Understanding and adjusting for Berkson error arising from prediction equations

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- Victor Kipnis (NCI, STRATOS TG4 chair)
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Introduction

- In epidemiology, there are many measurements that are difficult to obtain directly:
  - Expensive (Resting Energy Expenditure)
  - Burdensome (24-hour urinary sodium)
  - Impossible (Usual energy intake)

- One strategy is to use prediction equations to measure them indirectly

- Many analyses proceed with predicted values as if they were observed data

- Using predicted values instead of observed data in study analyses can corrupt study results if the (Berkson) prediction error is not handled appropriately

Planning a series of papers examining issues that arise when predicted values are used in data analysis:

- Paper 1: Introductory concepts + Example of estimating of a distribution
- Paper 2: Analytical issues that arise when applying regression calibration

Paper 1: Introduction + Estimation of a distribution

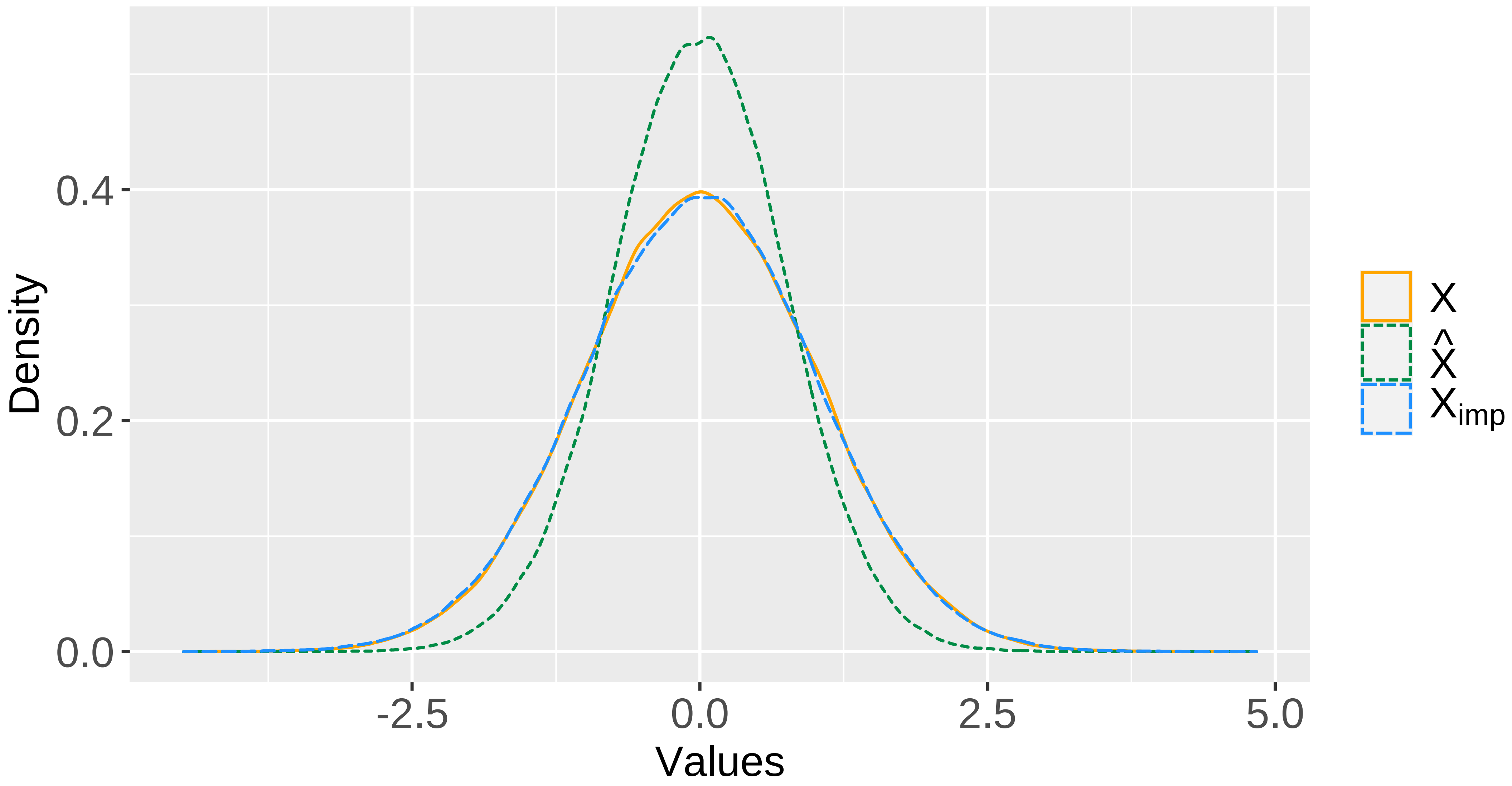
- Consider setting where have an error prone X* and use a predicted value $\hat{X}$ to correct for systematic and random error
- Introduction to prediction error as Berkson measurement error

  $X = \hat{X} + \text{error}$
- Examine effects of ignoring prediction/Berkson error when estimating a distribution
- Present a simple, novel method to handle Berkson error in this setting
- Concepts illustrated with simulated data where truth is known
- Data example from a complex survey design

A simple fix for Berkson error

- **A fundamental attribute of predicted values is their Berkson error makes them less variable than they should be**
- **A simple fix is to add back the missing variance to the calibrated value.**
  - This can be accomplished from simulating error e ~ $(0,\sigma^2)$
  - $X_{imp} = \hat{X} + e$
  - A multiple imputation approach is applied to estimate quantities (Baldoni et al 2021)
    - Applied in the context of a complex survey design

Simulation study results



Berkson error biases quantiles and standard errors

	X			$\hat{X}$			X_{imp}		
%-tile	Mean	ESE	CP	Mean	ESE	CP	Mean	ESE	CP
25th	-0.672	0.043	94.8	-0.501	0.079	8.0	-0.679	0.089	96.6
50th	-0.001	0.039	96.1	-0.002	0.067	6.0	-0.002	0.074	97.4
75th	0.674	0.043	94.5	0.498	0.078	8.3	0.675	0.087	96.5

Example from the Hispanic Community Health Study

(Lavange et al 2010)

Question of interest: Does sodium intake vary by Hispanic ethnicity?

HCHS main cohort: n = 16,415 (Chicago, Miami, New York, San Diego)

Male: 40%

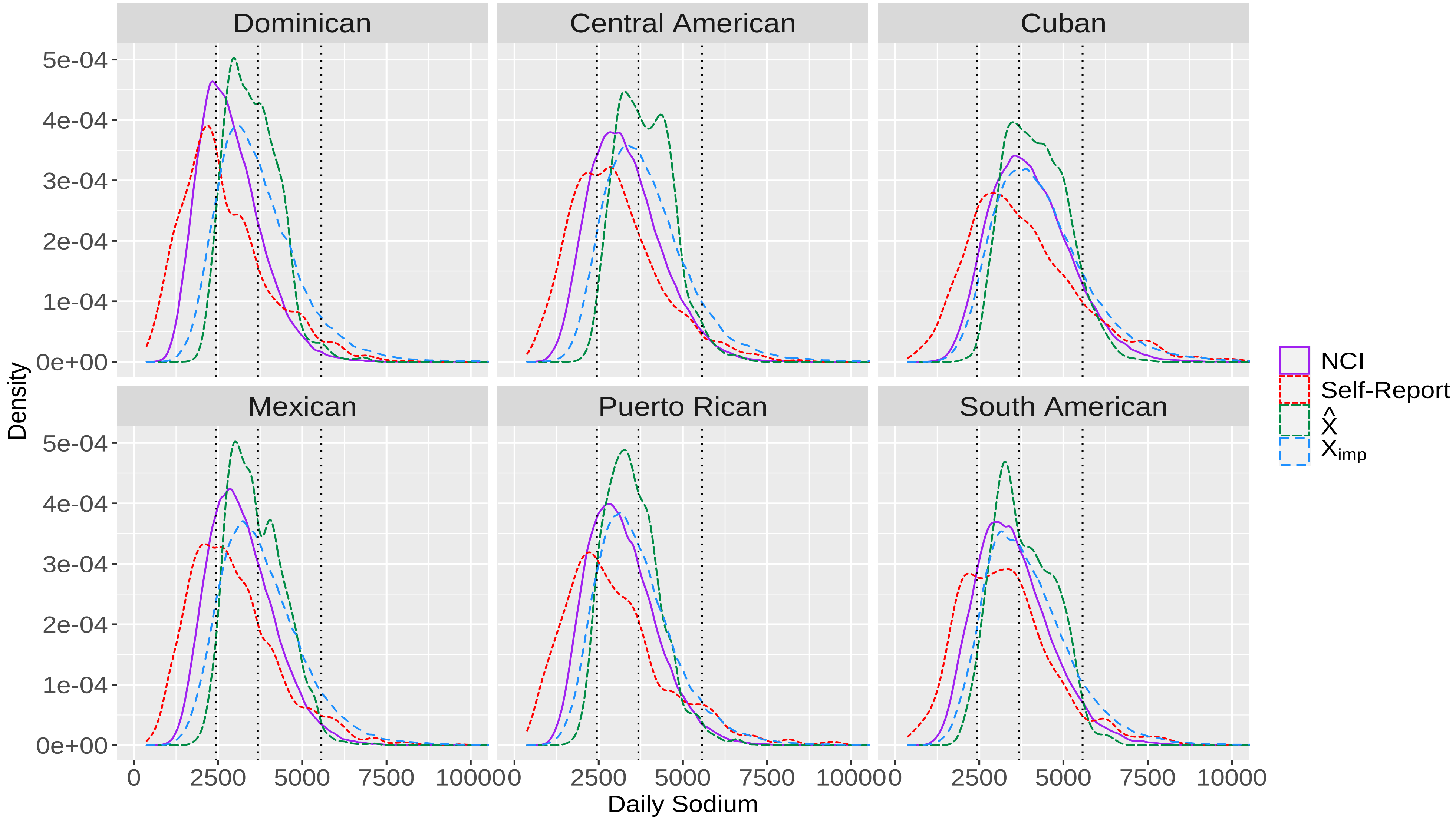
Age: mean 43y; range: 18-74y

Main dietary assessment X*: two 24-hour recalls, known to be subject to bias

SOLNAS: Calibration sub-study: n = 477

Biomarkers X**: Doubly-labeled water (energy) and 24-hour urinary markers (protein, potassium, sodium) were obtained to create calibration equations that correct for the measurement error/bias in self-reported sodium (Mossavar-Rahmani et al 2017)

Similar results seen in HCHS/SOL



Paper 2: Analytical issues that arise when applying regression calibration (RC)

- RC is the most common method to address covariate measurement error
- RC involves replacing unobserved error-free covariate X with a predicted value in outcome model (e.g. $\hat{X}$=E[X|X*,Z])
- Analytical issues generalize setting with a predicted covariate in a regression model

Considerations for analysis

Regression calibration relies on:

- All the covariates in the outcome model to be in the calibration model
- Prediction error independent of the outcome
- Adjustment to the standard error calculation to account for extra uncertainty
  - The usual standard errors from regression software are too small
  - The bootstrap or sandwich estimators are two options.
- Interesting analytical issues arise if there is a mediator in the model

Regression calibration and mediation: a dilemma

- Generally, if you are interested in the total effect of X on Y then you should not include M in the outcome model
- If M is an important variable in the calibration model, it should generally be included in the outcome model to avoid bias when applying regression calibration

Example:

BMI is one of the strongest predictors of energy intake and may mediate the effect of energy intake on outcomes like heart disease, cancer, diabetes

Mediation

Some notation

- Y = outcome variable
- X = exposure of interest
- Z = confounder(s)
- M = mediator

The models

- $M = \gamma_0 + \gamma_X X + \gamma_Z Z + \delta,$ (1) Mediation model
- $Y = \beta_0 + \beta_X X + \beta_Z Z + \beta_M M + \varepsilon,$ (2) Outcome model

Substituting the right-hand side of equation (1) for M in equation (2), we get

- $Y = \tilde{\beta}_0 + \tilde{\beta}_X X + \tilde{\beta}_Z Z + \tilde{\varepsilon},$ **where $\tilde{\boldsymbol{\beta}}_X = \boldsymbol{\beta}_X + \boldsymbol{\beta}_M \boldsymbol{\gamma}_X$**

Where β_X is the direct effect, and $\beta_M \gamma_X$ is the indirect effect
(this method is approximate for non-linear models)

Addressing Mediation with Regression Calibration

The Models:

- $M = \gamma_0 + \gamma_X X + \gamma_Z Z + \delta,$ (1) Mediation model
- $Y = \beta_0 + \beta_X X + \beta_Z Z + \beta_M M + \varepsilon,$ (2) Outcome model

Midthune Method (Freedman et al (2011))

Step 1 Estimate γ_X from equation (1) using RC to adjust for ME

Step 2: estimate β_X and β_Z from equation (2) using RC to adjust for ME

Step 3: Estimate $\tilde{\beta}_X$ using the equation $\tilde{\beta}_X = \beta_X + \beta_M \gamma_X$.

Mediation Results from HCHS/SOL

Binary Outcome Y: High risk for metabolic syndrome
Exposure of interest X: Energy Intake – estimated OR for 20% increase
Mediator M: BMI
X*: self-reported intake using 24 hour recalls
Z: age, Hispanic/Latino background, education, income, and current smoking.

Method of Estimation	OR	95% CI
Including BMI in outcome model	0.85	0.46 – 1.58
Omitting BMI from outcome model	3.76	3.03 – 4.67
Midthune's method	1.52	1.02 – 2.25

Discussion

- There is increasing use of prediction and calibration equations in medicine
- Naïve analyses with predicted outcomes are subject to multiple biases
- Presented methods do not address when error is differential
- Awareness of the effects of Berkson error and methods to adjust for it need more attention

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