Use of clinical tolerance limits for assessing agreement

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Introduction

A new methodology to assess agreement between two quantitative measurement methods has been developed, which overcomes the main deficiencies of the conventional Bland & Altman limits of agreement (LoA) method (i.e. constant bias, homoscedasticity of measurement error variances) and directly assesses the level of agreement. The latter, however, is allowed to vary with the underlying latent trait.

The investigator has to define a priori upper and lower tolerance limits between which the differences between the two measurement methods are allowed to vary and agreement is deemed acceptable.

The methodology requires repeated measurements for each individual by at least one of the two measurement methods (for identification of proportional bias and heteroscedasticity).

Methods

Consider the general ***measurement error model***:

$$y_{1ij} = \alpha_1 + \beta_1 x_{ij} + \varepsilon_{1ij}, \quad \varepsilon_{1ij} \mid x_{ij} \sim N(0, \sigma^2_{\varepsilon_1}(x_{ij}; \boldsymbol{\theta}_1))$$
$$y_{2ij} = x_i + \varepsilon_{2ij}, \quad \varepsilon_{2ij} \mid x_i \sim N(0, \sigma^2_{\varepsilon_2}(x_i; \boldsymbol{\theta}_2))$$
$$x_{ij} \sim f_x(\mu_x, \sigma^2_x)$$

where y_{1ij} be the jth replicate measurement by method 1 on individual i, $j = 1, ..., n_i$ and $i = 1, ..., N$, whereas y_{2ij} is obtained by method 2 (the reference), x_{ij} is a latent variable with density f_x representing the true unknown trait, and ε_{1ij} and ε_{2ij} represent measurement errors.

The ***conditional probability of agreement*** is defined as $\mathrm{P}(C_L(x_i) < d_{ij} < C_U(x_i) \mid x_i) \equiv \pi(x_i)$ where $d_{ij} = y_{1ij} - y_{2ij}$, $C_L(x_i)$ and $C_U(x_i)$ define the lower and upper ***clinical tolerance limits***, and the ***overall/marginal agreement*** is given by $\mathrm{P}(C_L(x_i) < d_{ij} < C_U(x_i)) \equiv \pi = \int_{-\infty}^{\infty} \pi(x_i) f_X(x_i) dx$.

Results

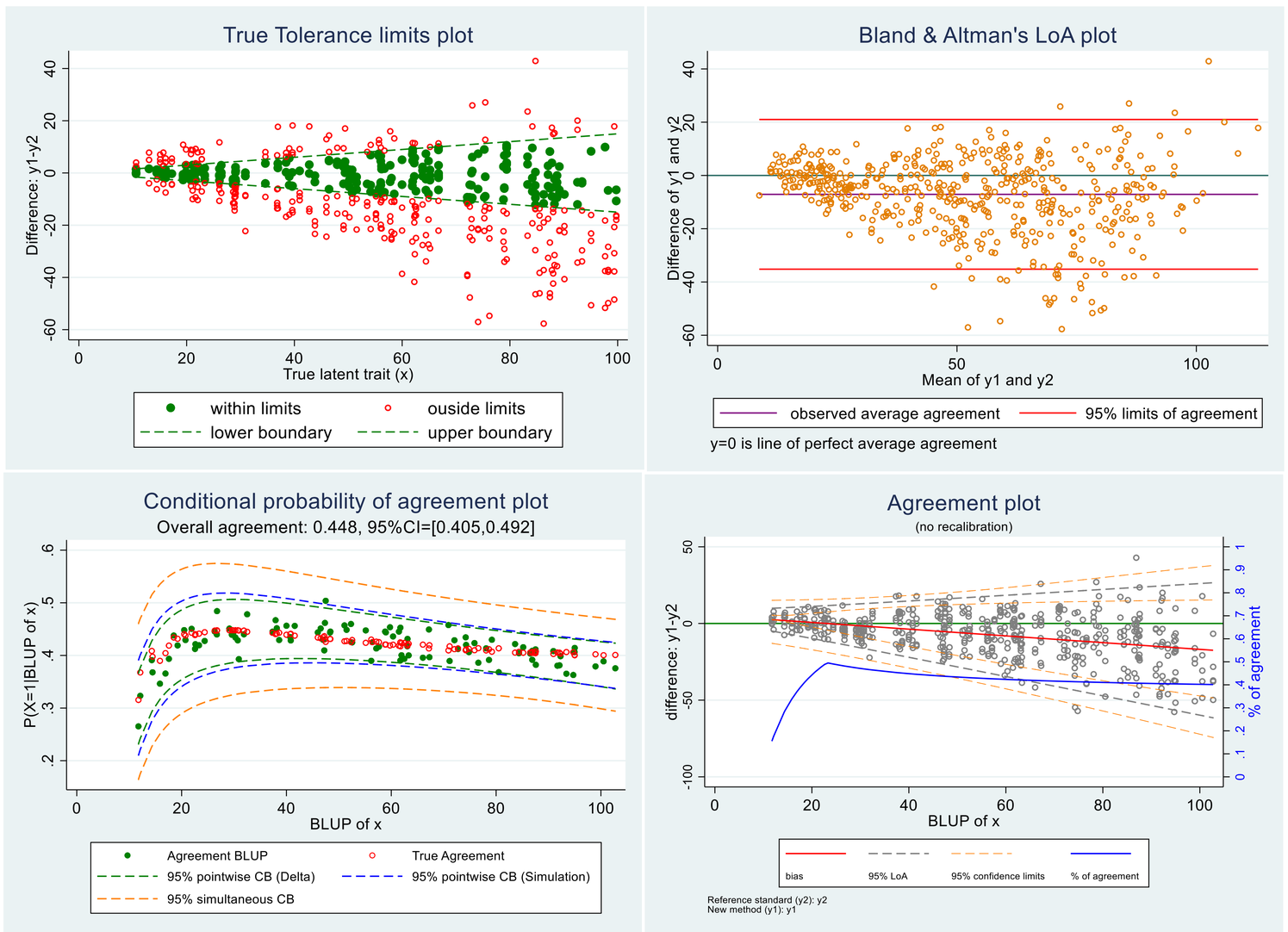

Figure 1 (top left) Scatter plot of the differences y1-y2 versus the BLUP of x with non-constant tolerance limits, (top right) Standard Bland & Altman' LoA plot, (bottom left) Conditional probability of agreement plot, (bottom right) Agreement plot.

Discussion

While the Bland & Altman LoA methodology does not provide a direct measure of the agreement level, the Conditional probability of agreement and the Agreement plots show that agreement varies with the true level of the latent trait.

References

Taffé P. Effective plots to assess bias and precision in method comparison studies. *Stat Meth Med Res* 2018; **27**: 1650-1660.
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