Effects of Covariate Measurement Error in Mixed Models with Application to Longitudinal Studies of Physical Activity

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PA and Health Outcomes

- PA has been linked to many health outcomes (cancer, diabetes, cardiovascular disease, obesity, quality of life)
- Epidemiologic studies usually concentrate on *long-term* average ("*usual*") PA assessed by *self-report* questionnaires
- Recent intervention studies have been focusing on repeated *objective short-term* PA *measures* using accelerometers
- Problem: measurement error in assessment of PA should be taken into account

PA and Longitudinal Studies

- PA is characterized by both short-term (e.g., month to month) and long-term (over years) changes
- Dynamic nature of PA is especially critical in intervention studies but may also be important in longer-term epi studies
- To properly analyze *individual* relationships of PA with health outcomes it is crucial to carry out longitudinal studies

Longitudinal studies

- Defining feature: measurements are taken of the same subjects repeatedly over time
- Primary goal: analysis of within-subject change in health outcome and factors that influence this change over time
- Analyzing within-subject change removes extraneous variation among subjects because they serve as their own controls

Longitudinal studies: three effects

- Longitudinal studies generally lead to *three effects* of exposure on response:

  – *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

Statistical analysis: Mixed effects models

- 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 allow estimation of all three effects but require specification of latent random effects

Mixed effects models

- **Traditional assumption**: random effects are independent of covariates leading to the same within- and between-subject effects (in linear mixed models, the same three effects)
- Neuhaus & Kalbfleisch (1998) empirically demonstrated that within- and between-subject effects could be different
- In econometrics, allowing for different within- and between-subject effects has been common since 1970's
- **Theorem**: dependence of random effects on covariates *always* leads to three different 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 linear mixed effects regression model

$$y_{ij} = E(y_{ij}|x_{ij}, u_{yi}) + \epsilon_{yij} = \beta_0 + \beta_x x_{ij} + u_{yi} + \epsilon_{yij}$$

- Random effect u_{yi} may be interpreted as representing effects of unknown subject-level covariates related to outcome
- If some of unknown covariates are confounders, u_{yi} is **by definition** correlated with x_{ij}

Simple example: linear mixed model (LMM)

- Linear mixed effects regression model

$$y_{ij} = E(y_{ij}|x_{ij}, u_{yi}) + \epsilon_{yij} = \beta_0 + \beta_x x_{ij} + u_{yi} + \epsilon_{yij}$$

where all random variables are normally distributed

- Time-varying exposure may also be specified as LMM

$$x_{ij} = E(x_{ij}|u_{xi}) + \delta_{xij} = \underbrace{(\alpha_0 + u_{xi})}_{\mu_{xi}} + \delta_{xij}$$

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

Linear mixed model

- Consider linear regression $E(u_{yi}|\mu_{xi})$ so that

$$u_{yi} = \frac{\sigma_{u_{xy}}}{\sigma^2_{u_x}}(\mu_{xi} - \alpha_0) + \eta_{yi}, \;\; \eta_{yi} \perp (\mu_{xi}, \delta_{xij})$$

- Then the model can be reparameterized as

$$y_{ij} = \underbrace{\left(\beta_0 - \frac{\sigma_{u_{xy}}}{\sigma^2_{u_x}}\alpha_0\right)}_{\beta_0^*} + \underbrace{\left(\beta_x + \frac{\sigma_{u_{xy}}}{\sigma^2_{u_x}}\right)}_{\beta_B}\mu_{xi} + \underbrace{\beta_x}_{\beta_W}\delta_{xij} + \eta_{yi} + \epsilon_{yij}$$

Linear mixed model

- Reparameterized LMM includes fixed effects of two covariates and an independent random effect

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

- Marginal effect is represented by the slope in linear regression $E(y_{ij}|x_{ij})$ and is given by the weighted average of within- and between-subject effects

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

Mixed effects model with error-prone exposure

- Consider the case when instead of true exposure x_{ij} we observe x_{ij}^*
- **Theorem**: in the naive model with error-prone exposure, 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}^*

Mixed effects models with error-prone exposure

- **To sum up**: in the naive model with error-prone exposure, correlation of the induced random effects with exposure leads to *three different exposure effects*, even if this is not the case in the model for true exposure
- If ignored, the estimated exposure effect would be biased due to two sources: measurement error and model misspecification

Longitudinal measurement error model

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

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

where

$\gamma_x =$ exposure-related bias (often flattened slope)
$u_{x^*i} =$ person-specific bias (random effect)
$e_{x^*ij} =$ within-person random error
$\boldsymbol{z}_i =$ vector of either subject-level or error-free covariates with specified by design values

Effects of exposure measurement error

- Consider non-differentiality assumption regarding between and within components of error-prone exposure, i.e.,

$$F\left(y_{ij}|\mu_{x_i}, \delta_{x_{ij}}, \mu_{x_i^*}, \delta_{x_{ij}^*}, \boldsymbol{z}_i\right) = F\left(y_{ij}|\mu_{x_i}, \delta_{x_{ij}}, \boldsymbol{z}_i\right),$$

where

$$\mu_{x_i^*} = E\left(x_{ij}^*|\mu_{x_i}, u_{x^*i}, \boldsymbol{z}_i\right), \delta_{x_{ij}^*} = x_{ij}^* - \mu_{x_i^*}$$

- Regression slopes in the naive model representing three different effects 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:
  - flattened slope *exaggerates* each of 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,

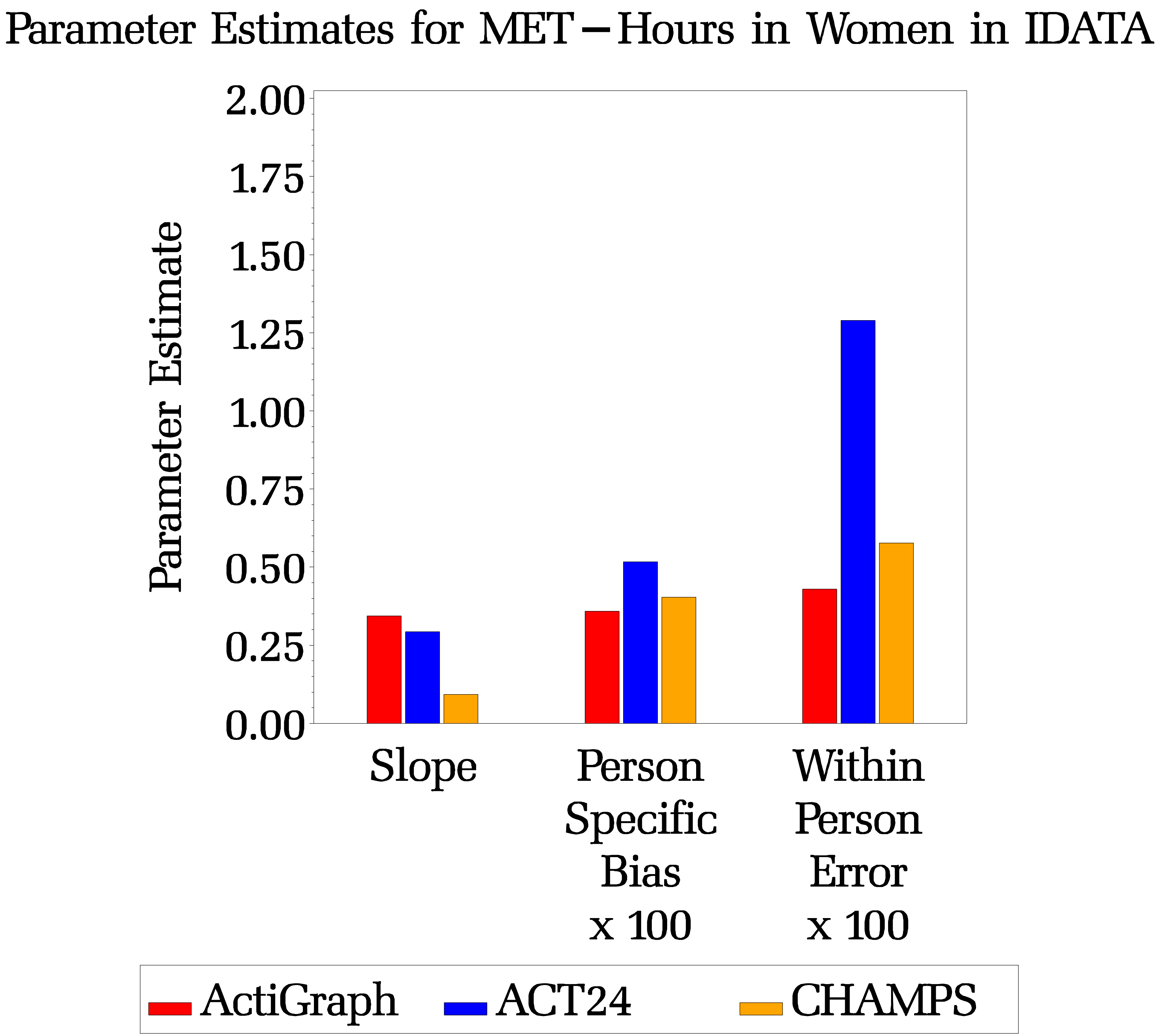
  2 CHAMPS, 2 DLW, and 3 BMI measurements evenly spread over one year

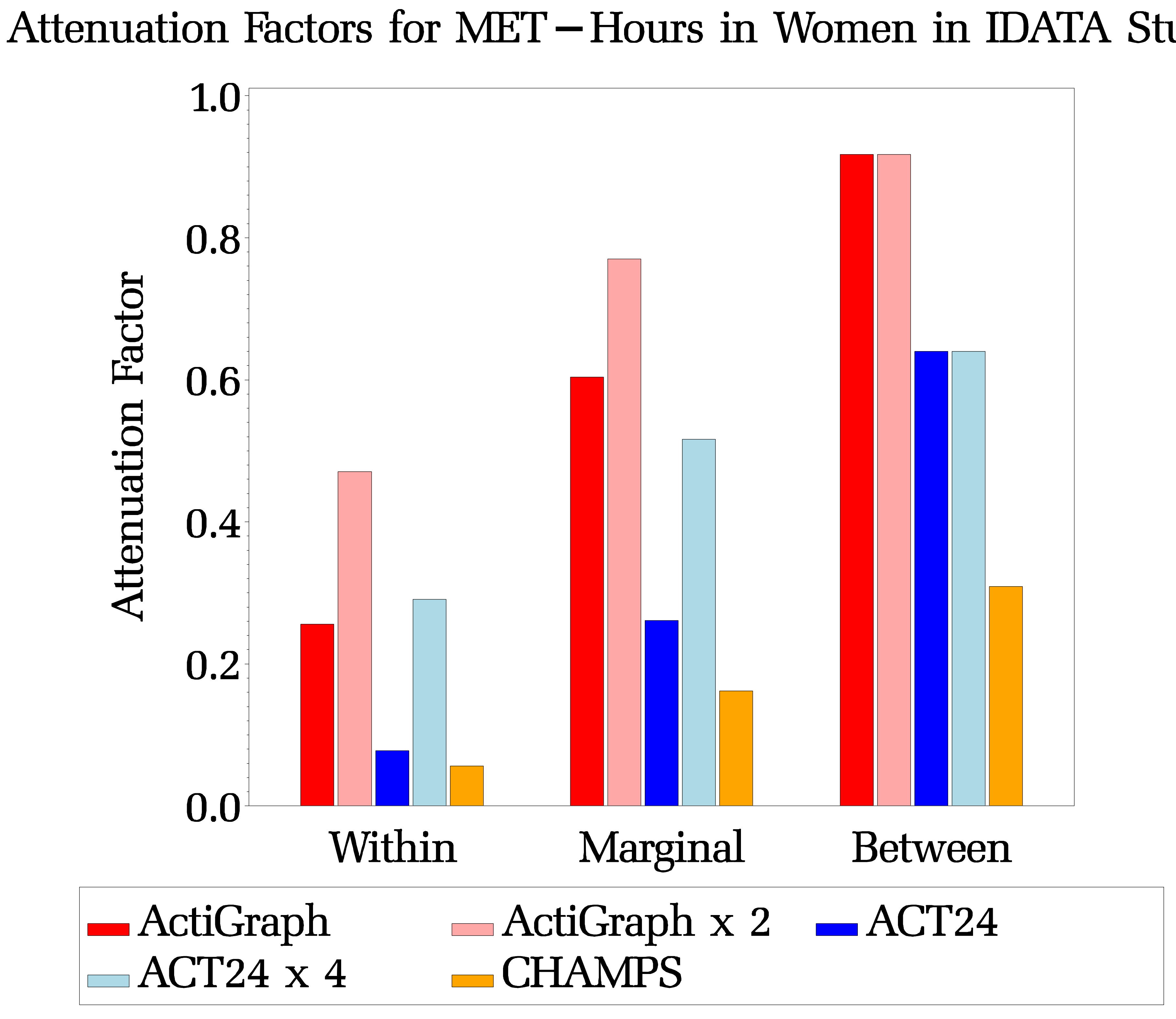
Measurement Error Model in IDATA

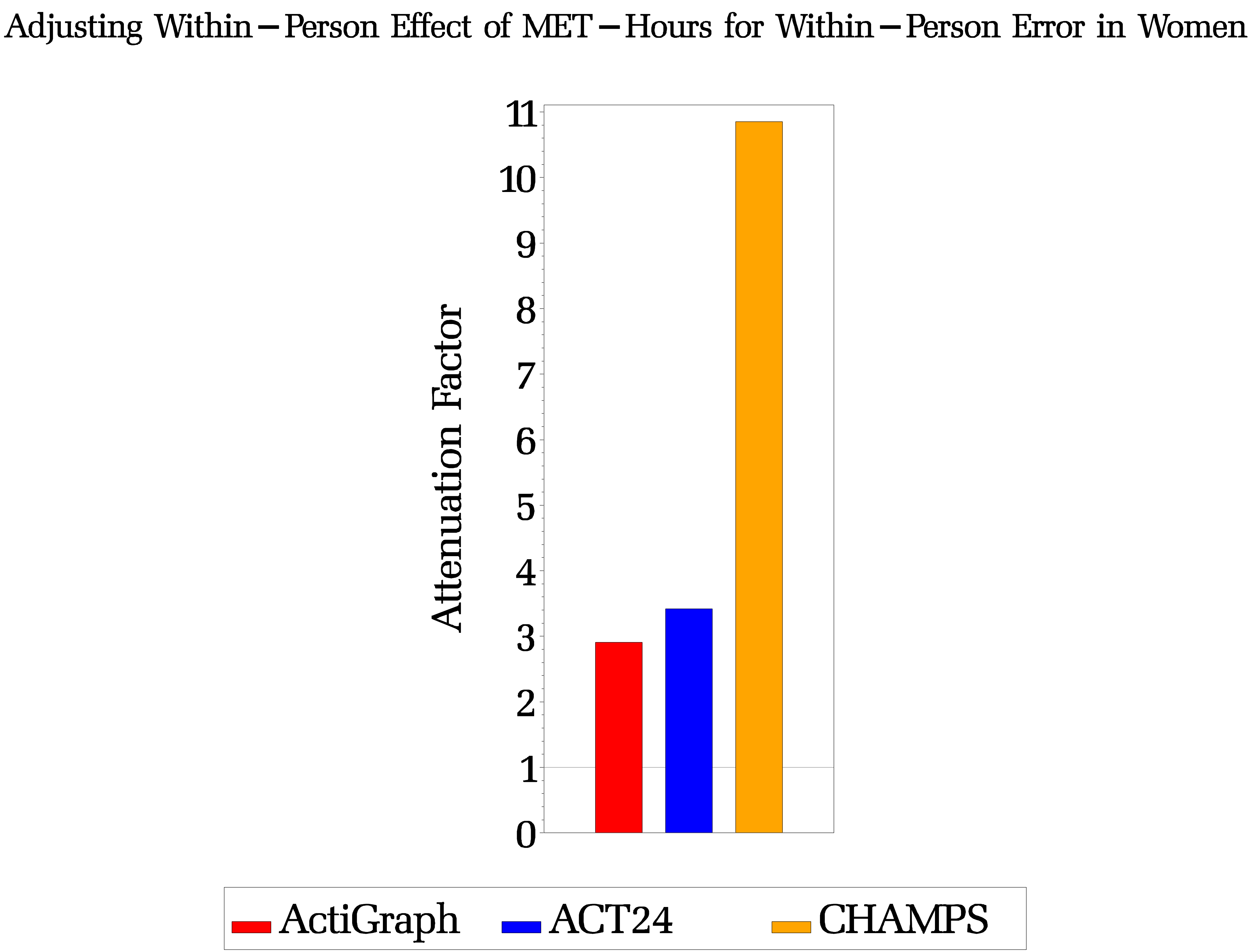
- For person i, denote true and measured log MET-hours in time period j as x_{ij} and x^*_{ij}, respectively; with $\boldsymbol{z}_{ij}$ consisting of baseline log BMI and age as subject level covariates, and calendar months as design covariates
- Measurement error model is specified as

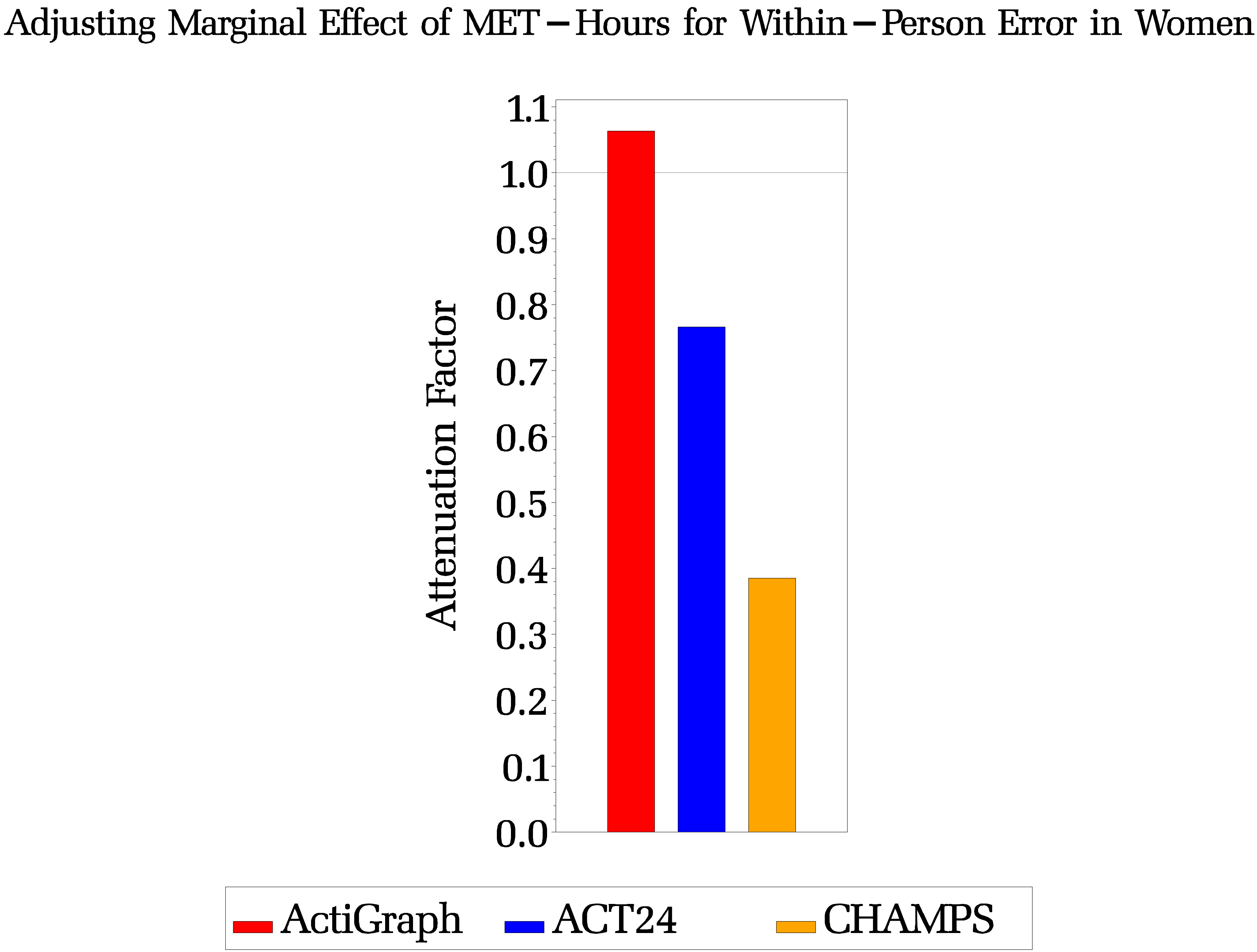
$$x^*_{ij} = \gamma_o + \gamma_x x_{ij} + \boldsymbol{\gamma}'_z \boldsymbol{z}_i + u_{x^*i} + e_{x^*ij}$$
$$M_{ij} = x_{ij} + \nu_{ij}, \nu_{ij} \perp x_{ij}$$

where M denote $log(DLW)$


Parameter Estimates for MET−Hours in Women in IDATA
Parameter Estimate
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
Slope
Person Specific Bias x 100
Within Person Error x 100
ActiGraph
ACT24
CHAMPS


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


Adjusting Within−Person Effect of MET−Hours for Within−Person Error in Women
Attenuation Factor
0
1
2
3
4
5
6
7
8
9
10
11
ActiGraph
ACT24
CHAMPS



Adjusting Marginal Effect of MET−Hours for Within−Person Error in Women
Attenuation Factor
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
ActiGraph
ACT24
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

Discussion (3)

- Repeat applications of instruments reduces within-person random error, but ONLY if applied in the same time period (here one month) and requires care:
  - complete adjustment for within-person error leads to substantial *exaggeration* of the within-subject effect by a factor equal to the inverse of flattened slope
  - on the other hand, it seems to reduce bias of estimated marginal effect in all 3 instruments