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ORIGINAL PAPER

Neighborhood Disadvantage, Syndemic Conditions, and PrEP Non-Adherence in Young Sexual and Gender Minority Men

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Abstract

Adherence to Pre-Exposure Prophylaxis (PrEP) among young sexual and gender minority men who have sex with men (YSGMMSM) has been suboptimal for reducing HIV incidence in the United States. Using the syndemic framework, the present study characterized how neighborhood disadvantage and clustering of two or more syndemic conditions (depression, anxiety, polysubstance use, history of arrest, BIPOC racial identity, unemployment) was related to PrEP non-adherence among 212 YSGMMSM aged 16–24. This study is a secondary analysis of an efficacy trial testing a PrEP adherence digital intervention for YSGMMSM combining participant survey and biological PrEP adherence data with measures of neighborhood disadvantage. Using multilevel models, we found that YSGMMSM residing in high-disadvantage neighborhoods were 2.79 (CI = 1.11, 7.00) times more likely to have a cluster of syndemic conditions compared to those in low-disadvantage neighborhoods. YSGMMSM residing in high-disadvantage neighborhoods were 3.14 (OR = 3.14, CI = 1.17, 8.44) times more likely to be PrEP non-adherent. YSGMMSM with two or more syndemic conditions were 2.64 (CI = 1.01, 6.94) times more likely to be PrEP non-adherent compared to those with 0 or 1 condition. Among participants living in high-disadvantage neighborhoods, 38% had a cluster of a syndemic conditions compared 20% in low-disadvantage neighborhoods. Despite this, neighborhood disadvantage did not significantly moderate the relationship between clustering of syndemic conditions and PrEP non-adherence among YSGMMSM. Further research into multilevel syndemic influences on PrEP adherence is needed to develop strategies for improving HIV vulnerability among YSGMMSM.

Keywords HIV prevention · PrEP adherence · Syndemics · Neighborhood effects · Structural disparities

Introduction

Young sexual and gender minority men who have sex with men (YSGMMSM) have a disproportionate and growing vulnerability to HIV in the United States (US) [1–7]. 67% of the incident HIV cases in 2022 were among men who have sex with men (MSM) with 24% among MSM aged 13-24.[1–7] YSGMMSM include a spectrum of gender identities, including transgender women. Transgender women aged 15 and older have 48 times higher odds of having HIV compared to other adults of reproductive age [6]. Pre-exposure prophylaxis (PrEP) is efficacious in reducing HIV incidence in US YSGMMSM in randomized controlled trials and could reduce HIV transmission by as much as 44% [8–10]. However, adherence to PrEP outside of clinical trial settings has been suboptimal for reducing transmission [8, 11].

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Syndemics are the interactive co-occurrence or clustering of diseases within a population that disproportionately increase disease burden or vulnerability. The role of syndemics in HIV vulnerability (increased likelihood of HIV acquisition or increased disease burden for people with HIV) has been extensively explicated since the introduction of the SAVA (substance abuse, violence, and HIV/AIDS) syndemic construct in 1996, which utilized anthropological and sociological methods to describe the syndemic interaction of substance abuse, violence, and HIV vulnerability among Puerto Ricans living in Hartford, Connecticut [12–18]. Since then, syndemic models have been similarly applied to characterize how clusters of individual health conditions are associated with HIV vulnerability in YSGMMSM [12, 13, 19–31]. Most individuals identifying as a sexual or gender minority experience two or more syndemic conditions simultaneously (e.g., polysubstance use and depression), with HIV vulnerability increasing synergistically for each additional condition [25, 27]. Past syndemics research with YSGMMSM has shown that depression, substance use, and unemployment are associated with synergistic increases in HIV vulnerability [20–29, 32, 33]. Notably, two past studies have characterized how MSM with HIV have an increased likelihood to be non-adherent to antiretroviral therapy (ART) for each additional syndemic condition they have [32, 33]. This example of syndemic interaction among MSM with HIV with respect to ART non-adherence suggests that syndemic interaction may also exist for YSGMMSM with respect to PrEP non-adherence.

In addition to syndemic interaction among individual health conditions, another fundamental criterion for a syndemic is that "contextual and social factors create the conditions in which two (or more) diseases or health conditions cluster" [12, 13]. Contextual factors, including neighborhood attributes such as neighborhood disadvantage, play a crucial role in the development of disease clusters and are hypothesized to interact with diseases to exacerbate burden [12, 13]. Past work has shown that neighborhood disadvantage (e.g., income inequality) is associated with HIV vulnerability, including lower ART adherence [34–41]. It is likely that neighborhood disadvantage is also related to HIV vulnerability in the form of PrEP non-adherence. To date, no studies have characterized syndemic interaction between neighborhood disadvantage, other syndemic conditions, and HIV vulnerability in the form of PrEP non-adherence among YSGMMSM.

Research to characterize the role of contextual factors such as neighborhood disadvantage using a syndemics model is a needed next step. Previous syndemics research with YSGMMSM has indicated the importance of social determinants of health such as poverty, incarceration, and social demographics (e.g., race) on HIV vulnerability but often omit direct measures of contextual factors such as neighborhood disadvantage [12, 20–29, 42, 43]. In syndemic models, social and structural determinants of health are framed as "reflections of power and inequality – expressed directly or mediated by the environment" [12]. Therefore, direct measures of contextual factors such as neighborhood disadvantage are needed to fully model HIV syndemics in YSGMMSM. Multilevel modeling is an apt statistical framework to tackle syndemics research with respect to HIV vulnerability in YSGMMSM [19]. Multilevel models incorporate factors that occur at different levels (e.g., individual and neighborhood), taking into account correlation within clusters at a given level. This is a fitting statistical approach to characterize the relationship between neighborhood disadvantage and clustering of syndemic conditions as these fundamentally occur at different levels.

The present study leveraged secondary data from the randomized controlled trial (RCT) testing the efficacy of P3 (Prepared, Protected, emPowered), a digital health intervention to improve PrEP adherence among YSGMMSM. This multilevel secondary analysis combines measures of neighborhood disadvantage, syndemic condition clustering, and PrEP non-adherence in YSGMMSM to achieve the following aims: (1) identify if neighborhood disadvantage, defined through the Social Vulnerability Index (SVI), is associated with clustering of syndemic conditions (e.g., depression, polysubstance use), (2) characterize how neighborhood disadvantage and clustering of syndemic conditions are independently and interactively associated with PrEP non-adherence in eligible YSGMMSM from the P3 RCT sample.

Methods

Overview

This secondary analysis combined a measure of neighborhood disadvantage with clinical survey and biological data collected from the three-arm primary efficacy RCT testing P3, a PrEP adherence digital intervention for YSGMMSM aged 16–24. Utilizing a multilevel modeling approach, we evaluated how neighborhood disadvantage is related to clustering of baseline syndemic conditions at the individual level. Subsequently, we quantified how neighborhood disadvantage and baseline individual-level syndemic condition clustering were independently and interactively related to PrEP non-adherence at 3 months in RCT participants. The parent study was reviewed and approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, USA (17-9551). A Certificate of Confidentiality was obtained from the National Institute of Child Health and Human Development. For participants between the ages of

15 and 17, a waiver of parental consent was obtained. This trial is registered at ClinicalTrials.gov (NCT03320512). The secondary analysis described herein was reviewed by the Northeastern University Institutional Review Board and classified as exempt determination, category 4 (secondary research for which consent is not required). We utilized a de-identified analytic dataset curated by the parent study's staff and the secondary analysis principal investigator had no contact with participants and made no attempts to re-identify participants post hoc.

Parent Study

P3 is a user-centered PrEP adherence phone application (app) that incorporates a variety of content in multiple formats to serve the diverse needs, challenges, and motivations of YSGMMSM. This includes text, videos, quizzes, and a social wall in which participants can share experiences, from success stories to challenges. P3 + is an extended version of the P3 app, where in addition to all the standard features of P3, participants are connected with an adherence coach who provided in-app coaching based on an adapted Next Step Counseling (NSC) adherence counseling curriculum [44–47]. Participants were recruited from nine study sites: Tampa, Florida; Boston, Massachusetts; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Chapel Hill, North Carolina; Atlanta, Georgia; Bronx, New York; Charlotte, North Carolina. A mix of in-person, venue-based, and web-based recruitment methods were utilized. Residential zip code was collected from each participant. Inclusion criteria were as follows: (1) 16–24 years of age; (2) assigned male sex at birth; (3) report sex with or intentions to have sex with men or transwomen; (4) have reliable daily access to an Android or iOS smartphone with a data plan; (5) are able to speak and read English; (6) are HIV-uninfected (confirmed by self-report at enrollment visit); and (7) are not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) or currently on PrEP and have an active PrEP prescription (prescription confirmed by study staff). After providing informed consent either in-person or electronically, participants were randomized to one of three treatment arms (standard of care, P3, or P3+) using a 1:1:1 randomization scheme. The study took place from March 2019 to September 2021. Clinical survey assessments and laboratory specimens were collected at baseline and 3 months in the trial period. Study visits were initially planned to be conducted in person at the same study site where participants enrolled. All study sites stopped in-person study activities on March 17, 2020 to reduce the transmission of COVID-19. Virtual enrollment and virtual study activities began in June 2020. Additionally, some study sites were able to conduct limited in-person activities based on local regulations and COVID-19 restrictions.

Secondary Analysis Eligibility

Participants from all three trial arms of the primary study were eligible for inclusion in this secondary data analysis ($n = 246$). Participants who were lost to follow-up (LTFU, defined as participants who did not begin the month 3 survey) were excluded ($n = 34$). This resulted in a dataset of 212 participants (86% of all participants enrolled).

Measures

Neighborhood Disadvantage

Each participant's self-reported residential zip code was cross-walked to a Zip Code Tabulation Area (ZCTA) and used as a proxy for the participant's neighborhood. ZCTAs are a geographic unit described by the US census based on US zip codes and are a suitable proxy for a participant's residential neighborhood [48, 49]. ZCTA-level measures of neighborhood disadvantage were constructed using the SVI. This index is comprised of 15 factors across 4 themes (1: socioeconomic status, 2; household composition, 3: disability, minority status, and language, and 4: housing type and transportation) ascertained through the American Community Survey. The SVI was created to describe neighborhood vulnerability to natural disasters, including health-related disasters such as epidemics. The SVI is an ordinal scale ranging from 0 to 15, where each factor is assigned a point if that item is in the 90th percentile or higher across the entire US [50]. For example, if a given neighborhood is in the 90th percentile or higher in unemployment rate, that neighborhood receives one point on the ordinal scale. We defined high neighborhood disadvantage using a binary measure created from this scale, where neighborhoods in the 90th percentile across the entire US based on the SVI were considered high-disadvantage neighborhoods.

Depressive Symptoms

The patient health questionnaire-8 (PHQ8) [51, 52] questionnaire was used to assess baseline depressive symptoms. Participants were asked to rank how frequently they experience symptoms from: "not at all", "several days", "more than half the days", and "nearly every day". Scores range from 0 to 24 with lower scores representing less frequent symptoms and higher scores represent more frequent symptoms. A binary measure was constructed where participants who scored 10 or more on the PHQ-8 were considered as

having depressive symptoms. This is the recommended screening cutpoint for further evaluation and represent symptoms of moderate to severe depression [52, 53]. Prior research utilizing a syndemic framework has consistently found that depression among YSGMMSM contributes to increased HIV vulnerability or other syndemic conditions that co-occur with HIV (e.g., intimate partner violence) [21–23, 25–28].

Anxious Symptoms

The generalized anxiety disorder-7 (GAD-7) [54] questionnaire was used to assess baseline anxious symptoms. Participants were asked to rank how frequently they experience symptoms from: "not at all", "several days", "more than half the days", and "nearly every day". Scores range from 0 to 21. Lower scores represent less frequent symptoms and higher scores represent more frequent symptoms. Similar to depressive symptoms, we constructed a binary measure where participants who scored 10 or higher on the GAD-7 were considered as having anxious symptoms. The role of anxiety in HIV syndemics among YSGMMSM has yet to be characterized [21–23, 25–28].

Polysubstance Use

Polysubstance use was defined as reported use of two or more substances consistent with a brief or intensive intervention using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [55] at baseline. The following categories of substances were considered: opioids, stimulants, inhalants, hallucinogens, and sedatives. This is consistent with prior research into HIV vulnerability among YSGMMSM with the exception that we did not include cannabis use in our measure of polysubstance use [23, 25–29] as cannabis use has consistently been shown to have no positive or negative relationship to PrEP adherence in YSGMMSM [56, 57].

Lifetime History of Arrest

P3 participants who reported any previous history of being arrested in their lifetime at baseline were considered to have a lifetime history of arrest. Past literature has identified justice system involvement as co-occuring with other syndemic measures and related to HIV vulnerability [26, 29].

Not in Education, Employment, or Training

P3 participants who reported neither currently being in some form of education (high school, college, trade school, etc.) nor employed at baseline were considered not in education, employment, or training. Unemployment has been consistently linked to HIV vulnerability [58].

Sociodemographic characteristics.

Sociodemographic characteristics captured from the baseline survey include race/ethnicity and age. Participants were considered black, indigenous, people of color (BIPOC) if they disclosed any racial or ethnic identity other than non-Hispanic ethnicity and Caucasian. This measure was used as a proxy for individual health-related disadvantages experienced by BIPOC persons living in the US. The experiences of health-related disadvantage among BIPOC persons living in the US is a distinct phenomenon that exists within and across strata of socioeconomic status [59–62]. Furthermore, BIPOC racial and ethnic status has been linked to HIV vulnerability in studies without a syndemic framing [63–68]. Several other sociodemographic characteristics were collected by the primary RCT but not utilized in this analysis due to the lack of variability (e.g., gender identity) or lack of suitability (e.g., income, as many participants are minors or are in school).

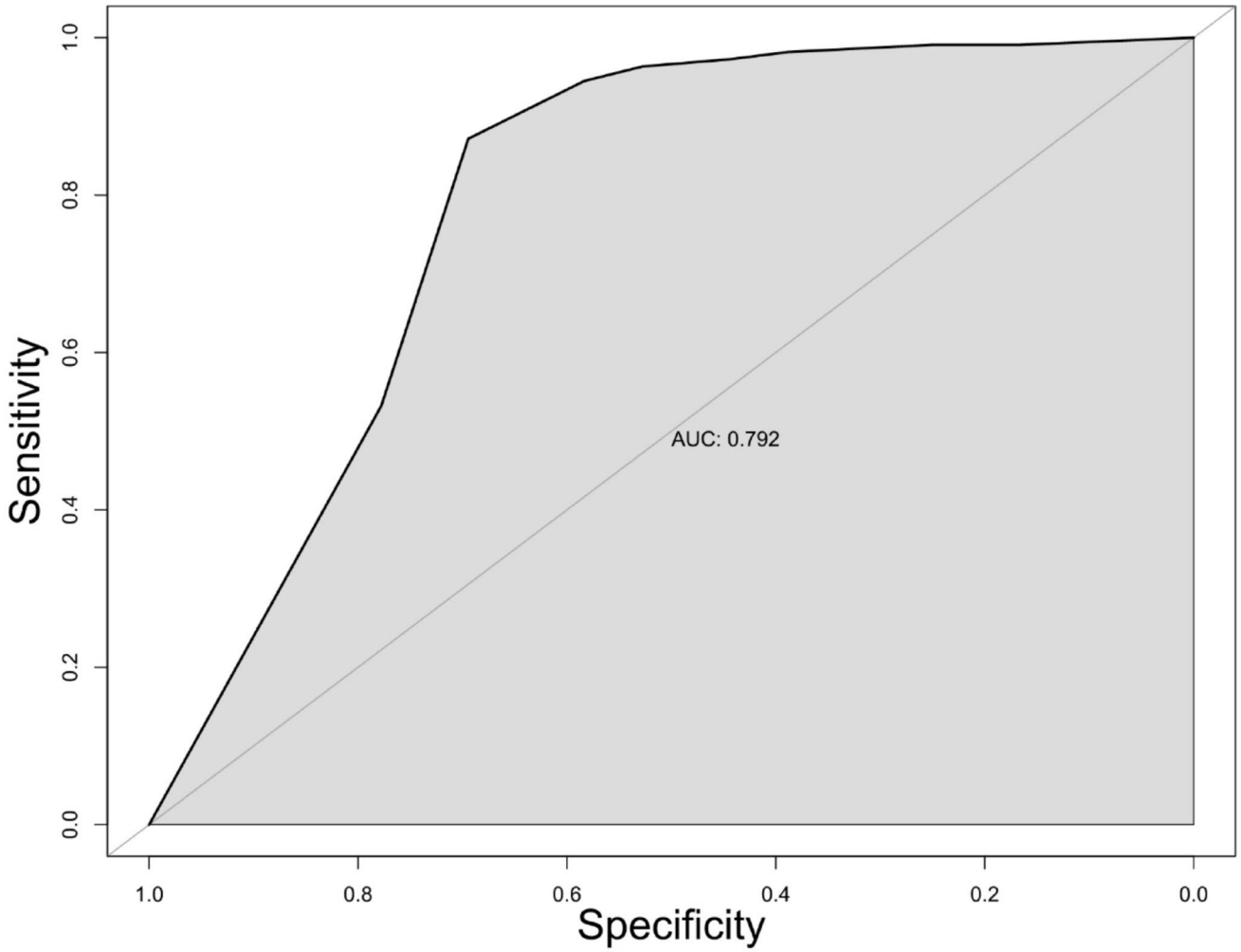
Syndemic Condition Clustering

Consistent with several prior studies, we defined syndemic condition clustering among P3 participants as a binary measure. We considered the following binary syndemic conditions at baseline: depression, anxiety, polysubstance use, not employed or in school, BIPOC racial identity (as a proxy for experienced racism), and lifetime history of arrest [23, 25–29]. Participants who reported two or more of these conditions were considered to have a cluster of syndemic conditions.

PrEP Non-Adherence

PrEP non-adherence at 3 months is the primary outcome measure used in this analysis and defined as a binary measure (adherent/non-adherent). We defined PrEP non-adherence at 3 months using a combination of dried blood spot (DBS)-derived estimates of tenofovir diphosphate (TFV-DP) levels and self-reported PrEP adherence in the past month. Participants were considered PrEP non-adherent if their DBS-derived TFV-DP levels were consistent with ≤ 4 doses per week. Due to study operation interruptions related to the COVID-19 pandemic, 31% (66/212) of eligible participants were unable to provide biological specimens. Where DBS-derived measures were missing, self-reported PrEP non-adherence in the past month was used, ascertained through the following survey question: "in the last month, what percent of the time did you take your PrEP as prescribed (once a day)". Responses could range from 0% (none of the time) to 100% (all of the time). Non-adherence

was defined as participants who self-reported less than 60%. While there is mixed evidence regarding the accuracy of self-reported measures of PrEP adherence, issues of over-reporting in young men who have sex with men decrease significantly with age. Two studies have found that self-report measures of PrEP adherence correlate with protective serum levels among adults [69, 70]. Another study found that among young MSM, the odds of over-reporting PrEP adherence decreased by 24% (OR = 0.74, 95% CI = 0.65, 0.90) per year of age [71]. In the present study, we found that the area under the receiver operating characteristic curve (AUC) between self-report measures and biological measures among participants with biological and self-report PrEP non-adherence measures at 3-month follow up was high (Fig. 1, AUC = 0.79). Given that the AUC was high and that the median age of secondary-analysis-eligible participants is 22, supplementing the missing biological PrEP



[a]Receiver operating characteristic curve was constructed by including participants at 3 month-follow up who submitted biological and self-reported measures (146/212)
[b]Biological PrEP adherence was determined using dried blood spot estimates of tenofovir diphosphate. Estimates correlating with > 4 doses per week were considered adherent
[c]Self-reported PrEP adherence was determined using the following question: "In the last month, what percent of the time did you take your PrEP as prescribed (once a day)". Adherence was defined as participants who self-reported > 60%

Fig. 1 Receiver Operating Characteristic Curve[a]: Relationship Between Biological[b] and Self-Reported[c] Measures of Pre-Exposure Prophylaxis Adherence Among US YSGMMSM Participants aged 16–24 ($n = 146$) at 3-Month Follow Up

adherence measures with self-report is likely sufficiently accurate.

Statistical Analyses

We described eligible participants and participants who were LTFU using the characteristics above. To identify if neighborhood disadvantage is related to clustering of syndemic conditions, we constructed a generalized linear mixed model (GLMM) with logit link where the focal exposure was neighborhood disadvantage and the outcome was clustering of individual syndemic conditions. To characterize how neighborhood disadvantage and individual syndemic conditions are independently related to PrEP non-adherence at 3 months in the P3 sample, we constructed a GLMM model with logit link where the focal exposures were neighborhood disadvantage and clustering of individual syndemic conditions and the outcome was PrEP non-adherence at 3 months.

We used a combination of empirical and data visualization approaches to assess how neighborhood disadvantage moderates the relationship between syndemic conditions and PrEP non-adherence among YSGMMSM. We assessed multiplicative moderation using the interaction term from the GLMM model, and additive moderation using relative excess risk due to interaction (RERI) [72]. If the confidence interval (CI) did not contain the null value of 0, the RERI estimate was considered statistically significant. Finally, moderation was assessed visually using interaction plots described in Ward et al. (2019) [73]. These interaction plots combine visualizations of effect moderation with visualizations of disparities (which reflect differences in exposure levels). These plots are useful for determining if a given relationship is being moderated by a third variable, is related to exposure disparities, or both.

For all models, we derived the intraclass correlation coefficient (ICC) from the two-level unconditional model (participants nested in zip codes). While ICC should be considered as one measure of model feasibility, it is suggested that any data that is intrinsically nested should use hierarchical modeling [74, 75]. Since syndemic theory posits that neighborhood disadvantage constructs the environment for individual syndemic conditions to cluster, hierarchical modeling aptly reflects this dynamic and has been suggested in past work as a suitable tool to tackle quantitative syndemic analyses [19]. All GLMM models control for age and P3 trial arm. We exponentiated participant (level 1) beta coefficients from the regression output of all models to generate odds ratios (ORs) and corresponding 95% CIs for fixed effects. A parameter is considered statistically significant if the CI does not contain the null value of 1.

Table 1 Comparison of eligible secondary analysis sample and loss to follow up participant characteristics in a secondary analysis of the effect of syndemic conditions and neighborhood disadvantage on PrEP adherence among US YSGMMSM aged 16-24a

	Eligible	LTFU
Participants	212	34
PrEP Non-Adherent (%)	49 (23.1)	
BIPOC (%)	113 (53.3)	19 (55.9)
Not in Education or Employment (%)	15 (7.1)	2 (5.9)
Lifetime History of Arrest (%)	12 (5.8)	3 (8.8)
Polysubstance Use	17 (8.0)	6 (17.6)
Depressive Symptoms (%)	29 (13.7)	4 (11.8)
Anxious Symptoms (%)	36 (17.0)	6 (17.6)
Syndemic Score (median [IQR])[b]	1.00 [0.00, 1.00]	1.00 [1.00, 1.00]
Syndemic Cluster (%)	51 (24.1)	8 (23.5)
Neighborhood Disadvantage Score (median [IQR])[bc]	3.00 [1.00, 5.00]	2.00 [1.00, 4.75]
Neighborhood Disadvantage (binary, %)[c]	50 (23.6)	8 (23.5)
Age (median [IQR])[b]	22.00 [20.00, 23.00]	22.00 [20.25, 23.00]
Male Gender (%)	194 (91.5)	32 (94.1)
Trial Arm (%)		
Standard of Care	71 (33.5)	12 (35.3)
P3 Intervention	69 (32.5)	13 (38.2)
P3 + Intervention	72 (34.0)	9 (26.5)
Trial Site (%)		
Tampa	34 (16.0)	9 (26.5)
Atlanta	16 (7.5)	5 (14.7)
Boston	33 (15.6)	4 (11.8)
Philadelphia	24 (11.3)	4 (11.8)
Chicago	31 (14.6)	4 (11.8)
Houston	29 (13.7)	4 (11.8)
Bronx	14 (6.6)	3 (8.8)
Chapel Hill	23 (10.8)	0 (0.0)
Charlotte	8 (3.8)	1 (2.9)

*Statistical significance (alpha = 0.5). [a]Continuous measures tested with t-test, categorical measures tested with Fishers exact. [b]Non-normal distribution, Kruskal-Wallis Rank Sum Test used. [c]Based on the Social Vulnerability Index developed by the Centers for Disease Control and Prevention

Results

Neighborhood and Participant Characteristics

Table 1 compares eligible and LTFU participants. Of the 246 total participants from the original P3 RCT, 212 were included in this secondary analysis and 34 were LTFU. There were no significant differences on any exposure or control measures between the 212 retained participants and the 34 LTFU. The median age of P3 participants was 22 years of age (interquartile range [IQR] = 20–23). Fifty-one (24%) participants reported a cluster (two or more)

syndemic conditions at baseline, 94 (44%) reported one syndemic condition at baseline, and 67 (32%) reported no conditions at baseline. Fifty (24%) participants reported a residential address in a zip code corresponding to high (>=90th percentile) neighborhood disadvantage with a median SVI score of 3.0 (IQR=1.0–5.00), which is higher than the national average of 1.4 (CI=2.7, 3.3, $p<.0001$). Forty-nine (23%) participants were considered PrEP non-adherent at the 3-month follow-up.

Neighborhood Disadvantage and Syndemic Condition Clustering

Table 2 describes the association between neighborhood disadvantage and clustering of individual syndemic conditions. The ICC corresponding to this model was 0.025 (binary clustering of syndemic conditions regressed against intercepts clustered within zip codes). The full multivariate model estimated that participants living in zip codes that corresponded to high neighborhood disadvantage have 2.79 times the odds of having a cluster (2 or more) syndemic conditions simultaneously (OR=2.79, CI=1.11, 7.00) compared to those living in low neighborhood disadvantage zip codes.

Neighborhood Disadvantage, Syndemic Condition Clustering, and PrEP Non-Adherence

Table 3 describes the association of neighborhood disadvantage and clustering of individual syndemic conditions on PrEP non-adherence. The ICC corresponding to this model was 0.23 (binary PrEP non-adherence regressed against intercepts clustered within zip codes). The full multivariate model estimated that participants residing in high-neighborhood disadvantage zip codes had 3.14 times the odds of being PrEP non-adherent at 3 months (OR=3.14, CI=1.17, 8.44) compared to those in low-disadvantage neighborhoods. Similarly, participants with a cluster of 2 or more syndemic conditions had 2.64 times the odds of being PrEP non-adherent at 3 months (OR=2.64, CI=1.01, 6.94) compared to those with 1 or 0 syndemic conditions.

Table 4 characterizes if and to what extent neighborhood disadvantage quantitatively moderates the association between syndemic condition clustering and PrEP non-adherence. Participants who had a cluster of syndemic conditions and resided in high-disadvantaged neighborhoods had 5.23 times the odds of being PrEP non-adherent at 3 months (OR=5.23, CI=1.67, 16.4) compared to those without a cluster of syndemic conditions and lived in low-disadvantaged neighborhoods. Despite this, interaction measures were not statistically significant on the additive (RERI) or multiplicative scale (interaction regression term). Figure 2

Table 2 Effect of neighborhood disadvantage on clustering of individual syndemic conditions in US YSGMMSM aged 16–24 ($n=212$)

Exposures	OR	CI	*p*
Neighborhood Disadvantage[a]	2.79	1.11, 7.00	0.029*
Arm: [P3 Intervention]	0.30	0.11, 0.82	0.018*
Arm: [P3+Intervention]	0.94	0.42, 2.12	0.889
Age	0.90	0.75, 1.08	0.263
σ^2	3.29		
τ_{00}	0.42		
N (ZCTA)	156		

*Statistical significance (alpha=0.5). [a] Based on the Social Vulnerability Index developed by the Centers for Disease Control and Prevention

Table 3 Effect of neighborhood disadvantage and clustering of individual syndemic conditions on PrEP Non-Adherence in US YSGMMSM aged 16–24 ($n=212$)

Exposures	OR	CI	*p*
Neighborhood Disadvantage [a]	3.14	1.17, 8.44	0.024*
Cluster of 2 or More Syndemic Conditions	2.64	1.01, 6.94	0.049*
Arm: [P3 Intervention]	0.78	0.33, 1.85	0.572
Arm: [P3+Intervention]	0.56	0.23, 1.33	0.187
Age	0.96	0.80, 1.15	0.662
σ^2	3.29		
τ_{00}	0.31		
N (ZCTA)	156		

*Statistical significance (alpha=0.5). [a]Based on the Social Vulnerability Index developed by the Centers for Disease Control and Prevention

Table 4 Moderating effects of neighborhood disadvantage on the relationship between syndemic condition clustering and PrEP Non-Adherence US YSGMMSM aged 16–24 ($n=212$)

Syndemic Condition Clustering (2+Conditions)	Neighborhood Disadvantage	
	Low-disadvantage	High-disadvantage
0–1 Syndemic Conditions	Reference [$n=130$][a]	3.14 (1.17, 8.44) [$n=31$][b]
2+Syndemic Conditions	2.64 (1.01, 6.94) [$n=32$][c]	5.23 (1.67, 16.4) [$n=19$][d]
Multiplicative Interaction[e]	0.63 (0.22, 1.31)	
Additive Interaction[f]	0.45 (-5.59, 6.5)	

*Statistical significance (alpha=0.05). [a]Participants without syndemic clustering and not living in a disadvantaged neighborhood (OR_{00}). [b]Participants without syndemic clustering and living in a disadvantaged neighborhood (OR_{01}). [c]Participants with syndemic clustering and not living in a disadvantaged neighborhood (OR_{10}). [d]Participants with syndemic clustering and living in a disadvantaged neighborhood (OR_{11}). [e]Multiplicative interaction defined as: OR_{11} / (OR_{10} * OR_{01}). Null value of 1, 95% confidence interval. [f]Additive interaction defined as: $OR_{11} - OR_{10} - OR_{01} + 1$. Null value of 0, 95% confidence interval. [g]Estimates represented as odds ratios with corresponding confidence intervals and participant counts

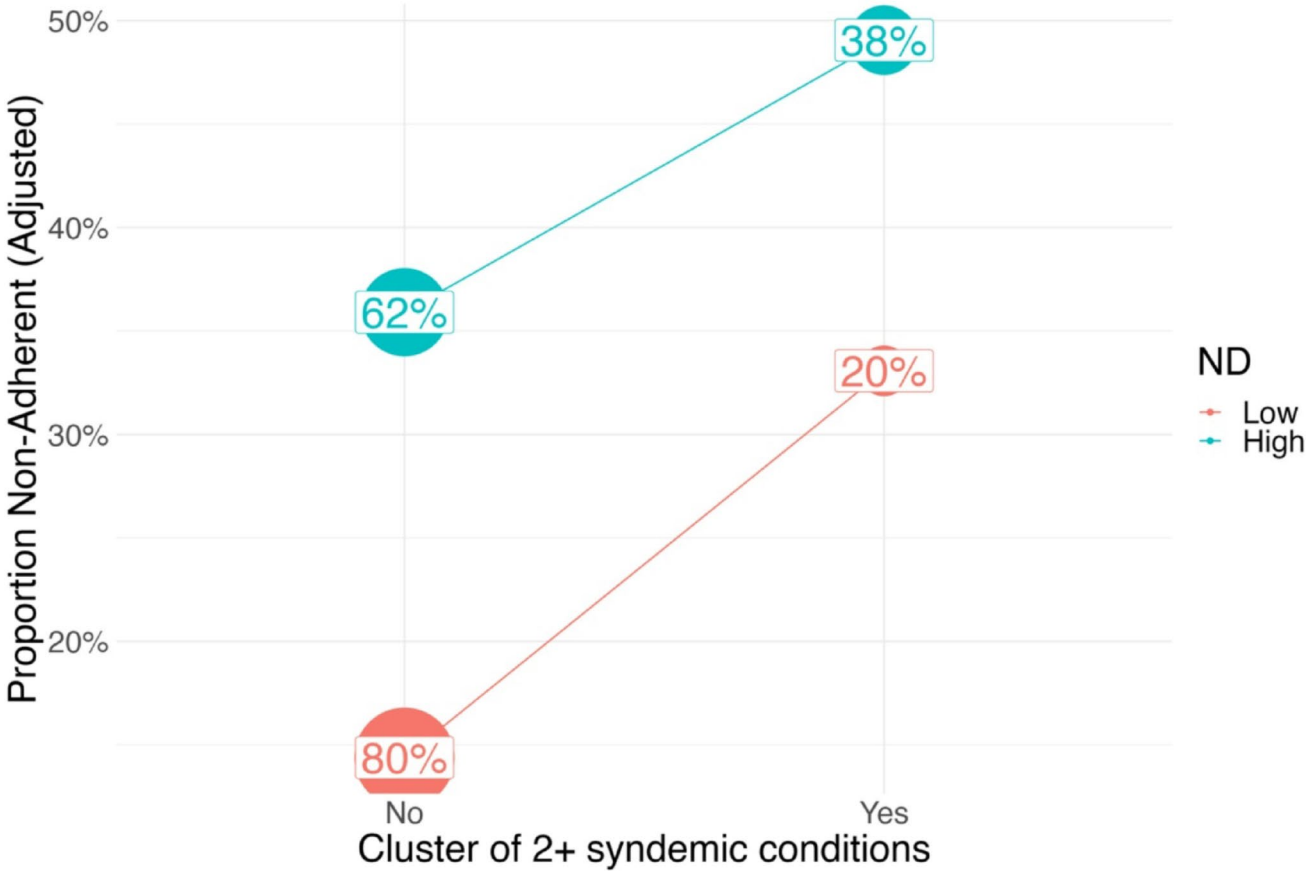


Fig. 2 Moderating Effects of Neighborhood Disadvantage on the Relationship Between Syndemic Condition Clustering and PrEP Non-Adherence US YSGMMSM aged 16–24 ($n=212$). ND = Neighborhood disadvantage. Proportion Non-Adherent: covariate adjusted predicted proportion non-adherent to PrEP bubble percentages: Prevalence of syndemic condition clustering within strata of neighborhood disadvantage and sum to 100% within strata of neighborhood disadvantage

displays the Ward-style visualizations which graphically characterize the moderating role of neighborhood disadvantage in the association between syndemic conditions and PrEP non-adherence in the P3 sample. The model-fitted PrEP non-adherence rate among participants who lived in high-disadvantage neighborhoods without a cluster of syndemic conditions was 36%, compared to 48% among participants who lived in high-disadvantage neighborhoods with a cluster of syndemic conditions. Participants who lived in a low-disadvantage neighborhood without a cluster of syndemic conditions and had a model-fitted PrEP non-adherence rate of 14%, compared to 34% among participants who lived in low-disadvantage neighborhoods with a cluster of syndemic conditions. Figure 2 also describes the proportion with syndemic condition clustering among those in high-disadvantage neighborhoods and those in low-disadvantage neighborhoods as a measure of health disparity. In high-disadvantage neighborhoods, 38% (19/50) of participants had a cluster of 2 or more syndemic conditions, compared to 20% (32/162) in low-disadvantage neighborhoods.

Discussion

We described the distribution of syndemic conditions and ZCTA-level neighborhood disadvantage among YSGMMSM participating in the P3 RCT. We found that P3 participants residing in high-disadvantage neighborhoods had an increased likelihood of having two or more syndemic conditions. Further, we found that both neighborhood disadvantage and clustering of syndemic conditions (two or more) were related to higher likelihood of PrEP non-adherence in the P3 sample. Finally, we described how neighborhood disadvantage relates to disparities in syndemic condition prevalence among P3 participants. Collectively, this work provides empirical support that contextual factors, such as neighborhood disadvantage, may play a role in the development of syndemic condition clustering and PrEP non-adherence among YSGMMSM.

Significant variability exists in estimates of syndemic condition clustering in YSGMMSM, with previous work finding that anywhere between 31% and 93% of participants in syndemic studies have two or more co-occurring

syndemic conditions. The present study found that 24% of P3 participants had two or more co-occuring syndemic conditions, which to our knowledge, is the lowest reported thus far. This lower prevalence of co-occurrence may reflect the lack of included measures for intimate partner violence and history of sexual assault, which are measures common to other syndemic analyses. Additionally, the lower prevalence of syndemic conditions may also be the result of the primary RCT eligibility (participants already connected to care, had a prescription, owned a smartphone). As many syndemic health conditions are also documented barriers to PrEP uptake, involvement in clinical care, and adherence [76–82], YSGMMSM who met the eligibility criteria for the primary study may have experienced fewer barriers to PrEP related care and therefore be less likely to experience a cluster of syndemic conditions.

Consistent with other studies outside of syndemics research on YSGMMSM utilizing multilevel modeling, we found that roughly a quarter of P3 participants lived in high-disadvantage neighborhoods. Further, we found that the sample of neighborhoods in which P3 participants resided had a higher average neighborhood disadvantage score compared to the broader US [34, 41]. As described in Ward et al. (2019) [73], differences in exposure levels among groups is a key feature of disparity, even when an exposure has the same magnitude of effect on an outcome. For example, even if neighborhood disadvantage affects all people similarly, if YSGMMSM are experiencing neighborhood disadvantage at a significantly higher prevalence, then a disparity still exists. However, while the high prevalence of participants in high-disadvantage neighborhoods and the statistically high mean neighborhood disadvantage score are compelling evidence of disparity, given that the present study is a secondary analysis of an RCT, further research is needed to quantify if and to what extent YSGMMSM experience neighborhood disadvantage at a significantly higher rate than other identity groups.

To our knowledge this is the first study to link direct measures of neighborhood disadvantage to clustering of syndemic conditions in YSGMMSM through multilevel models. This aligns with previous place-based research which has linked neighborhood disadvantage to standalone syndemic health conditions, such as depression or anxiety [83–87]. Further, research utilizing syndemic models with YSGMMSM has largely examined contextual factors through individual-level characteristics which represent social marginalization (e.g., homelessness) and do not include other contextual factors such as neighborhood characteristics [20–31]. For example, a syndemic study of 618 Black YSGMMSM with an average age of 23 years found that participants who either did not have enough money for rent, food, or utilities in the past six months or were homeless in the last 12 months were roughly three times more likely to have depression [26]. While social factors are central to the formation of syndemic disease clustering, the present study simultaneously aligns with the place-based research and research using syndemic models to suggest that other contextual factors such as neighborhood, policy, and institutional factors should be considered as well in the formation of syndemic disease clustering. Further, this demonstrates that multilevel modeling is a suitable statistical approach to modeling contextual factors that contribute to syndemic condition clustering.

We found that measures of neighborhood disadvantage and individual clustering of syndemic conditions were independently associated with higher rates of PrEP non-adherence among YSGMMSM from the P3 RCT sample. This aligns with past work which has linked neighborhood disparity to HIV vulnerability, notably ART adherence [34–41]. For example, a previous study of 1,891 adolescents and young adults living with HIV using a ZCTA-level composite score comprised of several American Community Survey measures also included in the SVI (e.g., percent unemployed, percent in poverty), found that for each additional point on this score the likelihood of current ART use decreased by 15% [40]. Similarly, syndemic studies of YSGMMSM have found that co-occuring syndemic conditions are related to a lower likelihood of ART adherence [32, 33]. While the results of the present study cannot be extended directly to ART adherence in YSGMMSM, this work complements the parallel lines of research into syndemics and ART adherence by focusing on YSGMMSM without HIV and PrEP. Building on the present study, future research into syndemics and HIV vulnerability (PrEP or ART adherence) may consider longitudinally examining relationships between clusters of syndemic characteristics (contextual, social, and individual) and HIV vulnerability.

We found that neighborhood disadvantage did not moderate the relationship between clustering of syndemic health conditions and PrEP non-adherence among YSGMMSM in the P3 sample. However, participants who were doubly exposed to neighborhood disadvantage and a cluster of syndemic health conditions were the most likely to be PrEP non-adherent. Further, the Ward-style plots visually demonstrate how syndemic condition clustering is roughly twice as prevalent in high-disadvantage neighborhoods than in low-disadvantage neighborhoods among eligible participants in this secondary analysis. Consistent with these findings, The Moving to Opportunity study demonstrated the long-term effects of moving from high to low-disadvantage neighborhoods on health outcomes, with particular effects on mental health [88–93]. For example, one analysis of the Moving to Opportunity study found that participants who moved from high to low-disadvantage neighborhoods were significantly

more likely to report an absence of mental health problems including depression, anxiety, and sleep issues. While the portfolio of Moving to Opportunity studies do not explicitly test for syndemic interaction between neighborhood and individual level characteristics, the observed change in mental health outcomes evidences the claim that neighborhood context may influence the development of individual health outcomes, including health and social conditions commonly included as syndemic conditions (e.g., depression). Overall, the mixed findings from the present study combined with the overall paucity of literature describing syndemic interaction between neighborhood and individual level characteristics suggests that future research is warranted.

Strengths and Limitations

There are several tradeoffs to consider due to the design of the present study as a secondary analysis of RCT data. The primary RCT design produces several strengths: clear temporality is established between exposure(s) and PrEP non-adherence, strict inclusion and exclusion criteria handle several sources of confounding (e.g., small age range, relatively high digital literacy, generally non-rural, same sexual orientation), and biological PrEP adherence measures. Further, the SVI used to measure neighborhood disadvantage is a validated scale [50] and the individual syndemic condition scale is based on several previous syndemic studies of HIV vulnerability in YSGMMSM [20–29]. This collection of primary RCT design attributes with a small but homogenous sample and validated secondary measures produce a strong foundation to model the relationships between neighborhood disadvantage, individual syndemic conditions, and PrEP non-adherence utilizing multilevel models.

However, there are several tradeoffs to consider. Firstly, the primary RCT had a degree of missingness (31%) in the biological measures of adherence due to study operation changes related to COVID-19 restrictions. Prior to the COVID-19 restrictions, participants completed study activities in-person at study sites, including collection of biologic specimens used to measure PrEP non-adherence by study site staff. Once COVID-19 restrictions were instantiated, many activities were completed remotely to enable the continuation of data collection. Participants were asked to complete at-home DBS collection. The change from site directed biologic specimen collection to DBS self-collection likely impacted the missingness observed in the biologic PrEP non-adherence measure. However, we found that the proportion of missingness in the biologic PrEP non-adherence measure was equivalent in both high- and low-disadvantage neighborhoods among participants eligible for the present secondary analysis. Given that neighborhood disadvantage was the moderator of interest for the present secondary analysis combined with overall evidence for the accuracy of self-report PrEP adherence measures, especially as young adults age, and the AUC of 0.79 examining self-report accuracy among those with biological PrEP non-adherence data at 3-month follow up, we believe this missingness largely does not bias the results.

Secondly, the set of individual syndemic conditions used in the present study could have been more comphrensive. Several previous studies included measures of intimate partner violence, and history of sexual assasult [23, 25–29]. Unfortuantely, measures of intimate partner violence and sexual assault were not collected in the primary RCT measures. Further, there are limitations to utilizing BIPOC racial identity as a proxy for experience racism. Implicitly this measure is not parimsimonous, as we cannot disentangle race-specific experiences of racism and how those might have differential effects on PrEP non-adherence. Further, while a direct self-report survey measures of experienced racism may be more appropriate, self-reported racial identity is still a minimally viable measure of racism, espicially with respect to HIV vulnerability. Race in the context of HIV vulnerability is a social construct (as opposed to a biological construct) which reflects power dynamics, stigma, and a history of oppression [59–62]. Therefore, while some BIPOC P3 participants may not have had direct experiences racism to report, many likely have encountered racism with respect to their HIV vulnerability.

Finally, while the small and relatively homogenous sample may be a strength with respect to confounding, it was a limitation in terms of power to detect effect moderation. Therefore, the present study cannot statistically substantiate nor refute claims on the effect modifying role of neighborhood disadvantage in the relationship between individual syndemic conditions and PrEP non-adherence. It would be beneficial to re-test this hypothesis utilizing a study design with a significantly larger sample size, such as a prospective cohort study.

Conclusion

The present study quantifies how neighborhood disadvantage is independently related to clustering of individual syndemic conditions among YSGMMSM participating in the P3 RCT. Further we characterized how neighborhood disadvantage and syndemic health conditions are associated with PrEP non-adherence among YSGMMSM. Finally, we described how neighborhood disadvantage is related to disparities in exposure to syndemic conditions. These findings provide a first step in exploring how contextual factors such as neighborhood disadvantage construct the circumstances through which syndemic condition clustering emerges.

Future work in this area should consider re-testing the same or similar hypothesis with different research designs which afford significantly higher sample sizes and geographic diversity across longer timespans (e.g., prospective cohort). Future work could also consider disentangling the effects of neighborhood disadvantage and syndemic condition clustering with respect to HIV vulnerability or examining these relationships longitudinally. For example, it is unclear whether neighborhood disadvantage and syndemic condition clustering are two independent forces related to HIV vulnerability in YSGMMSM or if neighborhood disadvantage prospectively leads to syndemic condition clustering which then leads to HIV vulnerability (i.e. mediation).

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