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Title: Generalizing Cluster Randomized Control Trial Results to a Target Population.

Background

The treatment effect observed in randomized controlled trials may not reflect the actual effect in the target population if the trial and target populations have differently distributed treatment effect modifiers. Cardiovascular diseases (CVDs) are responsible for more than 30% of global deaths, and their incidence is rising in low- and middle-income countries (LMICs), while high-income countries (HICs) have seen a decline. Hypertension, diabetes, hyperlipidemia, smoking, and obesity are the major modifiable risk factors for CVDs. However, LMICs face challenges such as inadequate healthcare spending, inefficient healthcare delivery systems, and limited healthcare workers, particularly in rural areas. Incorporating social determinants of health and strategies such as microfinance (MF) and group medical visits (GMVs) into care delivery can be cost-effective and culturally appropriate ways to address these obstacles.

Objective: To generalize the population average treatment effects from the Bridging Income Generation with Group Integrated Care (BIGPIC) study to a sample target population obtained from the Primary Health Integrated Care Project for Chronic Conditions (PIC4C) project.

Methods: BIGPIC study was a cluster randomized trial for cardiovascular risk reduction that assessed the effectiveness of GMVs and MF relative to the Usual Care (UC) arms on blood pressure reduction. We implemented the BIGPIC trial eligibility criteria to select a sample of the PIC4C population that included adults greater than 35 years who had either diabetes or hypertension. To compare the distribution of baseline characteristics between the two populations, standardized mean differences were utilized. A weighted linear mixed-effects model

was employed on the BIGPIC data to analyze the primary and secondary outcomes, with inverse estimated odds of trial participation used as weights. We obtained confidence intervals and adjusted for multiple comparisons using a Bonferroni correction.

Results: The study found that BIGPIC and PIC4C participants had several imbalanced characteristics. BIGPIC participants were on average slightly younger, less likely to have health insurance, were less likely to be formally employed, with lower monthly earning indices, and had more diagnosed comorbidities (diabetes and hypertension), when compared to the target population. The transportability analyses in the PIC4C sample showed that compared to UC arm, the mean reduction in systolic blood pressure was 0.4 mm Hg lesser in the GMV- MF arm (95% CI, -4.9 to 5.8 mm Hg), 0.9 mm Hg greater in the GMV arm (95% CI, -6.2 to 4.4 mm Hg), and 0.9 mm Hg lesser in the MF arm (95% CI, -4.7 to 6.4 mm Hg).

Conclusions: The attenuated point estimates of the treatment effect and increased uncertainties in the target population estimates compared to the BIGPIC study reflect the major differences in demographics and comorbidities between the two populations. The study emphasizes the importance of incorporating social health determinants into healthcare delivery for chronic diseases to improve cardiovascular outcomes for a subgroup of patients and highlights the lack of generalizability of trial results to intended target populations, suggesting a need for more discussion on this issue.