Generalizing Cluster Randomized Control Trial Results to a Target Population.

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Overview

We generalize findings from a randomized control trial, the Bridging Income Generation with Group Integrated Care (BIGPIC) study for cardiovascular risk reduction to a target population obtained from the Primary Health Integrated Care Project for Chronic Conditions (PIC4C) project.

Background

- Randomized control trials (RCTs) are usually considered the gold standard for estimation of causal effects.
- When treatment effect modifiers, are differently distributed between the trial and target population the sample average treatment effect (SATE) in the population of trial participants is biased for the target population average treatment effect (PATE).
- Statistical methods do exist that use trial data and covariate information, but no outcome or treatment information, from the target population to estimate the average treatment effect in the target population.

Study Design and Methods

- The BIGPIC study was a cluster randomized trial that evaluated the impact of group medical visits and/or microfinance on blood pressure reduction. The trial had 4 arms; usual care (UC), usual care plus microfinance (MF), group medical visits (GMVs) and GMVs integrated with microfinance (GMV-MF) and 24 clusters (Geographical locations-served by health facility).
  - A total of 2890 individuals were enrolled in the study and the primary outcome of interest was a one-year change in systolic blood pressure (SBP) while change one-year change in diastolic blood pressure (DBP) was a key secondary outcome.
- PIC4C was established in 2018 based on AMPATH HIV care model in Western Kenya to improve primary care services for diagnosis and management of diabetes, hypertension, breast and/or cervical cancer.
  - The target population with covariate, but no outcome or treatment, data comes from the PIC4C study and was collected between October 2019 to January 2020.
- We used standardized mean differences (SMD) to assess differences in distribution of baseline characteristics between the two populations (PIC4C and BIGPIC) and implemented inverse odds of trial participation weighting to extend inferences from the BIGPIC findings, obtained confidence intervals and adjusted for multiple comparisons using a Bonferroni correction.

Study Flowchart

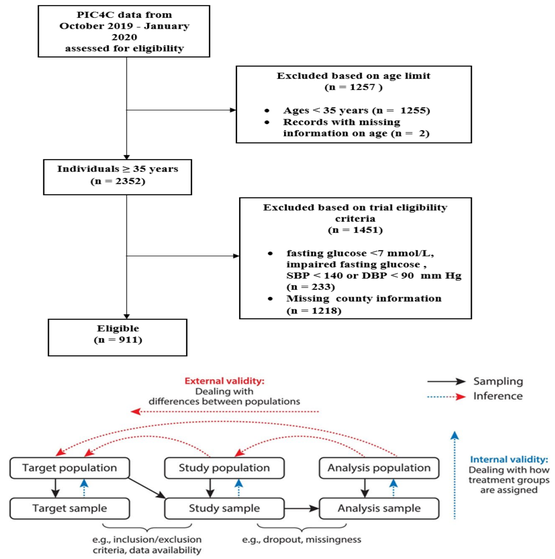

Figure 1: Target, study, and analysis populations in relation to internal and external validity [Degtiar and Rose, 2022].

Distribution of baseline Covariates

Table 1: Baseline characteristics in the target populations and BIGPIC study.

	Analysis Populations			
	Overall	Target Population	Study Population	SMD
N	3801	911	2890	
County Demographics				
County (%)				0.192
Busia/Vihiga	1863 (49.0)	464 (50.9)	1399 (48.4)	
Kisumu/Siaya	469 (12.3)	148 (16.2)	321 (11.1)	
Trans-Nzoia/Uasin Gishu	1469 (38.6)	299 (32.8)	1170 (40.5)	
Health Facility				0.297
Dispensary	1158 (30.5)	269 (29.7)	889 (30.8)	
County/Sub-county	1358 (35.8)	412 (45.5)	946 (32.7)	
Health Center	1280 (33.7)	225 (24.8)	1055 (36.5)	
Health Demographics				
Age Group				0.301
35-54	1316 (34.6)	403 (44.2)	913 (31.6)	
55-74	2031 (53.4)	443 (48.6)	1588 (54.9)	
≥75	454 (11.9)	65 (7.1)	389 (13.5)	
Female	2518 (66.2)	498 (54.7)	2020 (69.9)	0.318
Body Mass Index (BMI)	25.30 (5.69)	25.37 (6.30)	25.28 (5.48)	0.015
Diabetes	664 (17.5)	57 (6.3)	607 (21.1)	0.441
Hypertension	3444 (90.7)	746 (81.9)	2698 (93.5)	0.357
Baseline SBP, mmHG	155.65 (20.57)	149.89 (23.71)	157.47 (19.11)	0.352
Baseline DBP, mmHG	92.63 (12.04)	93.01 (12.89)	92.52 (11.76)	0.040
Lifestyle Demographics/Health Insurance				
Occupation				1.834
Unemployed	1870 (51.4)	32 (4.3)	1838 (63.6)	
Agribusiness	1128 (31.0)	546 (72.8)	582 (20.2)	
Casual	242 (6.7)	116 (15.5)	126 (4.4)	
Govt employee	89 (2.4)	29 (3.9)	60 (2.1)	
Other	309 (8.5)	27 (3.6)	282 (9.8)	
Monthly Earnings				1.680
Not formally employed	1897 (52.2)	32 (4.3)	1865 (64.7)	
Kshs <5,000	1166 (32.1)	420 (56.0)	746 (25.9)	
Kshs 5,000-10,000	276 (7.6)	138 (18.4)	138 (4.8)	
Kshs >10,000	294 (8.1)	160 (21.3)	134 (4.6)	
Education level				0.249
No formal	329 (8.7)	129 (14.2)	200 (6.9)	
Primary	2273 (59.8)	489 (53.7)	1784 (61.8)	
Secondary+	1197 (31.5)	293 (32.2)	904 (31.3)	
NHIF Status	714 (19.6)	225 (29.8)	489 (16.9)	0.307

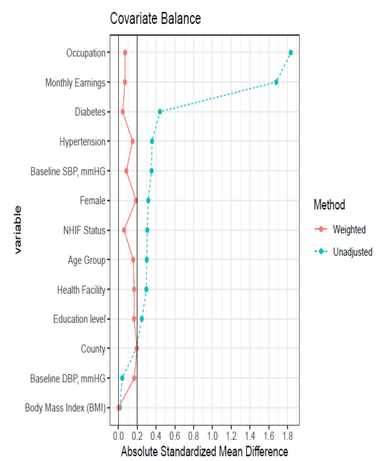

Figure 3: Absolute standardized mean differences comparing the BIGPIC study and target population before and after weighting to account for differences in baseline characteristics

Results

Table 2: Model-based estimates (with 98.3 % confidence intervals) for BIGPIC study vs transportability findings

Outcomes	BIGPIC Study			Target Population		
	UCMF-UC	GMV-UC	GMVMF-UC	UCMF-UC	GMV-UC	GMVMF-UC
SBP change 3m	-3.25(-7.97, 1.46)	-3.24(-7.75, 1.26)	1.01 (-5.64, 3.63)	-2.80 (-8.15, 2.55)	-6.56 (-11.65, -1.46)	-5.00 (-10.20, 0.21)
SBP change 12m	-2.31(-7.02, 2.40)	-3.29(-7.80, 1.21)	-3.91 (-8.53, 0.72)	0.25 (-5.09, 5.60)	-0.64 (-5.73, 4.46)	0.16 (-5.04, 5.37)
DBP change 3m	-3.34(-5.41, -1.27)	-1.66(-3.76, 0.45)	-1.36 (-3.50, 0.79)	-1.94 (-4.46, 0.58)	-1.52 (-4.02, 0.98)	-1.17 (-3.73, 1.39)
DBP change 12m	-2.35(-4.42, -0.28)	-1.64(-3.74, 0.47)	-3.25 (-5.40, -1.11)	-2.60 (-5.11, -0.08)	-1.84 (-4.34, 0.66)	-2.16 (-4.72, 0.40)

Table 3: Sub-group and Sensitivity Analysis in BIGPIC study and Target populations

12 month change in SBP	Sub-group Analysis for BIGPIC Study			Sensitivity Analysis in the Target Population		
	UCMF-UC	GMV-UC	GMVMF-UC	UCMF-UC	GMV-UC	GMVMF-UC
Unemployed	-3.31 (-7.67, 1.07)	-2.52 (-6.75, 1.75)	-4.93 (-9.29, -0.6)	Results adjusted for occupation and monthly earnings		
Lower monthly earnings	-3.23 (-7.58, 1.13)	-2.57 (-6.78, 1.68)	-4.61 (-8.95, -0.3)	-3.19 (-7.98, 1.60)	-3.55 (-8.16, 1.06)	-3.11 (-7.84, 1.62)
Women	-3.34 (-7.51, 0.82)	-4.0 (-7.99, -0.03)	-4.65 (-8.75, -0.57)	-3.9 (-3.9, -3.83)	-3.91 (-3.91, -3.85)	-2.36 (-2.36, -2.29)
Age 35-45 years	-3.72 (-8.44, 1.02)	-5.62 (-10.34, -0.9)	-4.0 (-8.82, 0.81)	-4.43 (-4.43, -4.35)	-4.54 (-4.54, -4.46)	-2.26 (-2.26, -2.18)
Age 55- 74 years	-2.59 (-6.95, 1.78)	-2.79 (-6.95, 1.35)	-2.79 (-6.95, 1.35)	-2.59 (-2.59, -2.51)	-3.11 (-3.11, -3.04)	-3.21 (-3.21, -3.14)

- We employed linear mixed-effects models and adjusted for baseline value of the outcome, baseline cluster-specific mean of the outcome, gender, recruitment pathway, type of health facility, age, and amount of pre-trial MF activity in the cluster.
  - Analyses adjusted for missing baseline covariates in the both populations produced equivalent results to complete case analyses.

Conclusion

- The estimated mean reduction in systolic blood pressure was attenuated in the target population, compared with the BIGPIC study.
- The reduced point estimates of the treatment effect and increased uncertainties in the target population estimates compared to the BIGPIC study reflect the major differences in gender, age, occupation, monthly earnings, and comorbidities between the two populations.
- The findings of this study underscore the need for more discussions on the issue of external validity and emphasize the importance of researchers paying attention to the challenges of generalizing treatment effects from a sample to a target population.

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