recover correct estimates have been proposed in the past. The problems concerning interaction terms, however, have only rarely been in the focus of the ME literature, and if so, attenuation effects for homoscedastic ME were discussed.

The aim of this work was to draw attention to biases in interaction parameters that may occur in GLMs when classical or Berkson ME is present in a continuous covariate $\boldsymbol{x}$. We considered the case where $\boldsymbol{x}$ is directly involved in an interaction $\boldsymbol{sx}$, and $\boldsymbol{s}$ was assumed to be independent of $\boldsymbol{x}$ and measured without error. In particular, we have shown that certain types of heteroscedasticities in the ME variance or sampling variance of the mismeasured covariate may lead to reverse attenuation of interaction parameters $\beta_{sx}$. We discussed two special types of heteroscedasticities, namely when the error variance or the sampling variance of $\boldsymbol{x}$ depends on $\boldsymbol{s}$. If the true interaction parameter $\beta_{sx}$ equals zero, such heteroscedasticities may lead to naive parameters $|\beta^{\star}_{sx}| > 0$, and thus to spurious interaction terms. In the simplest situation, $\boldsymbol{s}$ is binary and thus indicates two groups, for example, males and females. The measured values for $\boldsymbol{x}$ have then either different precisions for individuals in the two groups, or $\boldsymbol{x}$ is more variable in one of the groups (or both). Note that the heteroscedastic sampling variance case for $\boldsymbol{x}$ may be relevant in practice, but has so far been neglected in the context of error-correction methods. Importantly, apart from the special case where $\beta_{sx} = 0$, it is hard to predict the direction of the bias in $\beta^{\star}_{sx}$ when heteroscedastic error or sampling variances in $\boldsymbol{x}$ are present.

We have proposed a Bayesian approach to recover approximately correct parameter estimates that allows to properly scale the ME variance and the sampling variance. The application to the Framingham heart study of Section 6 illustrated that it is straightforward to model heteroscedastic Gaussian measurement error using INLA, and the results indicate that the approximations are good. Possible generalizations of regression and error models were already discussed in Muff et al. (2015), such as the inclusion of random effects in the regression equation (GLMMs), the treatment of correlation between covariate error, and regression error in linear regression, or more complex GMRF structures for the unobserved covariate $\boldsymbol{x}$.

The unexpected emergence of interaction parameters in scientific studies often gives raise to new hypotheses, as the authors need to interpret the interactions, even if they are hard to understand (Vandewater et al., 2004; Hagen et al., 2006; Reid et al., 2007). An important implication of the work presented here is that the palette of interpretations for unexpectedly emerging interaction parameters is extended by a new option: the result could be spurious due to heteroscedastic error or sampling variance of a covariate that is involved in the interaction. Of course, such a hypothesis is hard to prove if the error cannot be quantified because repeated measurements, validation data, or instrumental variables are lacking. An indicator for the presence of heteroscedasticities are the sampling variances of different subgroups for the measured covariate $\boldsymbol{w}$, for example, $\boldsymbol{w}^{(0)}$ and $\boldsymbol{w}^{(1)}$, if $\boldsymbol{s}$ is binary. For instance, Vandewater et al. (2004) report standard deviations of covariate measurements for boys and girls separately, and some values differ by a factor of up to almost three between the two genders in certain age groups. Given that the covariates themselves are prone to error, and that an unexpected interaction between this covariate and sex emerges, the influence of ME could be relevant in this study. Of course, reporting the sampling variance of $\boldsymbol{w}$ can never replace a careful estimation of the ME and must be treated with absolute care. Moreover, when the sampling variance of $\boldsymbol{w}$ is heterogeneous, but no additional information about the error is available, it remains impossible to identify if the heterogeneity is in the error or in the sampling variance of $\boldsymbol{x}$, or both. This is, however, a very important distinction, because error correction for the interaction parameters may otherwise be in the wrong direction, as illustrated in Section 3 and in case 4 of the example in Section 6. Generally, the critical point remains the correct specification and quantification of the error model. Hence, information about the underlying measurement process is essential. Possible errors must be identified early in a study and the entire data-collection process should be driven by such considerations. The requirements on the data, respectively on the data-collection process, increase with more complex error structures, and high sampling costs might be limiting.

Analytical expressions for the bias in the naive interaction coefficient $\beta^{\star}_{sx}$ were derived here only for linear regression with classical covariate error in $\boldsymbol{x}$ and a binary covariate $\boldsymbol{s}$. As briefly mentioned at the end of Section 3, theory is more challenging in GLMs, and separate analytical derivations would be required for different likelihoods. Despite this, the fundamental idea remains the same: whenever ME leads to biased regression slopes, and when heteroscedastic error or sampling variances are present, interaction terms can be attenuated or reversely attenuated, and common testing procedures might not give valid answers.

We have discussed effects in the parameters when a mismeasured covariate $\boldsymbol{x}$ is involved in an interaction term $\boldsymbol{sx}$. However, as highlighted in Section 3, parameters of an observed covariate $z$ can also be biased when $z$ is correlated to $\boldsymbol{x}$ (Carroll et al., 1985; Gleser et al., 1987), and the magnitude and the direction of the bias depend on the error variance and the strength of collinearity (Zidek et al., 1996; Carroll et al., 2006; Freckleton, 2011). When an interaction is formed between $z$ and $\boldsymbol{s}$, and the former is correlated to $\boldsymbol{x}$, the interaction $\boldsymbol{s}z$ might thus also be affected by such a bias.

In summary, we have shown that ME can attenuate *or* reversely attenuate multiplicative interaction terms in GLMs, depending on the exact nature of the ME. This highlights the importance of a careful evaluation and parameterization of ME models. If prior knowledge about the nature of the ME is missing, error modeling is difficult or even counterproductive. We hope that the work presented here further motivates researchers from applied fields to pay attention to ME when planning and carrying out studies, because suitable error modeling can be crucial to obtain precise answers to research questions.

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**Conflict of interest**

*The authors have declared no conflict of interest.*

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