Effects of Error-prone Exposure in the Analysis of Longitudinal Studies with Mixed Models with Application to Physical Activity Assessment Instruments in a Large Biomarker Validation Study

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Motivating example: Longitudinal studies of PA

- PA has been linked to many health outcomes (cancer, diabetes, cardiovascular disease, obesity, quality of life)
- PA is characterized by both short-term (e.g., month to month) and long-term (over years) changes
- To take account of dynamic nature of PA in the analysis of its relationship with health outcomes, it is important to carry out longitudinal studies
- No less important is evaluation of measurement error in assessing PA with different instruments

Statistical analysis of longitudinal studies

- Mixed effects models have become one of the major approaches to the analysis of longitudinal studies
- Those models include both *fixed* and *random effects*
  - *fixed effects* are population level functions of covariates
  - *random effects* are subject-specific realizations of latent random variables that account for between-subject heterogeneity and induce within-subject correlation structure

Mixed effects models

- **Traditional assumption**: random effects are independent of covariates
- If both the exposure and outcome vary with time, it is natural to specify mixed effects models for both
- If heterogeneity in temporal trajectories is related to unknown subject-level *confounders*, random effects in those models will be correlated inducing correlation between random effects in the outcome model and the exposure

Mixed effects models

- Dependence of random effects on exposure *always* leads to three different effects:
  - *within-subject* (*individual level*) *effect* of the exposure for a particular subject on this subject's mean outcome
  - *between-subject effect* of the mean (over time) exposure on the mean outcome in the population
  - *marginal* (*population-average*) *effect* of the exposure on the contemporaneous mean outcome in the population
- Ignoring existing dependence leads to biased estimates of all three effects

Simple example: linear mixed model (LMM)

- Let x_{ij}, y_{ij} denote the exposure and outcome for person i, $i = 1, ..., n$, time $j = 1, ..., m$
- Consider a simple joint linear mixed regression model

$$y_{ij} = \beta_0 + \beta_x x_{ij} + u_{yi} + \epsilon_{yij}$$
$$x_{ij} = \alpha_0 + u_{xi} + \delta_{xij}$$

where, in general, $\sigma_{u_{xy}} \equiv cov(u_{yi}, u_{xi}) \neq 0$

Linear mixed model

- Consider linear regression

$$u_{yi} = \frac{\sigma_{u_{xy}}}{\sigma^2_{u_x}} u_{xi} + \eta_{yi}, \;\; \eta_{yi} \perp (u_{xi}, \delta_{xij})$$

- Then the model can be reparameterized as

$$y_{ij} = \beta_0^* + \underbrace{\left(\beta_x + \frac{\sigma_{u_{xy}}}{\sigma^2_{u_x}}\right)}_{\beta_B} u_{xi} + \underbrace{\beta_x}_{\beta_W} \delta_{xij} + \eta_{yi} + \epsilon_{yij}$$

Linear mixed model

- Reparameterized LMM includes fixed between (β_B) and within (β_W) effects of two covariates (u_{xi} & δ_{xij}) and an independent random effect η_{yi}

$$y_{ij} = \beta_0^* + \beta_B u_{xi} + \beta_W \delta_{xij} + \eta_{yi} + \epsilon_{yij}$$

- Marginal effect is given by the weighted average of within- and between-subject effects

$$\beta_M = \frac{\sigma^2_{\delta_x}}{\sigma^2_{u_x} + \sigma^2_{\delta_x}} \beta_W + \frac{\sigma^2_{u_x}}{\sigma^2_{u_x} + \sigma^2_{\delta_x}} \beta_B$$

Linear mixed model

- Let $\delta_{xij} \overset{iid}{\sim} N\left(0, \sigma^2_{\delta_x}\right),\ \epsilon_{yij} \overset{iid}{\sim} N\left(0, \sigma^2_{\epsilon_y}\right)$
- Assuming $\sigma_{u_{xy}} = 0$, MLE $\widehat{\beta}_x$ converges in probability to

$$\widehat{\beta}_x \xrightarrow{\text{P}} \beta_x + \frac{\sigma_{u_{xy}} \sigma^2_{\epsilon_y}}{\sigma^2_x \sigma^2_{\epsilon_y} + (m-1)\sigma^2_{u_y} \sigma^2_{\delta_x}}$$

- If in fact $\sigma_{u_{xy}} \neq 0$, $\widehat{\beta}_x$ is **biased** for all three effects

Mixed effects model with error-prone exposure

- **Theorem**: in the naive model with error-prone exposure x_{ij}^* , induced random effects are *always* correlated with exposure
- Proof (main idea):
  - re-write naive model as true model where exposure x_{ij} is replaced by $x_{ij} = E\left(x_{ij}|x_{ij}^*\right) + b_i^{(1)} + b_{ij}^{(2)}$
  - show that induced random effects in the naive model are always correlated with error-prone exposure x_{ij}^*

Longitudinal measurement error model

- For continuous exposure on an appropriate scale, longitudinal measurement error model may be specified as

$$x^*_{ij} = \gamma_o + \gamma_x x_{ij} + \boldsymbol{\gamma}_z^t \boldsymbol{z}_i + u_{x^*i} + e_{x^*ij}$$
$$x_{ij} = \alpha_0 + \boldsymbol{\alpha}_z^t \boldsymbol{z}_i + u_{xi} + \delta_{xij},$$

  where $\boldsymbol{z}_i$ is vector of error-free covariates, γ_x – true exposure related slope, u_{x^*i} – subject-specific bias, and e_{x^*ij} – within-subject random error
- Three different effects in the naive model have multiplicative bias: $\widetilde{\beta}_k = \lambda_k \beta_k,\ k = W, B, M$

Effects of exposure measurement error

- Impact of ME structure depends on the effect of interest:
  - true exposure related slope *biases* (often exaggerates) all three effects
  - subject-specific bias *does not* change within-subject effect, but *attenuates* between-subject and marginal effects
  - within-subject random error *attenuates* within-subject and marginal effects, but *does not* change between-subject effect

Interactive Diet and Activity Tracking in AARP (IDATA)

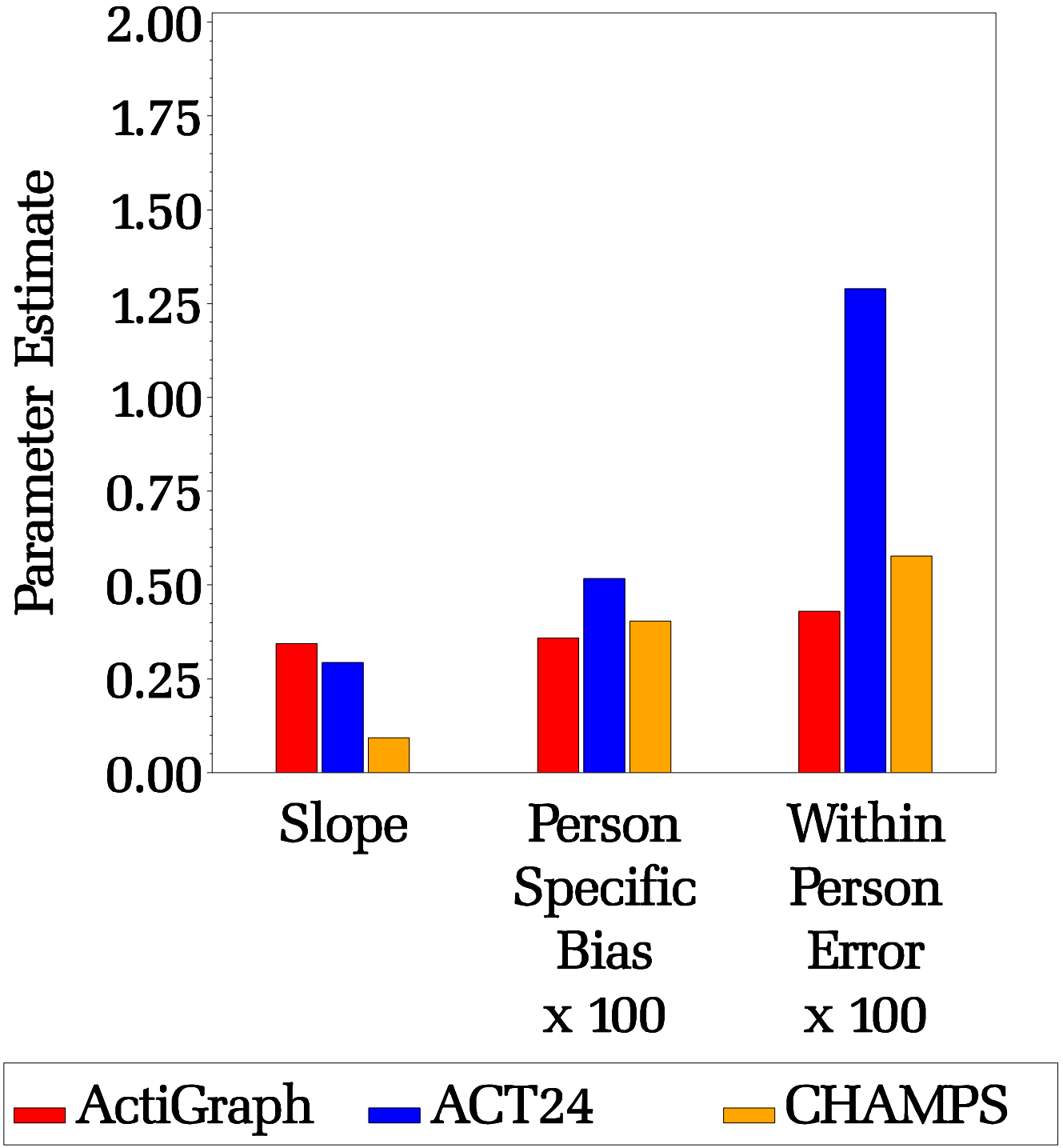
- IDATA is a validation study of 1100 participants (550 men and 550 women), aged 50-74, with a variety of diet, PA, and biomarker measurements over a course of one year
- Focus here: evaluation of ME structure in assessing daily MET-hours (kcal/kg/day) with
  - CHAMPS questionnaire over the previous month
  - ACT24 web-based 24-hour recall
  - ActiGraph GTX3 accelerometer (first 4 full days out of 7)

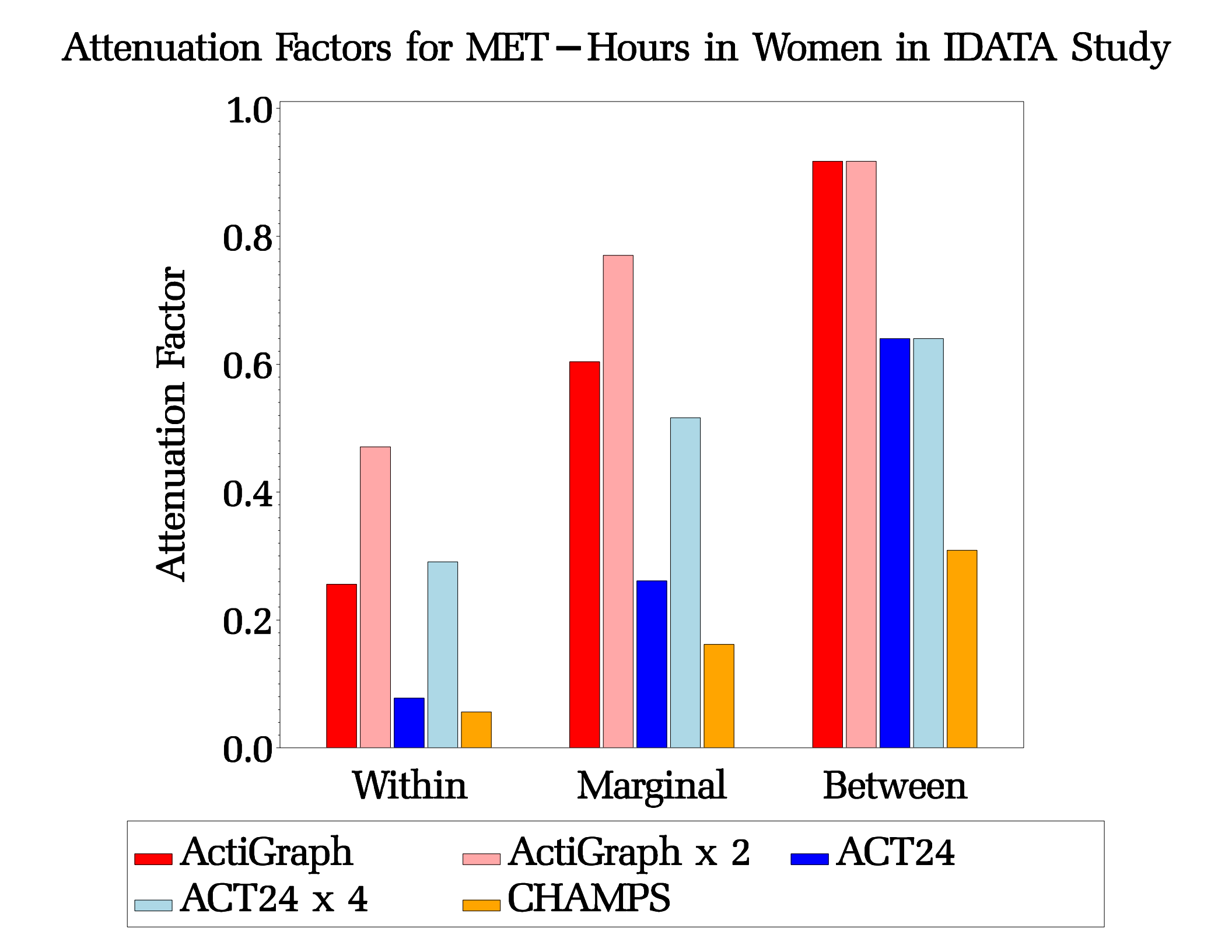
IDATA Study

- Time period in time-varying PA exposure: one month
- On the log scale, unbiased biomarker for within-period MET-hours: doubly labeled water (DLW) divided by weight
- By design, participants had 6 ACT24, 2 ActiGraph,

  2 CHAMPS, 2 DLW, and 3 BMI measurements evenly spread over one year
- Vector $\boldsymbol{z}_i$ included baseline BMI, age, and calendar months

Parameter Estimates for MET−Hours in Women in IDATA




Attenuation Factors for MET−Hours in Women in IDATA Study
Attenuation Factor
1.0
0.8
0.6
0.4
0.2
0.0
Within
Marginal
Between
ActiGraph
ActiGraph x 2
ACT24
ACT24 x 4
CHAMPS

Discussion (1)

- All 3 PA instruments involve flattened slope, person-specific biases, and within-person random errors
- Flattening of slope is the largest in CHAMPS and smallest in ActiGraph accelerometer
- Person-specific bias is the largest in ACT24 and smallest in ActiGraph
- Within-person random errors are about 3 times larger in ACT24 and $\sim$ 20% larger in CHAMPS compared to ActiGraph accelerometer

Discussion (2)

- Bias due to ME is the smallest for estimating between-person and largest for within-person effects in all 3 instruments
- Results show a definite advantage of using ActiGraph accelerometer vs self-report ACT24 or CHAMPS for estimating all three effects