A new longitudinal time-varying measurement error model with application to physical activity assessment instruments in a large biomarker validation study

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Outline

- Introduction: Dynamic nature of physical activity (PA)
- Longitudinal studies: three different exposure effects and their interpretation
- Effect of exposure measurement error
- IDATA validation study
- Structure of measurement error in assessing time-varying PA and its implications in longitudinal studies
- Discussion

PA and Health Outcomes

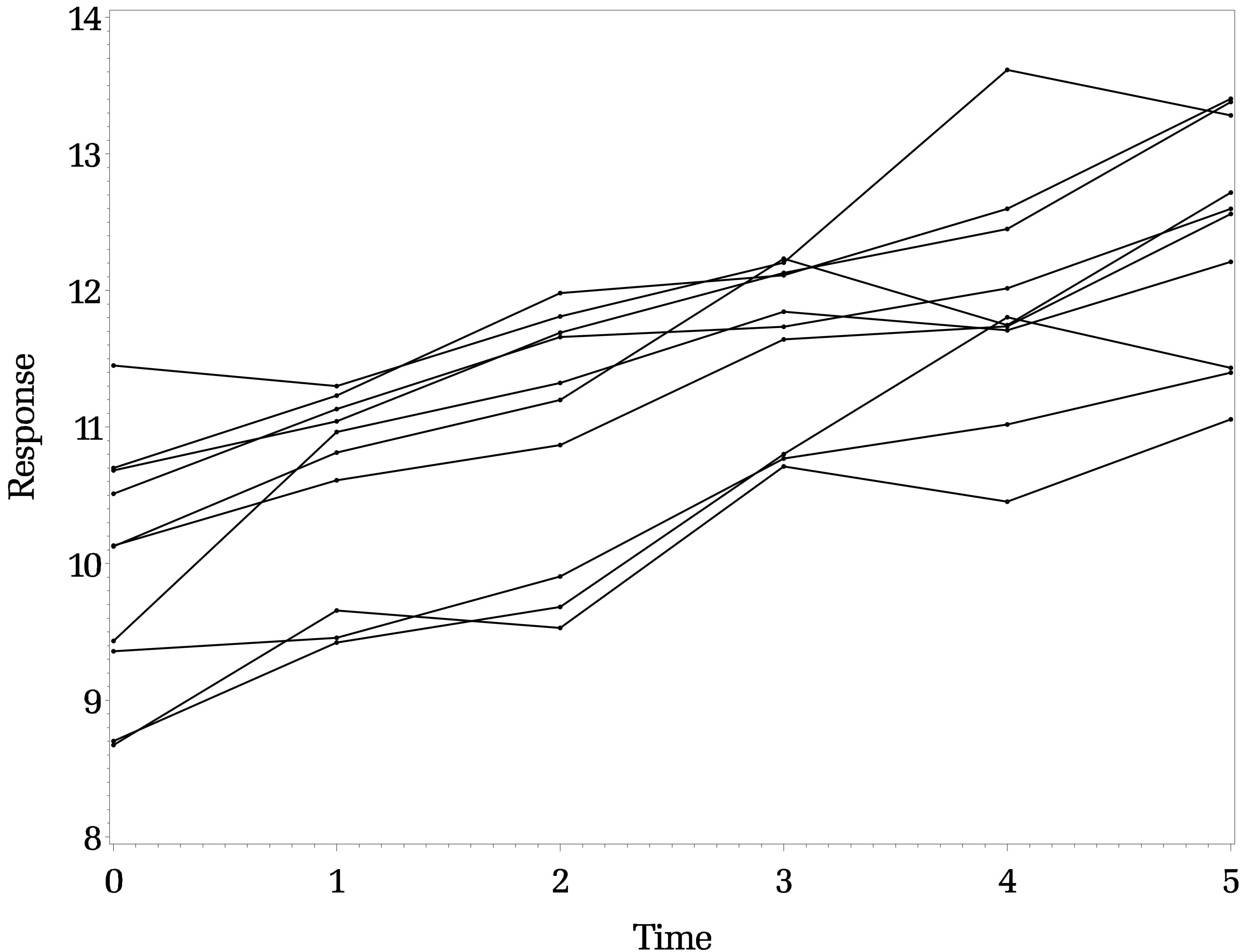
- PA has been linked to many health outcomes (cancer, diabetes, cardiovascular disease, obesity, quality of life)
- Epidemiologic studies usually concentrate on *long-term* average ("*usual*") PA assessed by *self-report* questionnaires
- Recent intervention studies have been focusing on repeated *objective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

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 long-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: measurement are taken of the same subjects repeatedly over time
- Primary goal: analysis of the effect of subject-specific exposure on this subject's health outcome
- Analyzing such within-subject effect removes extraneous variation among subjects because they serve as their own controls



Response
Time
14
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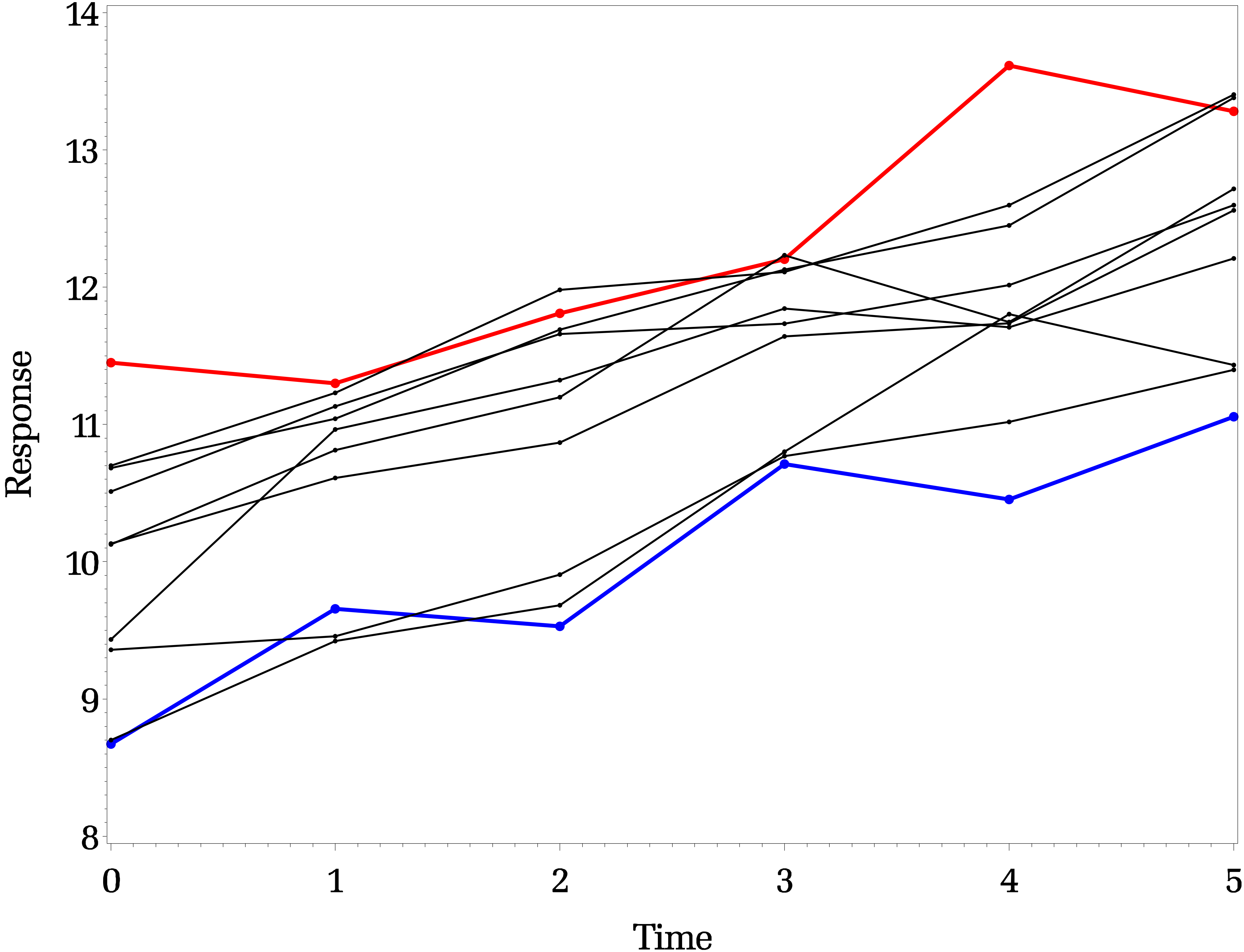

14
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Response
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4
5
Time

Longitudinal Studies: Three Effects

- Longitudinal studies generally lead to *three effects* of exposure on outcome:
  - *within-subject* (*individual level*) *effect* of the exposure for a particular subject on this subject's outcome
  - *between-subject effect* of the subject's mean exposure on mean outcome
  - *marginal* (*population-average*) *effect* of the exposure in the population on mean population's outcome

Statistical Analysis of Longitudinal Studies

- Distinctive feature: observations on the same subject are typically positively *correlated*, and this correlation needs to be accounted for in the statistical analysis
- Major statistical approach: mixed effects models that include both *fixed* and *random* effects

Statistical Analysis: Mixed Effects Models

- *Fixed effects* are population-specific functions of covariates that contribute to temporal trends
- *Random effects* are subject-specific:
  - they are constant within but vary across subjects
  - they account for between-subject heterogeneity in temporal trends and induce within-subject correlation structure

Linear Mixed Model (LMMs)

- **Traditional assumption** in mixed models: random effects are independent of covariates
- In LMMs, the traditional assumption leads to all three effects being the same
- Yet, Neuhaus & Kalbfleisch (1998) empirically demonstrated that three effects could be different in LMMs
- Three exposure effects are *always* different if random effects in LMM are *correlated* with exposure (e.g., Neuhaus & McGulloch, 2006)

Linear Mixed Model: a Simple Example

- Let X_{ij}, Y_{ij} denote the exposure and outcome for person i, $i = 1, ..., n$, time $j = 1, ..., m_i$
- Simple linear mixed effects model

$$Y_{ij} = \beta_o + \beta_x X_{ij} + u_{yi} + \epsilon_{yij}$$

- Exposure may vary with time and be specified as

$$X_{ij} = \alpha_0 + u_{xi} + \epsilon_{xij}$$

Linear Mixed Model: a Simple Example

- Joint mixed model:

$$Y_{ij} = \beta_o + \beta_x X_{ij} + u_{yi} + \epsilon_{yij}$$

$$X_{ij} = \alpha_0 + u_{xi} + \epsilon_{xij}$$

- Traditional assumption that u_{yi} is independent of X_{ij} may be too strong: both random effects u_{yi} and u_{xi} represent heterogeneity between subjects in response and exposure, respectively, and therefore may be *correlated*

Linear Mixed Model: a Simple Example

- Correlation between u_{yi} and u_{xi} leads to linear regression

$$u_{yi} = \frac{\sigma_{u_{x,y}}}{\sigma^2_{u_x}} u_{xi} + \eta_{yi}, \;\; \eta_{yi} \perp u_{xi}$$

- Denoting subject-specific mean $\mu_{xi} = \alpha_0 + u_{xi}$, the model can be reparameterized as LMM with *two exposures* μ_{xi} and ϵ_{xij} and independent random effect η_{yi}

$$Y_{ij} = \beta_0 + \left(\beta_x + \frac{\sigma_{u_{x,y}}}{\sigma^2_{u_x}}\right)\mu_{xi} + \beta_x \epsilon_{xij} + \eta_{yi} + \epsilon_{yij}$$

Linear Mixed Model: a Simple Example

- Generally, there are *three different effects* of x_{ij} on y_{ij}:
  - within-subject $\beta_W = \frac{cov(X_{ij},Y_{ij}|\mu_{xi})}{var(X_{ij}|\mu_{xi})} = \beta_x$
  - between-subject $\beta_B = \frac{cov(X_{ij},Y_{ij}|\epsilon_{xij})}{var(X_{ij}|\epsilon_{xij})} = \beta_x + \frac{\sigma_{u_{x,y}}}{\sigma^2_{u_x}}$
  - marginal $\beta_M = \frac{cov(X_{ij},Y_{ij})}{var(X_{ij})} = \beta_x + \frac{\sigma_{u_{x,y}}}{\sigma^2_x}$;
- It follows that $\beta_M = \frac{\sigma^2_{\epsilon_x}}{\sigma^2_{u_x}+\sigma^2_{\epsilon_x}}\beta_W + \frac{\sigma^2_{u_x}}{\sigma^2_{u_x}+\sigma^2_{\epsilon_x}}\beta_B$

Effect of Exposure Measurement Error

- Measurement error (ME) in exposure leads to:
  - biases in estimated effects
  - reduced statistical power to detect the effects
  - invalid statistical tests/confidence intervals in presence of other error-prone covariates
- It is critical to evaluate the structure of ME and its 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 within-month usual 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 longitudinal model: one month
- Unbiased biomarker for within-period MET-hours: doubly labeled water (DLW) divided by weight
- By design, participants had 6 ACT24, 2 ActiGraph,

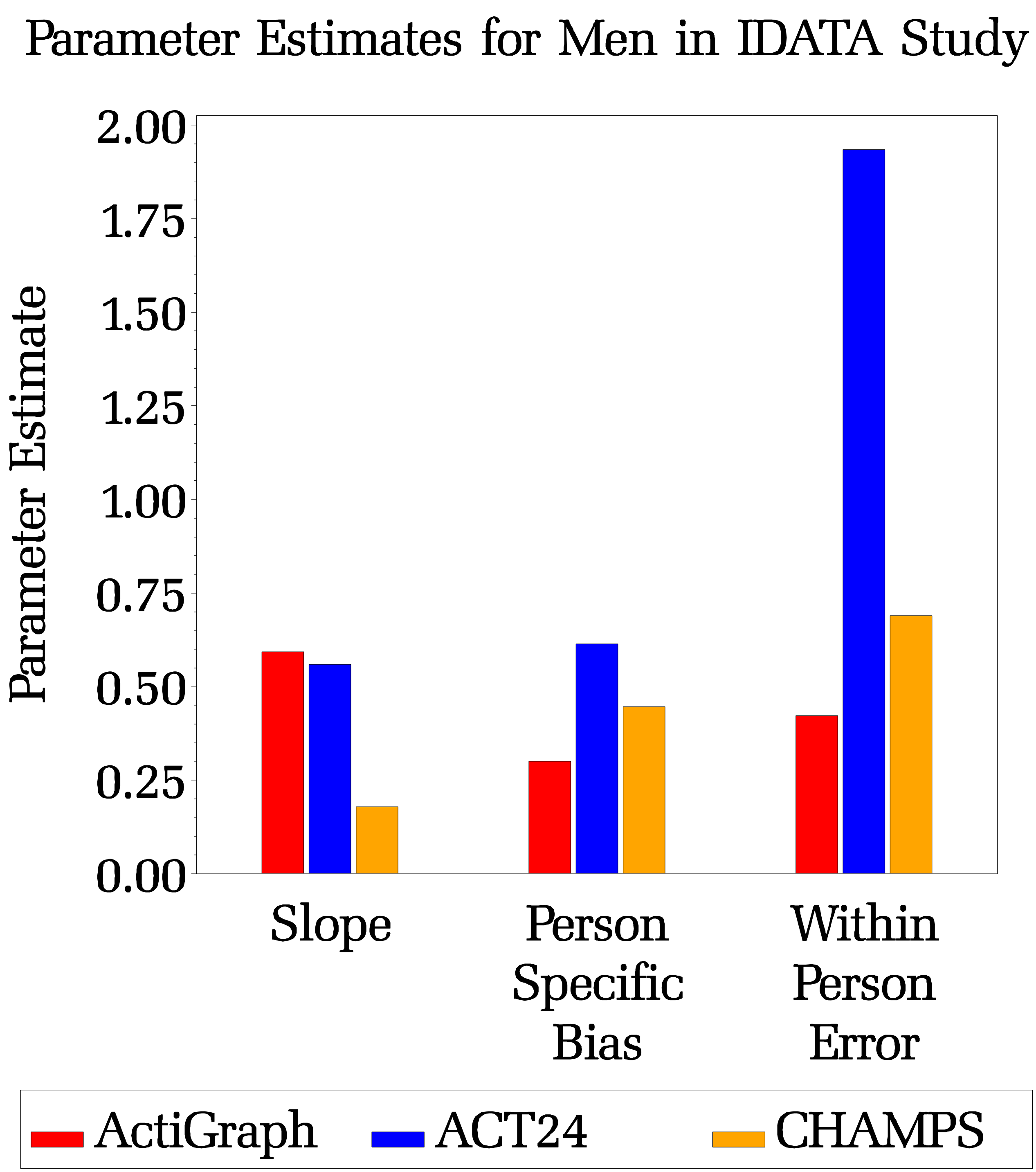
  2 CHAMPS, 2 DLW, and 3 BMI measurements evenly spread over one year

Measurement Error Model in IDATA

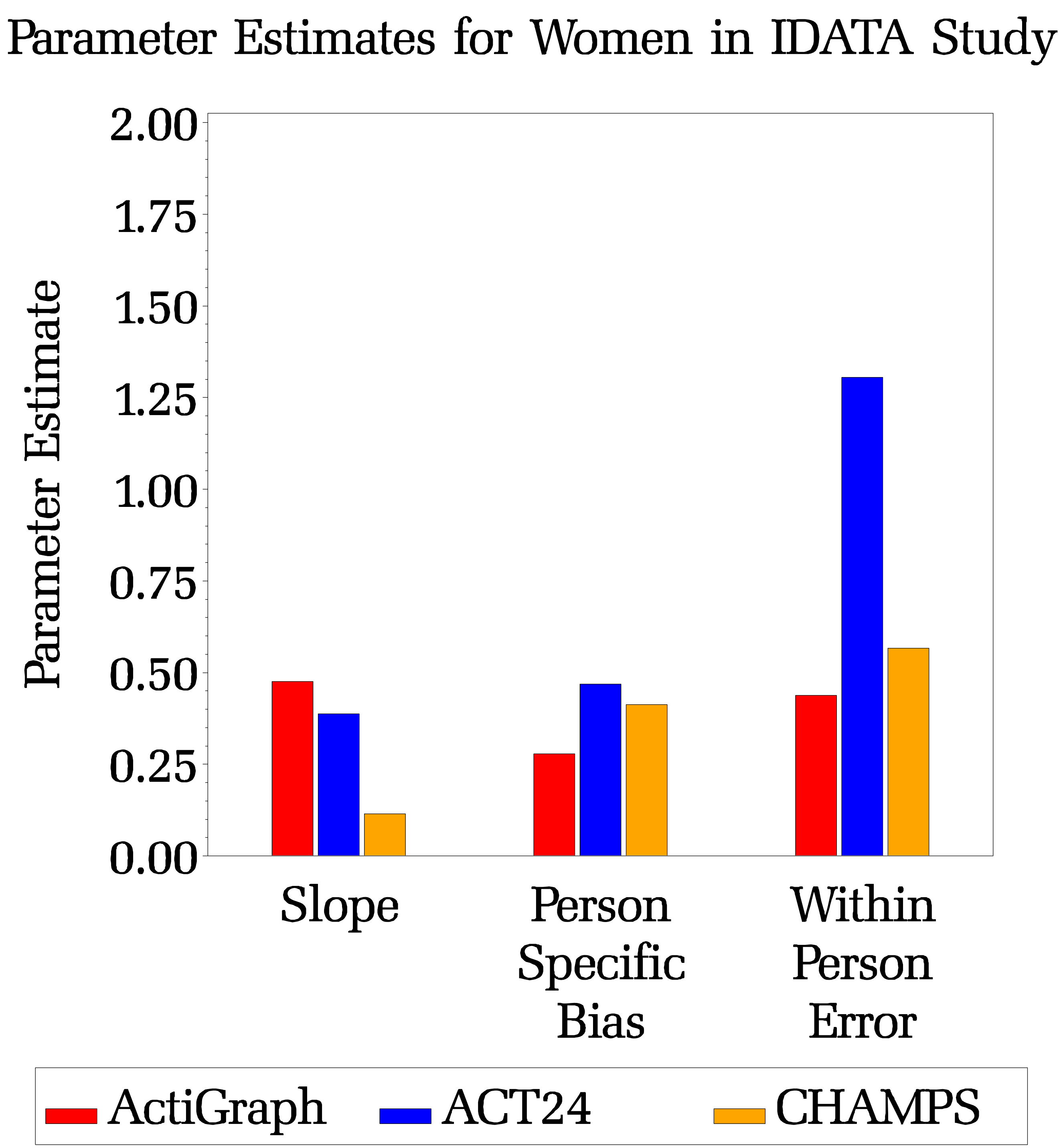
- For person i, denote true and measured log MET-hours in time period t as X_{it} and W_{it}, respectively; with log BMI, age, and calendar month as covariates $\boldsymbol{Z}_{it}$
- Measurement error model is specified as

$$W_{it} = \gamma_o + \gamma_x X_{it} + \boldsymbol{\gamma}_z' \boldsymbol{Z}_t + u_{wi} + e_{wit},$$

$\gamma_x =$ true exposure-related bias (flattened slope)
$u_{wi} =$ person-specific bias
$e_{wit} =$ within-person error



Parameter Estimates for Men in IDATA Study
Parameter Estimate
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
Slope
Person Specific Bias
Within Person Error
ActiGraph
ACT24
CHAMPS

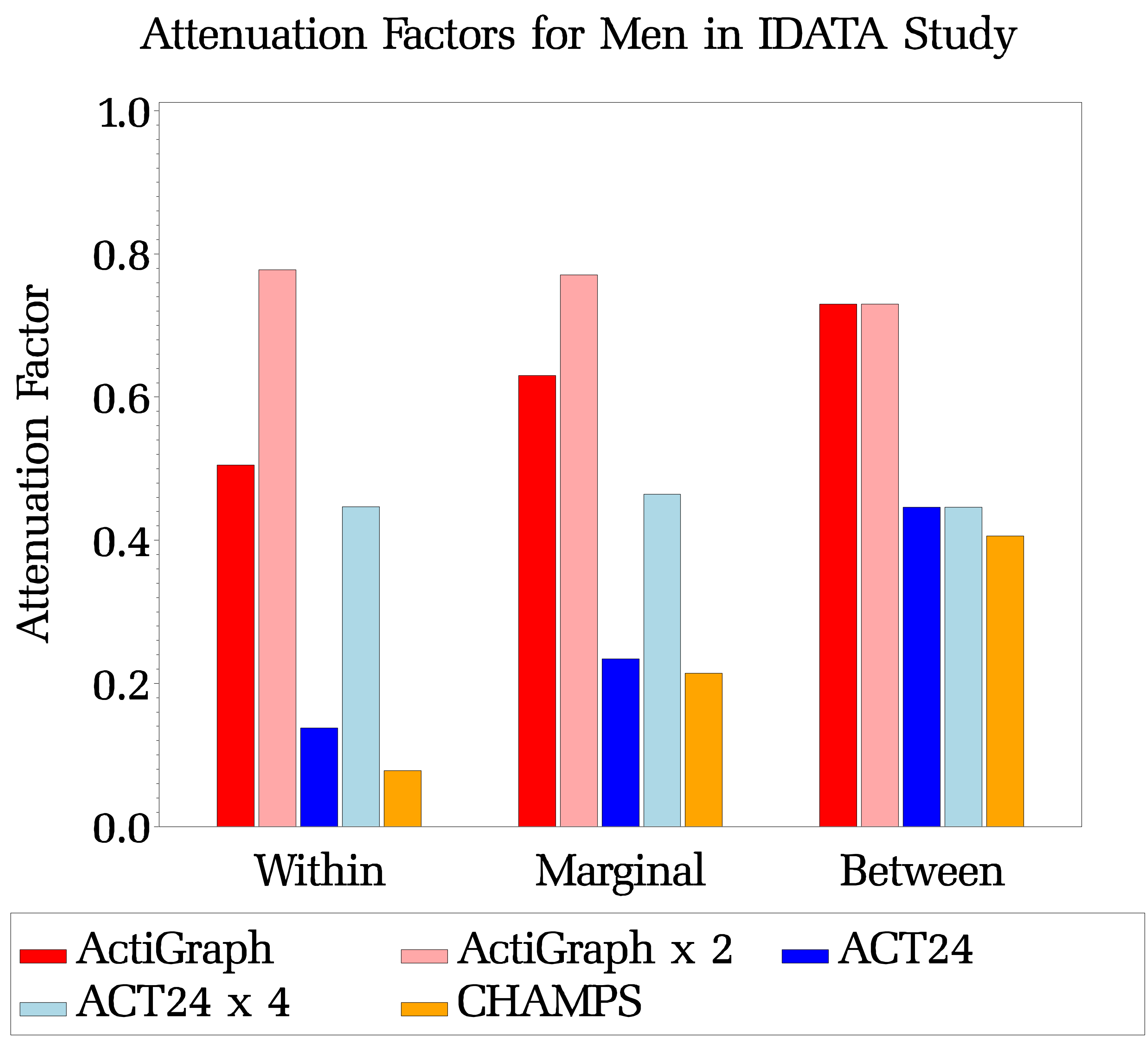

Parameter Estimates for Women in IDATA Study
Parameter Estimate
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
Slope
Person Specific Bias
Within Person Error
ActiGraph
ACT24
CHAMPS

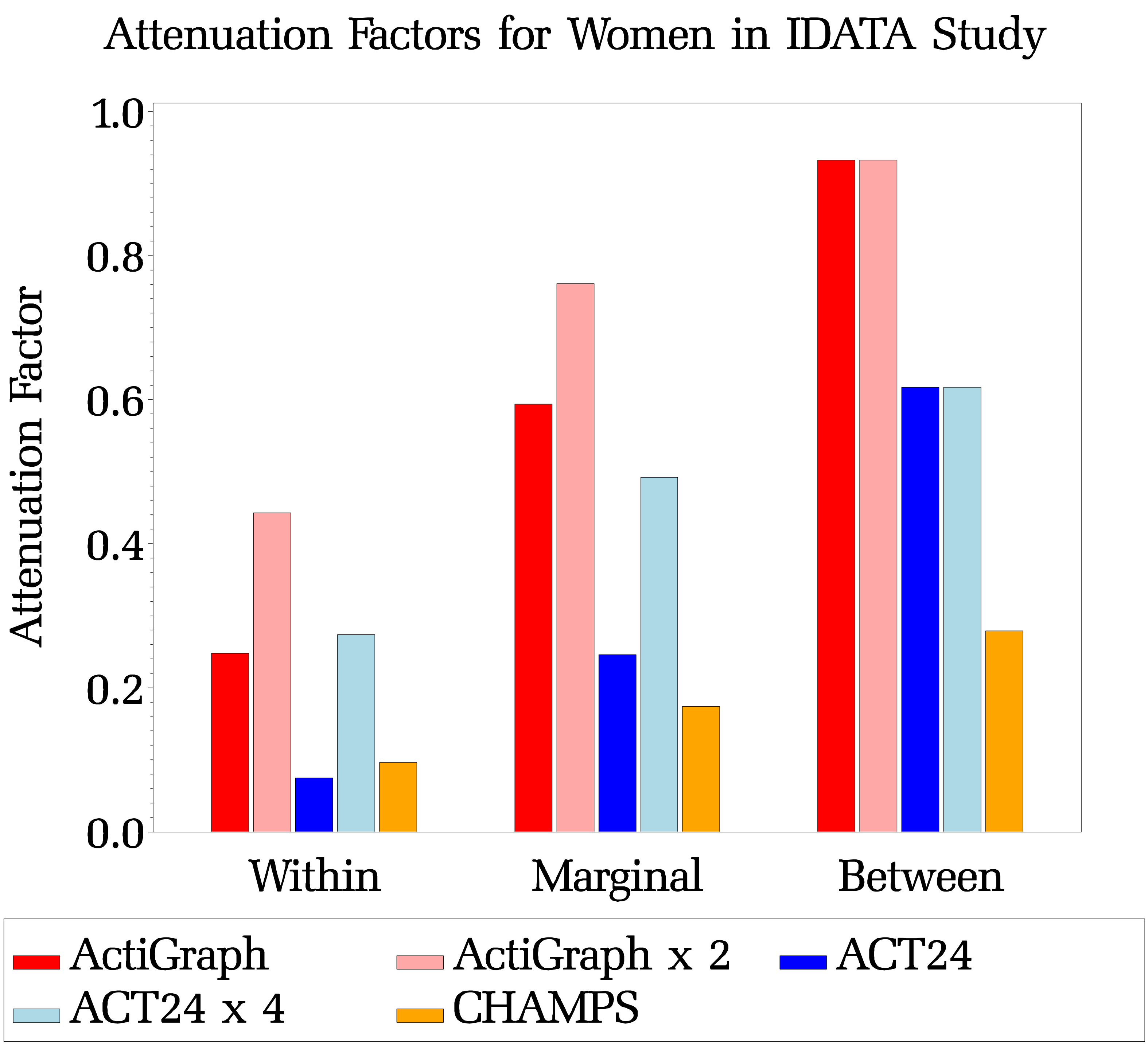
Effects of Measurement Error Components in Longitudinal Studies

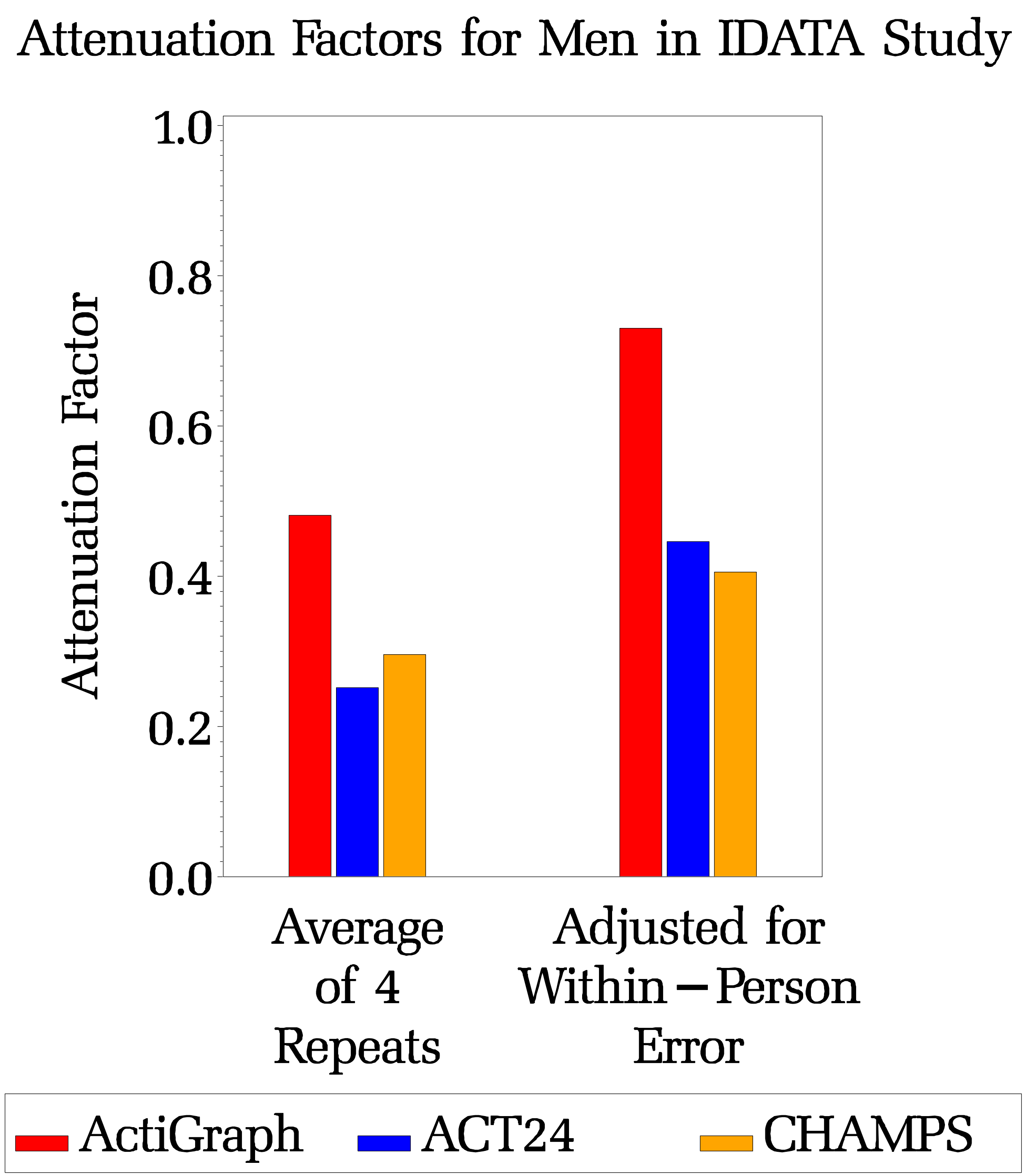
- The impact of different ME components varies depending on the estimated effect of interest in the outcome model:
  - flattened slope *exaggerates* each of three effects
  - person-specific bias *does not* affect within-subject effect, but *attenuates* between-subject and marginal effects
  - within-person random error *attenuates* within-subject and marginal effects, but *does not* affect between-subject effect

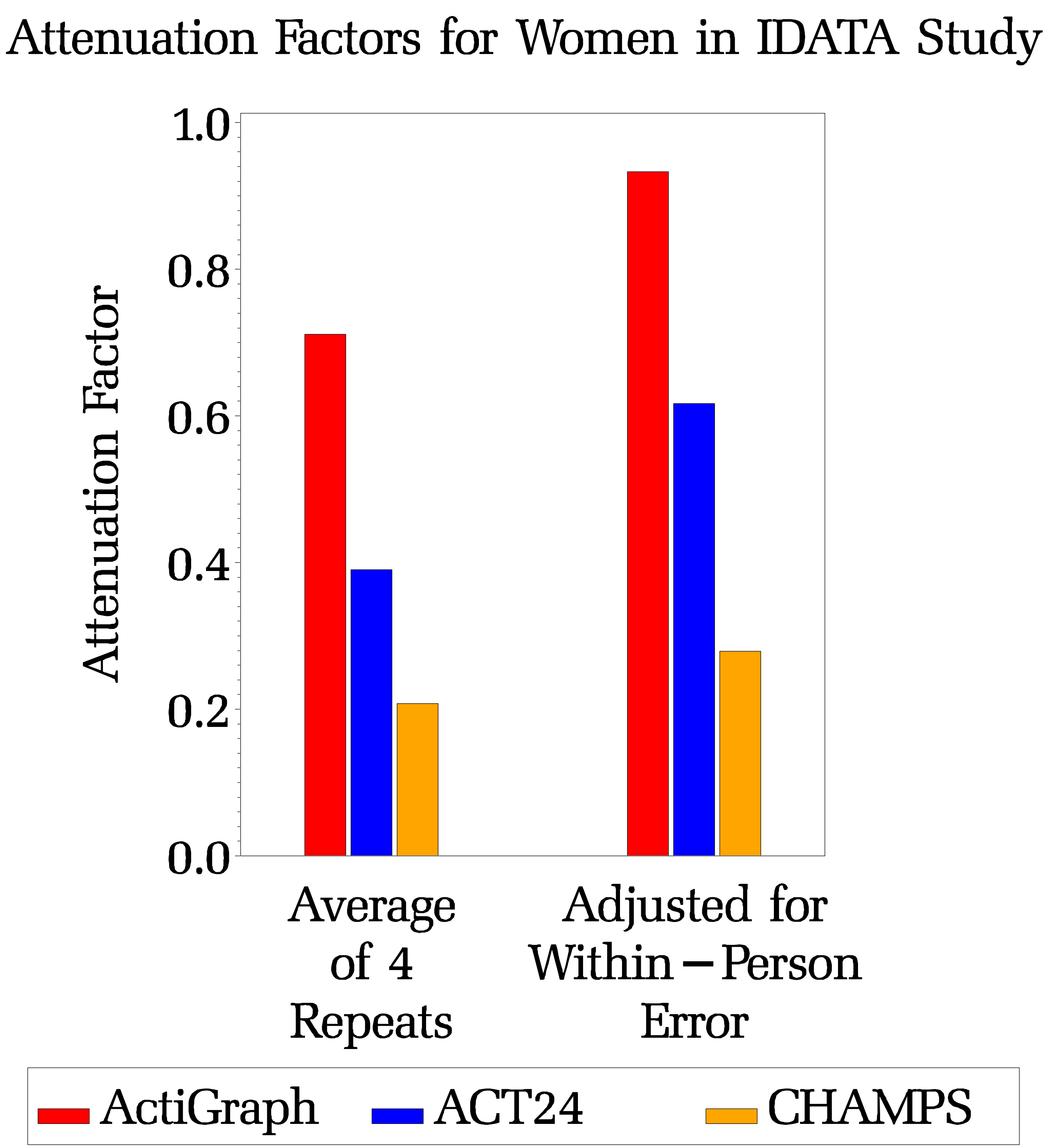
Effects of Measurement Error Components in Longitudinal Studies

- Using the mean of repeated measurements in the *same time-period* (here one month) decreases within-person error but leaves exposure-related and person-specific biases unchanged
- This affects bias in estimated within-subject and marginal but not between-subject effect
- Full adjustment for within-person error by statistical means leads to *exaggeration* of the within-subject effect by a factor equal to the inverse of flattened slope


Attenuation Factors for Men 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


Attenuation Factors for 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


Attenuation Factors for Men in IDATA Study
Attenuation Factor
1.0
0.8
0.6
0.4
0.2
0.0
Average of 4 Repeats
Adjusted for Within−Person Error
ActiGraph
ACT24
CHAMPS


Attenuation Factors for Women in IDATA Study
Attenuation Factor
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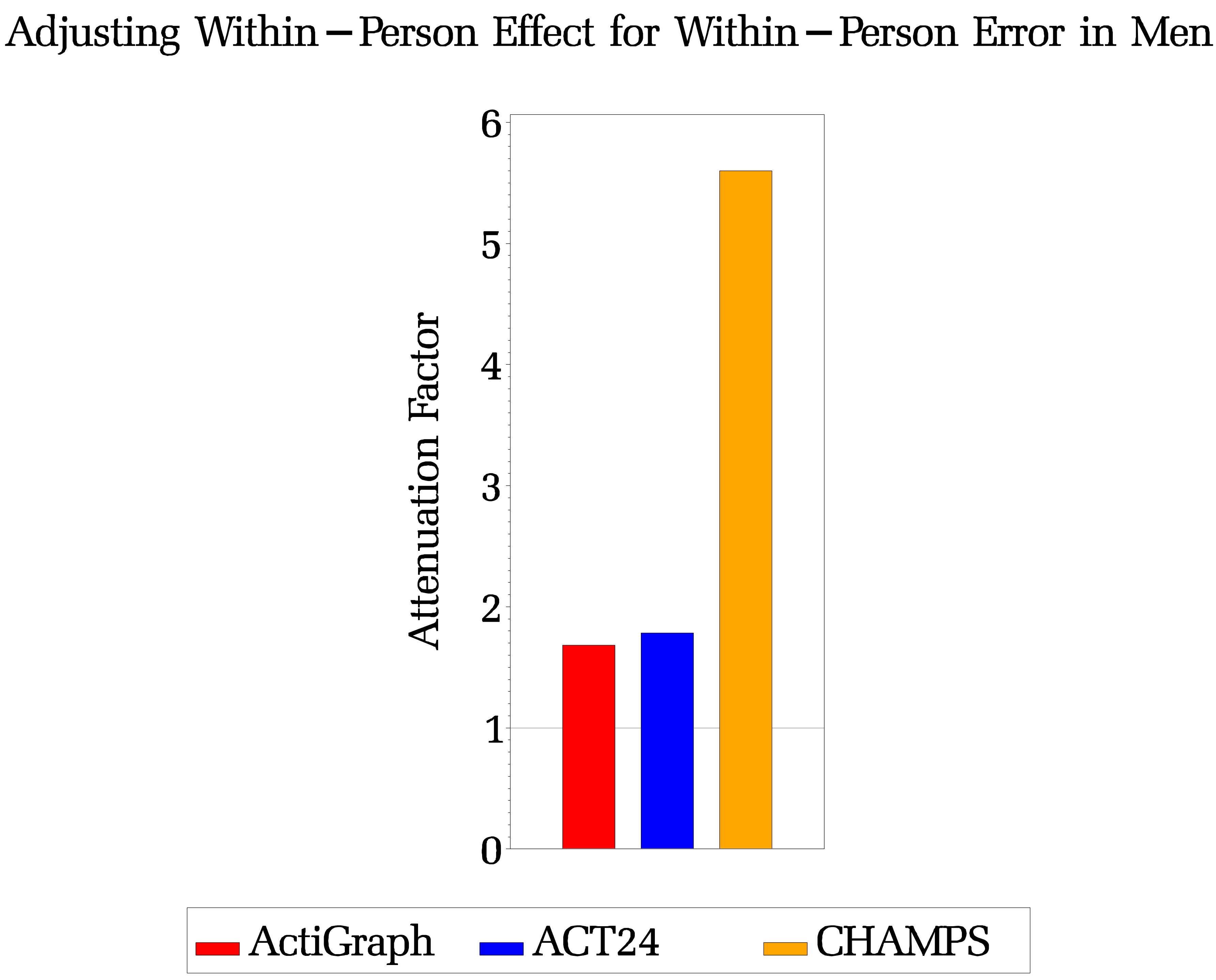
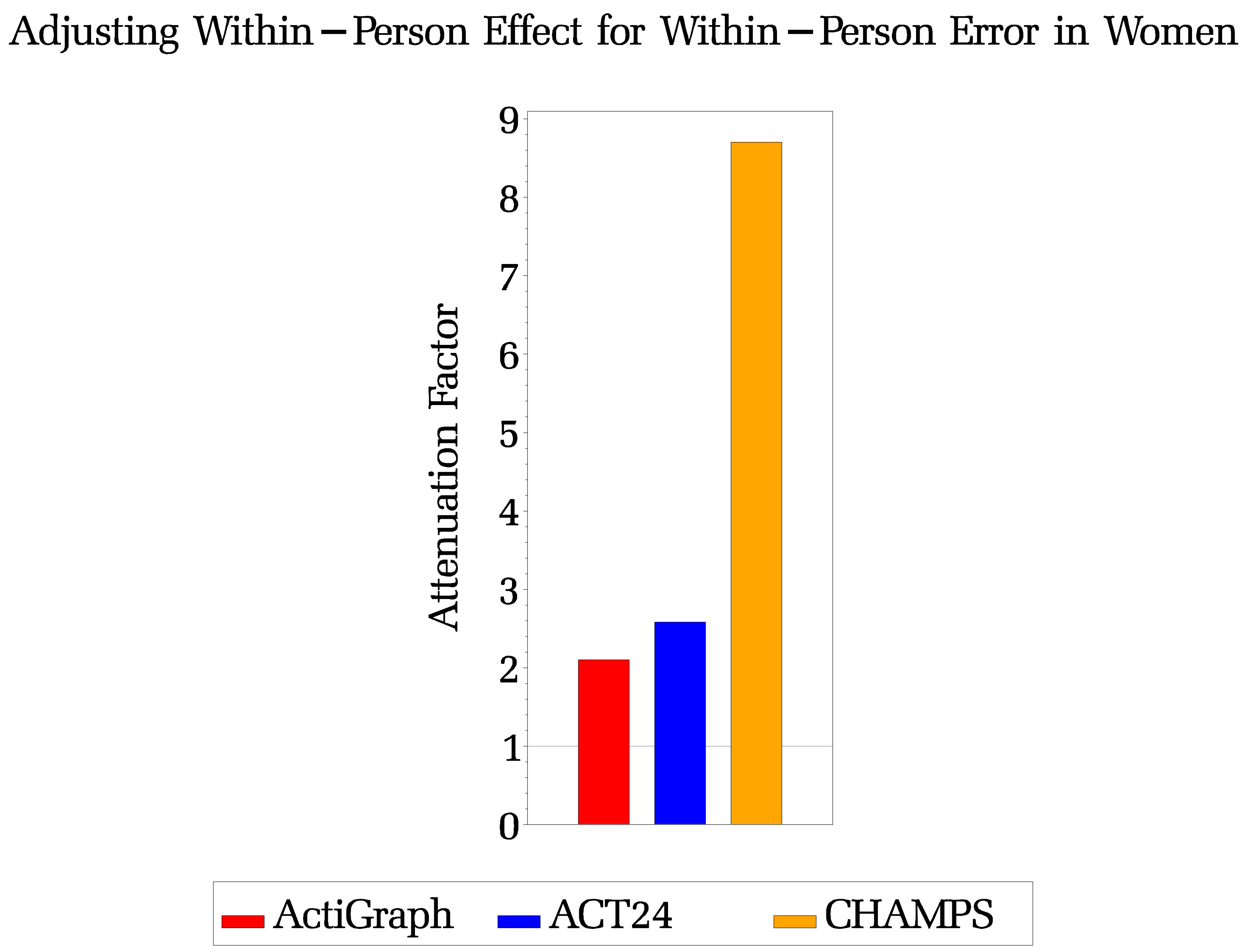
0.8
0.6
0.4
0.2
0.0
Average of 4 Repeats
Adjusted for Within−Person Error
ActiGraph
ACT24
CHAMPS


Adjusting Within−Person Effect for Within−Person Error in Men
Attenuation Factor
0
1
2
3
4
5
6
ActiGraph
ACT24
CHAMPS


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

Discussion (1)

- All 3 instruments involve flattened slope, person-specific biases, and within-person random errors
- Flattened slope and person-specific biases are the largest for CHAMPS and the smallest for ActiGraph accelerometer
- Within-person random errors are 3 (women) to 5 (men) times larger in ACT24 and $\sim$ 20% larger in CHAMPS compared to ActiGraph accelerometer

Discussion (2)

- Attenuation factors for all three effects show a definite advantage of using ActiGraph accelerometer vs self-report ACT24 or CHAMPS
- Repeat applications of the instruments impacts results ONLY if applied in the same time period and requires care:
  – adjustment for within-person error (assuming instrument is unbiased) leads to *exaggeration* of the within-subject effect by a factor equal to the inverse of flattened slope

Conclusions

- PA is a complex multidimensional behavior with relevant FITT (frequency, intensity, time, type) dimensions
- Energy expenditure (METS) is *only one aspect* of PA for which we have a reference (unbiased) biomarker
- Although accelerometer is a clear winner in measuring PA energy expenditure, it is important to examine other aspects while being aware of corresponding measurement error and its impact