EMORY UNIVERSITY
ADRC
Alzheimer's Disease Research Center

An Errors-in-Covariates Approach for Using Cross-Walk Data

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Goal: Use MoCA for Some Subjects, MMSE for Others

Dataset to be used in regression analysis:

Subject	Response	Cognitive Function	Other Predictors
1	Y_1	MMSE	Z_1
2	Y_2	MoCA	Z_2
3	Y_3	MoCA	Z_3
4	Y_4	MMSE	Z_4
$\vdots$	$\vdots$	$\vdots$	$\vdots$

So long as we carefully and objectively calibrate the MMSE & MoCA, what is the concern?

Noise in Calibration Can Lead to Results that are Systematically Misleading

If one predictor serves as an (unbiased but noisy) surrogate for another, then:

- Unadjusted regression results will be biased
- Results will be biased for all covariates related to cognition
- Regression coefficients will be less precise than is apparent

Attenuation: replacing the 'true' predictor with an error-prone surrogate often yields a weaker relationship with the response (i.e., bias towards null)

Special methods are needed to reduce the bias of regression results

Errors-in-Covariates Framework

Two types of covariates:

Gold standard: might be unobserved in many (or all) subjects

Surrogate: a noisy and error-prone proxy

Nondifferential measurement error:

Surrogate has no information about response other than what is contained in the gold standard predictors.

According to neuropsychologists, MoCA has more information on certain domains (e.g., executive function) than MMSE

- Gold standard: MoCA
- Surrogate: MMSE

Methods to Adjust for Errors-in-Covariates

Simple, approximate methods (use standard software - should bootstrap CI):

1. Simple Calibration
2. Regression Calibration (Rosner et al., 1989, 1990; Carroll et al., 1995)

Advanced methods (require special software):

1. Conditional Score (Stefanski & Carroll, 1987)
2. Corrected Likelihood (Nakamura, 1990)
3. Corrected Estimating Functions (Huang & Wang, 2001)
4. Simulation Extrapolation (Cook & Stefanski, 1995; Stefanski & Cook, 1996)
5. Instrumental Variables (Buzas & Stefanski, 1996)
6. Bayesian methods (Stephens & Dellaportas, 1992)

Simple Calibration Using Crosswalk Data

- Based on equipercentile equating of MoCA and MMSE by UDS Neuropsychological Work Group
- Linear interpolation used to resolve ambiguities

Raw MMSE	Equivalent MoCA	Raw MMSE	Equivalent MoCA
3	0	22	15
4	0.5	23	16
5	1	24	17
6	1.5	25	18.5
7	2	26	20
8	3	27	21.5
9	3.5	28	23
10	4	29	25
⋮	⋮	30	28.5

$\text{Var(Measurement error)}/\text{Var(MoCA)} = (3.23/6.30)^2 = 0.26$

Regression Calibration using Crosswalk Data

Linear regression of MoCA on covariates (n=946)

Covariate	Estimate	SE	Estimate	SE
Intercept	20.88	0.31	20.76	0.24
MMSE *	12.89	0.35	12.90	0.34
MMSE ^{2}	0.97	0.89	1.73	0.34
MMSE ^{3}	-0.46	0.49	-	-
Female	-0.08	0.20	-	-
Age *	-0.37	0.11	-0.37	0.10
Age ^{2}	0.01	0.07	-	-
Educ				
13-16 yrs	0.13	0.28	0.12	0.28
17+ yrs	0.75	0.29	0.75	0.28

$\text{MMSE}^* = (\text{MMSE} - 26)/10, \quad \text{Age}^* = (\text{Age} - 75)/10$

$\text{Var(Measurement error)}/\text{Var(MoCA)} = (2.97/6.30)^2 = 0.22$

Toy Example: Relationship Between Dementia & Covariates at Same Visit Using Crosswalk Data (n=946)

	Gold Standard: 100 % MoCA, 0 % MMSE		Simple Calibration: 50 % MoCA, 50 % MMSE		Simple Calibration w/ Conditional Score: 50 % MoCA, 50 % MMSE	
Covariate	OR	95 % CI	OR	95 % CI	OR	95 % CI
MoCA	0.64	(0.60,0.68)	0.64	(0.60,0.68)	0.63	(0.58,0.67)
Female	0.43	(0.26,0.70)	0.53	(0.33,0.85)	0.52	(0.32,0.86)
Age(decades)	0.68	(0.53,0.87)	0.71	(0.55,0.90)	0.69	(0.53,0.89)
Educ 13-16 yrs	1.21	(0.63, 2.37)	1.21	(0.64,2.32)	1.25	(0.63,2.47)
Educ 17+ yrs	2.91	(1.45,6.04)	2.07	(1.06,4.14)	2.31	(1.12,4.77)

Toy Example: Relationship Between Dementia & Covariates at Same Visit Using Crosswalk Data (n=946)

	Gold Standard: 100 % MoCA, 0 % MMSE		Regression Calibration: 50 % MoCA, 50 % MMSE		Regression Calibration w/ Conditional Score: 50 % MoCA, 50 % MMSE	
Covariate	OR	95 % CI	OR	95 % CI	OR	95 % CI
MoCA	0.64	(0.60,0.68)	0.64	(0.60,0.68)	0.62	(0.58,0.67)
Female	0.43	(0.26,0.70)	0.51	(0.32,0.81)	0.50	(0.31,0.83)
Age(decades)	0.68	(0.53,0.87)	0.65	(0.51,0.84)	0.64	(0.49,0.83)
Educ 13-16 yrs	1.21	(0.63, 2.37)	1.20	(0.63,2.33)	1.24	(0.62,2.46)
Educ 17+ yrs	2.91	(1.45,6.04)	2.40	(1.22,4.87)	2.66	(1.28,5.53)

Restrict Attention to MCI & Control Participants (n = 622)

Measurement error is relatively large:

Simple Calibration:
Var(Measurement error)/Var(MoCA) $= (3.22/3.68)^2 = 0.77$

Regression Calibration:
Var(Measurement error)/Var(MoCA) $= (2.82/3.68)^2 = 0.59$

Toy Example: Relationship Between MCI & Covariates at Same Visit Using Crosswalk Data (n=622)

	Gold Standard: 100 % MoCA, 0 % MMSE		Simple Calibration: 50 % MoCA, 50 % MMSE		Simple Calibration w/ Conditional Score: 50 % MoCA, 50 % MMSE	
Covariate	OR	95 % CI	OR	95 % CI	OR	95 % CI
MoCA	0.73	(0.68,0.78)	0.78	(0.73,0.83)	0.76	(0.70,0.81)
Female	0.41	(0.26,0.63)	0.46	(0.30,0.70)	0.46	(0.30,0.71)
Age(decades)	0.86	(0.68,1.10)	1.00	(0.80,1.26)	0.96	(0.76,1.22)
Educ 13-16 yrs	0.68	(0.38, 1.24)	0.69	(0.40,1.22)	0.70	(0.40,1.25)
Educ 17+ yrs	0.60	(0.33,1.13)	0.52	(0.28,0.94)	0.55	(0.30, 1.01)

Toy Example: Relationship Between MCI & Covariates at Same Visit Using Crosswalk Data (n=622)

	Gold Standard: 100 % MoCA, 0 % MMSE		Regression Calibration: 50 % MoCA, 50 % MMSE		Regression Calibration w/ Conditional Score: 50 % MoCA, 50 % MMSE	
Covariate	OR	95 % CI	OR	95 % CI	OR	95 % CI
MoCA	0.73	(0.68,0.78)	0.76	(0.71,0.81)	0.73	(0.67,0.79)
Female	0.41	(0.26,0.63)	0.44	(0.29,0.67)	0.44	(0.29,0.68)
Age(decades)	0.86	(0.68,1.10)	0.95	(0.75,1.20)	0.90	(0.71,1.15)
Educ 13-16 yrs	0.68	(0.38, 1.24)	0.68	(0.39,1.20)	0.69	(0.39,1.23)
Educ 17+ yrs	0.60	(0.33,1.13)	0.55	(0.31,1.01)	0.60	(0.32,1.11)

Summary

1. Converting MMSE to MoCA can affect results regarding other covariates related to cognition
2. Preliminary work suggests regression calibration might be preferred to simple calibration
3. While conditional score approach might be useful, we lack
   (a) user-friendly software, and
   (b) extension of method to longitudinal studies
4. Challenges grow worse when studying patient subsets with a more restricted range of MoCA scores (e.g., MCI patients)
5. More research is needed

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