Appendix. Proofs.

Residual association in situation 3

If $M^* = M + \gamma_0 + \gamma_1 X + U$ where U is normally distributed with mean 0 and variance σ_u^2, the observed regression coefficient for X is approximately $\beta_1^* = \beta_1 - \beta_2^* \gamma_1 + \beta_2^* (1-\lambda)\alpha_1 / \lambda$, where λ is the reliability ratio(5).

Proof. First ignore the random error term U and write $\tilde{M} = \gamma_0 + M + \gamma_1 X$. When we consider the model logit(Pr(Y=1| $\tilde{M}$, X, C)) = $\tilde{\beta}_0 + \tilde{\beta}_1 X + \tilde{\beta}_2 \tilde{M} + \tilde{\beta}_C^t C$, it immediately follows that $\tilde{\beta}_2 = \beta_2$, $\tilde{\beta}_C^t = \beta_C^t$, $\tilde{\beta}_0 = \beta_0 - \beta_2 \gamma_0$ and $\tilde{\beta}_1 = \beta_1 - \beta_2 \gamma_1$, with β_0, β_1, β_2 and β_C the coefficients from the true logistic model (1). The measured intermediate then is $M^* = \tilde{M} + U$, with U normally distributed with mean 0, and variance σ_u^2. Using the formulas of Carrol et al[3, p 52] for bias in the regression coefficients for random measurement error, yields that the regression coefficients for exposure and intermediate in the model logit(Pr(Y=1| M^*, X, C)) = $\beta_0^* + \beta_1^* X + \beta_2^* M^* + \beta_C^{*t} C$, are equal to $\beta_2^* = \lambda \beta_2$ and

$$\beta_1^* = \beta_1 - \beta_2 \gamma_1 + \beta_2 (1-\lambda)(E[M^* \mid X=1, C] - E[M^* \mid X=0, C]).$$

Using that $E[M^* \mid X=1, C] - E[M^* \mid X=0, C] = \alpha_1 + \gamma_1$, yields the required result.

Residual association in situation 5

Suppose there is an interacting trigger T, which interacts with X such that $M = c_0 + M^* + c_1 TX$, with M* the measured intermediate. It can be shown that in case of a rare disease

$$\Pr(Y=1 \mid M^*, X, C) \approx \exp(\beta_0 + \beta_1 X + \beta_2 (c_0 + M^*) + \beta_C^t C) \int \exp(\beta_2 c_1 t X) dF(t),$$

with F(t) the distribution function of T.

Proof: Because logit (Pr (Y=1| M, X, C)) = $\beta_0 + \beta_1 X + \beta_2 M + \beta_C^t C$, it follows that logit (Pr (Y=1| M^*, X, T, C)) = $\beta_0 + \beta_1 X + \beta_2 (c_0 + M^* + c_1 TX) + \beta_C^t C$.

Note that we do not observe T. If we perform a logistic regression analysis with M^* and X as covariates, we model Pr (Y=1| M*, X, C). This probability is equal to

$$\Pr(Y=1 \mid M^*, X, C) = \int \Pr(Y=1 \mid M^*, X, C, T=t) dF(t \mid M^*, X, C),$$

with F(t| M^*, X,C) the distribution function of T given M*, X and C. If the trigger is not affected by the confounders, then, because T is unconditionally independent of M^* and X, F(t| M^*, X, C) = F(t). When the disease prevalence is low, odds ratios and relative risks are nearly equivalent and logistic models can be approximate by relative risk models. Then

$$\Pr(Y=1 \mid M^*, X, C, T) \approx \exp(\beta_0 + \beta_1 X + \beta_2 (c_0 + M^* + c_1 TX) + \beta_C^t C).$$

It then follows that:

$$\Pr(Y=1 \mid M^*, X, C) \approx \exp(\beta_0 + \beta_1 X + \beta_2 (c_0 + M^*) + \beta_C^t C) \int \exp(\beta_2 c_1 tX) dF(t).$$

The integral in this expression can be simplified for several different distributions for T. For example if the trigger is binary with p_T=Pr(T=1), then

$\int \exp(\beta_2 c_1 tX) dF(t) = \exp(\beta_2 c_1 X) p_T + (1 - p_T)$. In this case,

$$\exp(\beta_1^*) = \Pr(Y=1 \mid M^*, X=1, C) / (\Pr(Y=1 \mid M^*, X=0, C)$$

$\approx \exp(\beta_1)[\exp(\beta_2 c_1) p_T + (1 - p_T)]$, which leads to the result in (9).

In case of additional random measurement error, assume that $M^* = \tilde{M} + U$, with $U \sim N(0, \sigma_u^2)$ and $M = c_0 + \tilde{M} + c_1 TX$. Because $E[M \mid X, C] = \alpha_0 + \alpha_1 X + \alpha_2^t C$, it follows that $E[\tilde{M} \mid X, C] = \alpha_0 + \alpha_1 X + \alpha_2^t C - c_0 - p_T c_1 X$. When using M* instead of $\tilde{M}$ in a logistic model, the formulas of Carrol et al[3, p 52] for bias in the regression coefficients for classical measurement error, yield that $\beta_1^* = \tilde{\beta}_1 + \beta_2^* (1 - \lambda)(\alpha_1 - p_T c_1) / \lambda$ and $\beta_2^* = \lambda \tilde{\beta}_2$. Combining this with (9) gives

$$\beta_1^* = \beta_1 + \log[\exp(\beta_2^* c_1 / \lambda) p_T + (1 - p_T)] + \beta_2^* (1 - \lambda)(\alpha_1 - p_T c_1) / \lambda$$

Residual association in situation 6

If there is a post-hoc phenomenon, such that $M^* = M + \gamma_0 + \gamma_1 Y + U$, where $U \sim N(0, \sigma_u^2)$, then approximately:

$$\beta_2^* \approx \lambda\beta_2 + \frac{\gamma_1}{\sigma_M^2 + \sigma_U^2} \text{ and}$$

$$\beta_1^* = \beta_1 - \frac{\gamma_1\alpha_1}{\sigma_M^2 + \sigma_U^2} + \left(\beta_2^* - \frac{\gamma_1}{\sigma_M^2 + \sigma_U^2}\right)(1-\lambda)\alpha_1 / \lambda \qquad .$$

Proof: First ignore the random error term U and write M*= γ_0 + M + γ_1Y . Bayes' theorem gives that

$$\text{odds}(\Pr(Y=1 \mid X, M^* = m^*, C)) = \frac{f_{X,C,M^*}(X, m^*, C \mid Y=1)}{f_{X,C,M^*}(X, m^*, C \mid Y=0)} \frac{\Pr[Y=1]}{\Pr[Y=0]},$$

where f indicates the density function.

Note that $f_{X,C,M^*}(X, m^*, C \mid Y=1) = f_{X,C,M}(X, m^* - \gamma_0 - \gamma_1, C \mid Y=1)$ and $f_{X,C,M^*}(X, m^*, C \mid Y=0) = f_{X,C,M}(X, m^* - \gamma_0, C \mid Y=0)$. Applying again Bayes' theorem yields:

$$\text{odds}(\Pr(Y=1 \mid X, M^* = m^*, C)) = \frac{\Pr(Y=1 \mid X, M = m^* - \gamma_0 - \gamma_1, C)}{\Pr(Y=0 \mid X, M = m^* - \gamma_0, C)} \frac{f_{M|X,C}(m^* - \gamma_0 - \gamma_1 \mid X, C) f(X,C)}{f_{M|X,C}(m^* - \gamma_0 \mid X, C) f(X,C)}$$

Because M|X,C is normally distributed with constant variance, it is straightforward to show that

$$\frac{f_{M|X,C}(m^* - \gamma_0 - \gamma_1 \mid X, C)}{f_{M|X,C}(m^* - \gamma_0 \mid X, C)} = \exp\left(\frac{1}{\sigma_M^2}\left[-0.5\gamma_1^2 - \gamma_0\gamma_1 - \gamma_1\alpha_0 - \gamma_1\alpha_1 X - \gamma_1\alpha_2^t C + \gamma_1 m^*\right]\right)$$

Using that, in case of a rare disease, Pr(Y=0|X, M,C)≈1, and that in case of a rare disease Pr(Y=1|X, M,C) can be approximate by a relative risk model, yields

$$\text{odds}(\Pr(Y=1 \mid X=1, M^*=m^*, C)) \approx$$

$$\exp\left(\beta_0 - \frac{0.5\gamma_1^2 + \gamma_0\gamma_1 + \gamma_1\alpha_0}{\sigma_M^2} + \beta_2(-\gamma_0 - \gamma_1) + (\beta_1 - \frac{\gamma_1\alpha_1}{\sigma_M^2})X + (\beta_c^t - \frac{\gamma_1\alpha_2^t}{\sigma_M^2})C + (\beta_2 + \frac{\gamma_1}{\sigma_M^2})m^*\right)$$

This gives $\beta_1^* \approx \beta_1 - \frac{\gamma_1\alpha_1}{\sigma_M^2}$ and $\beta_2^* \approx \beta_2 + \frac{\gamma_1}{\sigma_M^2}$

In case of random measurement error, with $M^* = M + \gamma_0 + \gamma_1 Y + U$, assume first that $\tilde{M}$ =M+U. If $\tilde{M}$ is used instead of M in the logistic model, the formulas of Carrol et al[3, p52] for bias in the regression coefficients for classical measurement error, yield $\tilde{\beta}_1 = \beta_1 + \beta_2(1-\lambda)\alpha_1$ and $\tilde{\beta}_2^* = \lambda\beta_2$. Since $M^* = \gamma_0 + \tilde{M} + \gamma_1 Y$, we have $\beta_1^* \approx \tilde{\beta}_1 - \frac{\gamma_1\alpha_1}{\sigma_{\tilde{M}}^2}$ and $\beta_2^* \approx \tilde{\beta}_2 + \frac{\gamma_1}{\sigma_{\tilde{M}}^2}$. This leads to the final results:

$$\beta_2^* \approx \lambda\beta_2 + \frac{\gamma_1}{\sigma_{\tilde{M}}^2}$$

and $\beta_1^* \approx \beta_1 - \gamma_1\alpha_1 / \sigma_{\tilde{M}}^2 + \beta_2(1-\lambda)\alpha_1 = \beta_1 - \gamma_1\alpha_1 / \sigma_{\tilde{M}}^2 + \left(\beta_2^* - \frac{\gamma_1}{\sigma_{\tilde{M}}^2}\right)(1-\lambda)\alpha_1 / \lambda$.