



Note on bias from averaging repeated measurements in heritability studies

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Ge et al. (1) consider the extension of Fisher's classic model for heritability to the case where there are repeated measurements on subjects. One approach to analyzing repeated measurements is to average observations. The authors show empirically and via simulations that estimates of heritability derived from averaging repeated measurements lead to underestimates of heritability. Some may find the bias revealed by Ge et al. (1) to be surprising because averaging is commonly justified in other settings such as repeated measures ANOVA. In this letter we detail the bias that arises from conflating measurement error and unique environmental variance. This elucidates the authors' empirical findings, which represent a case with large measurement error exacerbated by only two measurements per subject.

Consider the model for additive genetic, common environmental, and unique environmental components. We use the mixed-model formulation as in ref. 2 but include measurement error. For conciseness, we assume no nuisance covariates. Let y_{ijk} be the k th measurement for $k = 1, \dots, n$ (for simplicity, we assume the same n for all subjects) for the j th individual in the i th family. Let $a_i \sim N(0, \sigma_A^2)$ denote the additive genetic component, and for dizygotics (DZs) and siblings we add a_{ij} as in ref. 2. Let $c_i \sim N(0, \sigma_C^2)$ denote the common environmental component, $e_{ij} \sim N(0, \sigma_E^2)$ the unique environmental, and $\varepsilon_{ijk} \sim N(0, \sigma_M^2)$ the measurement error (as the authors note, ε_{ijk} can also include biological transients). For monozygotic twins (MZs),

$$y_{ijk} = a_i + c_i + e_{ij} + \varepsilon_{ijk}$$

and for DZs and full siblings,

$$y_{ijk} = \sqrt{0.5}a_i + \sqrt{0.5}a_{ij} + c_i + e_{ij} + \varepsilon_{ijk},$$

and, consequently, $\text{Var } y_{ijk} = \sigma_A^2 + \sigma_C^2 + \sigma_E^2 + \sigma_M^2$ for both cases. Ge et al. (1) observe σ_E^2 and σ_M^2 are identifiable if data are not averaged and define measurement-error corrected heritability: $h^2 = \sigma_A^2 / (\sigma_A^2 + \sigma_C^2 + \sigma_E^2)$.

Now consider $\bar{y}_{ij} = \frac{1}{n} \sum_{k=1}^n y_{ijk}$ (the averaged data). For MZs,

$$\bar{y}_{ij} = a_i + c_i + e_{ij} + \frac{1}{n} \sum_{k=1}^n \varepsilon_{ijk},$$

and then $\text{Var } \bar{y}_{ij} = \sigma_A^2 + \sigma_C^2 + \sigma_E^2 + \frac{1}{n} \sigma_M^2$, and similarly for DZs and full siblings. Now σ_E^2 and σ_M^2 are no longer identifiable, so they are conflated as a single term; define $\sigma_F^2 = \sigma_E^2 + \frac{1}{n} \sigma_M^2$. Consequently, $h_{bias}^2 = \sigma_A^2 / (\sigma_A^2 + \sigma_C^2 + \sigma_F^2)$; equivalently, $h_{bias}^2 = \sigma_A^2 / (\sigma_A^2 + \sigma_C^2 + \sigma_E^2 + \frac{1}{n} \sigma_M^2)$.

Thus, we see that the bias in the averaged data decreases as the number of repeated measurements increases, as well as when the measurement error decreases. Here we have only examined the model-based heritabilities based on identifiability issues, whereas in practice maximum likelihood or other estimators may introduce some additional biases, but the simple analysis here suffices to reveal the crux of the issue. The authors highlight a case with high variability and only two measurements ($n = 2$), and hence the differences between approaches are large. We commend the authors for pointing out the empirical differences that can arise but also note the role of the number of repeated measurements.

¹ Ge T, Holmes AJ, Buckner RL, Smoller JW, Sabuncu MR (2017) Heritability analysis with repeat measurements and its application to resting-state functional connectivity. *Proc Natl Acad Sci USA* 114:5521–5526.

² Rabe-Hasketh S, Skrondal A, Gjessing H (2008) Biometrical modeling of twin and family data using standard mixed model software. *Biometrics* 64:280–288.

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