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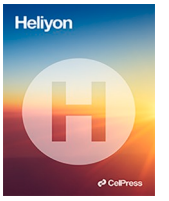

Research article

Recommendations for empirical syndemics analyses: A stepwise methodological guide

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ABSTRACT

Syndemic theory posits that co-occurring diseases interact in a manner that increases disease transmission, progression, and negative health outcomes. And that adverse socioeconomic and environmental conditions promote this disease or health condition clustering and interaction. The concept offers two important contributions to the health sciences. First, it positions socioeconomic, structural, and environmental conditions as central to disease burdens. Second, as a portmanteau – 'syn' for synergy and 'demic' for disease epidemics – syndemic theory indicates that in some cases diseases do not merely co-occur but synergistically interact to affect an outcome that is more than the accumulation of the individual disease effects. The difficulty in operationalizing these central elements has resulted in a divergence of scholarship from the centralizing principles of the theory towards a simpler accumulation perspective in which more conditions equate to worse health outcomes. In addition, all empirical syndemic assessments should include robust qualitative assessments of the dynamics, however, much syndemic scholarship focuses only on quantitative analyses. To address these issues, a five-step approach to quantitative analyses of syndemic arrangements is proposed: (1) identifying disease clusters within a defined population; (2) determining the relevant social and structural factors that support disease clustering; (3) determining if clusters are distinct by social/demographic groups within the population; (4) evaluating if the identified disease cluster contributes to worse health outcomes; and (5) assessing for synergy between clustering diseases. This stepwise strategy ensures not only a rigorous assessment of hypothesized syndemic interactions but also presents a closer alignment of scholarship with syndemics theory. As an illustration, the approach is applied to an assessment of a hypothesized HIV/cardiovascular disease syndemic in South Africa. While syndemics theory has proven valuable in guiding public health interventions and policy, progressive improvement must be made in the application of the theory to ensure that it continues to effectively inform comprehensive practice.

1. Introduction

Social determinants of disease [1] and co-occurring diseases [2] have informed our understanding of the complexity of disease burdens. Uniting these established theories, syndemic theory hypothesizes a more complex dynamic of disease interaction as a consequence of harmful social conditions. First emerging in the mid-1990s, syndemic theory explained the observed clustering of

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substance ab/use, violence, and HIV/AIDS (termed a SAVA syndemic) in inner-city populations in Hartford, CT [3–5]. Through ethnographic examination, anthropologist Merrill Singer proposed that unique social conditions including poverty, discrimination, and social marginalization generated the conditions to support disease clusters. And that clustering diseases interacted to not only increase the likelihood of the existence of the other but also worsen disease progression [3]. For example, the chemical effects of some illicit drugs can lead to aggression and violent behaviors [6]; drugs of abuse enhance the rate of viral replication [7]; violent sexual behavior is associated with an increased risk of HIV infection [8]; and the trauma of violence can promote illicit drug use [9].

Measuring these effects has proven elusive. Stall et al. (2003) presented the first approach to measure a syndemic arrangement employing an accumulation or "sum score" approach in their assessment of the effect of psychosocial comorbidities on HIV prevalence and risk among urban men who have sex with men in the United States. Multivariate regression analysis indicated that prevalence rates of HIV infection increased with greater numbers of health comorbidities. In this approach, the demonstrated effects focused on disease concentration, with a higher number of disease/health conditions worsening the HIV risk outcomes, not on disease interactions [10] or the social conditions supporting disease clusters. The simplicity of the disease concentration approach has contributed to its utility as both a model of syndemic analysis and the definition of syndemics. Recent reviews of syndemics literature [11–14], conclude that this approach currently dominates syndemics studies. As noted by Tsai [15], "While the theory of syndemics has become an increasingly popular heuristic for advocacy … most empirical studies purporting to validate the theory actually do no such thing. … rather than broadening the concept of a syndemic, the field needs to significantly sharpen the theory's empirical predictions so that investigators can have specific, falsifiable hypotheses to test using actual data. There is a danger that the haphazardly expanding concept of a syndemic will generate predictions so diffuse that the theory is rendered useless."

Given the analytical ambiguities present in syndemics scholarship, this paper presents a recommended approach to testing the existence of a syndemic arrangement. The proposed approach addresses the questions raised by syndemics theory: (1) are diseases clustering in a defined population?; (2) are adverse health outcomes a consequence of disease interactions?; and (3) what social, structural, and environmental factors are contributing to this clustering of disease?

1.1. The challenges of measuring a syndemic

Operationalizing the interaction of complex, multi-level phenomena presents a variety of challenges for researchers. First, syndemics scholars have argued that syndemics are not universal, but rather unique to a social, structural, and environmental context. This suggests that while there may be high rates of co-occurring diseases in a broader population, not everyone in the population is at equal risk. COVID-19, for example, was presented by Lancet editor, Richard Horton [16] as a syndemic not a pandemic given its interaction with other diseases such as diabetes. However, not everyone globally shares these disease burdens [17]. For example, in the United States, African Americans and Indigenous Americans are at highest risk for COVID-19 morbidity and mortality as a consequence of pre-existing health conditions and social, structural, and environmental factors that increase exposure to COVID-19 and lessen access to preventive and treatment services [18]. As such, the first challenge in measuring a syndemic is identifying disease clusters within specific populations. Even in an age of big data, such as electronic medical records or phone applications tracking personal behaviors, data does not universally exist to measure demographics, and social, structural, and environmental contexts that distinguish one population or community from another.

Determining what (and how) social, structural, and environmental factors are contributing to adverse disease interactions presents another challenge. Anthropologists draw on ethnography and existing literature to present an argument for how the unique arrangement of structures supports the clustering of diseases within specific communities. Examining diabetes in different populations, Mendenhall has drawn on extensive qualitative work (life histories) to detail out different disease and social arrangements in Chicago, United States; Soweto, South Africa; Mumbai, India; and Nairobi, Kenya [19]. Furthermore, communities cannot always be defined by one shared attribute, such as race or ethnicity. There are other related (or distinct) individual, interpersonal, community, and structural determinants to consider such as sexual identity, income level, distance to healthcare facilities, density of population, and reliance on public transportation. Formative qualitative assessments can inform what elements are likely influencing the disease cluster, but accounting for the multiple intersecting social elements, with varying levels of influence still proves difficult in a quantitative analysis.

Disciplines also account for social determinants differently. Anthropologists[1] regard race as a social construct, malleable and distinct relative to space and time [20]. In medical research, while it is "widely accepted that race is an indistinct construct that is not always measured accurately and standardized," serving as a poor surrogate of social constructs and biology [21], there are examples for which race has become part of the norm of accepted medical knowledge and practice including both therapeutics [22] and clinical tools for diagnosis and prognosis [23]. In traditional epidemiology, race is regarded as a demographic determinant, a factor that cannot be manipulated through intervention. A systematic review of articles published in *Epidemiology* and *American Journal of Epidemiology* between 2020 and 2021 found that of the 34 % of articles that used race data in analyses, race was most often used as a confounder (52 %) and descriptive variable (12 %), with fewer than a quarter presenting effect measure modification along with a discussion of disparities and mechanisms [24]. Given these disciplinary disparities, the second challenge in measuring a syndemic is determining how to include these interacting social determinants in an analysis of a syndemic arrangement. Are they factors in the syndemic arrangement or rather the structures that generate the context in which diseases cluster? Should we seek to identify unique syndemic

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arrangements based on demographic social variables? For example, could the COVID-19-related syndemics that affect African Americans be distinct from those that affect Indigenous Americans, not because the diseases that cluster are distinct, but the social drivers of disease clusters are different?

Defining the type of interactions between observed health conditions, as serial or mutually causal, co-existent, or synergistic is the third challenge in analyzing syndemic arrangements. Ethnographic and qualitative syndemics studies draw on observations, interviews, personal histories, and existing literature to establish an argument for biological and social interactions. As noted in the example of the SAVA syndemic, chemical changes in the body due to substance use affect immune responses, biological trauma from sexual violence damages the body's physical defensive barriers to disease, and the psychological trauma of violence promotes substance use as a coping/healing/self-medicating strategy, all of which are supported by a context of economic, social, and political marginalization. While the mechanisms of interaction can be explained, the quantified interaction of social and biological factors on a single adverse health outcome is not measured to determine synergy – an adverse outcome that is greater than the sum of two independent events. Finally, identified adverse health outcomes often used in syndemics scholarship are categorical (e.g., HIV risk, HIV status), rather than continuous variables (e.g., CD4 count, depression scale measures) that would offer greater sensitivity if the effect of A and B together is greater than the sum effect of disease A and B independently.

1.2. Current empirical approaches in syndemics literature

Beyond the highly popular "sum score" approach, path analysis [25–28] and structural equation modeling [29–32], have both been increasingly proposed or applied to measure syndemic relationships. Boateng et al. applied structural equation modeling to assess the impact of interactions between experiences of the health conditions of food and water insecurity, and HIV disease, on depression scores (the outcome) among Kenyan women [33]. In this study, experiences of food and water insecurity are defined as diseases or health conditions, consistent with syndemics theory, with the authors illustrating how these co-occurring health conditions/diseases influence the course and consequences of the disease of depression. Depression scale scores were regressed on the multiplicative interaction between food insecurity and water insecurity, and food insecurity, water insecurity, and HIV status. The three-way multiplicative interaction resulted in a 2 % increase in depression scores as compared to women with food and water insecurity in which the variables were not considered interacting.

Several epidemiologists have argued that biological interaction should be assessed on an additive scale rather than a multiplicative scale [34]. Interaction on an additive scale means that the combined effect of two exposures is larger than the sum of the individual effects of the two exposures, rather than the product of the individual effects, and is more consistent with syndemics theory. Applying an assessment of interaction on an additive scale, Hatcher et al. calculated the excess risk of HIV-related behaviors due to the additive interaction of intimate partner violence, gender inequitable views, and problem alcohol use among peri-urban heterosexual men in South Africa by calculating the proportion attributable to interaction (AP) [35]. The joint effect of gender inequitable views and problem alcohol use was associated with increased odds of risky sex (attributable proportion AP = 0.60, 95%CI 0.21–0.98). Socio-demographics of age, education, and relationship status were controlled for.

Utilizing a risk-difference approach, Diderichsen and Andersen [36] examined the syndemics of diabetes and depression in Brazil. Risk difference (or attributable risk) was calculated by subtracting the cumulative incidence of disability (measured as self-reported limited daily activities) in the unexposed group from the cumulative incidence in the exposed group. Interactions between two exposures (in this case joint diabetes and depression) were estimated as the difference in disease prevalence between those exposed to both compared to those exposed to none, minus the sum of the effects of single exposures. This study interpreted syndemics theory as the clustering and interaction between two or more diseases, with disease clusters generated by shared upstream individual or contextual causes which generate a differential exposure to the specific causes, and disease interaction influencing the course and consequences of another disease. The results indicated that in both men and women, the joint effect of both diabetes and depression on disability is higher than the sum of the two individual effects.

Increasingly in syndemics literature that relies on large datasets, latent class analysis (LCA) is used to identify disease or health condition clusters, then the use of multivariate/nomial analysis to determine if membership within a specific disease cluster is associated with an adverse health outcome. LCA is a statistical procedure used to identify qualitatively different subgroups, latent groups, or classes within populations that share certain outward characteristics [37]. It is a special case of person-centered mixture modeling that identifies latent subpopulations within a sample based on patterns of responses to observed variables [38]. The assumption underlying LCA is that membership in unobserved classes can cause or explain patterns of scores across survey questions, assessment indicators, or scales [38,39]. This approach presents theoretical advantages over the "sum score" approach, factor analysis, and cluster analyses.

The "sum score" approach, which has been widely used in syndemics research, adds the number of risk factors to which a participant has been exposed. The existence or measure of the adverse health outcome of individuals with one risk factor is compared with individuals with two, three, or more. This approach weighs risk factors equally and considers them interchangeable [40]. In addition, the "sum score" approach overlooks the possibility that there are a variety of ways an individual could achieve a set sum score, as such it ignores that salient and recurring combinations of indicators or syndemic factors exist with meaningful and unique associations with risk [41].

Latent factor modeling has been used to consider the relationship between syndemic factors (diseases or health conditions) and adverse health outcomes, but much like the "sum score" approach it also weighs factors equally and considers them interchangeable [41,42]. While statistically meaningful results have been presented in studies applying this approach, the approach is not consistent with syndemic theory. Latent factor modeling also fails to test for mutual causality or interaction among components or pathways

central to syndemic theory [40].

Cluster analysis and LCA are similar in many ways. They are both considered person-oriented approaches, using patterns of scores across cases to identify individuals who can be grouped together. In comparison, variable-centered approaches look for relationships among variables. In both, a series of solutions (or models) are generated, each with one more class than the previous one, with researchers determining the best solution based on statistical and theoretical criteria. However, LCA and cluster analysis make different assumptions about the data and use different statistical procedures [43]. LCA assumes that latent classes exist and explain patterns of observed scores across cases, whereas cluster analysis assumes that the cases with the most similar scores across the variables belong in the same cluster. In cluster analysis, variable means are used to define "nearness" of cases, therefore variables should be continuous. In LCA, analysis variables are categorical, with cross-tabulations used as the input information. In LCA, the probabilities of class membership are obtained, which in turn allows statistical inference when determining the most appropriate number of classes for a population [44], not clear-cut class assignments as occurs in cluster analysis. Both procedures generate categorical classification class variables for use in other analyses.

Several recent systematic reviews have been conducted to summarize the LCA literature [45–47], revealing that reporting practices vary widely. Its application to syndemics theory is equally diverse. Of the 24 publications listed on PubMed that use LCA to explore syndemic relationships, the items in a class are either all diseases or health conditions, all social determinants, or a combination of both [40,48–54]. This varies relative to perceptions of the determinants of the health outcome of interest and interpretations of syndemic theory. For example, in their assessment of experiences of cisgender and transgender female sex workers living with HIV in the Dominican Republic, Maclin et al. use LCA to assess the effects of typologies of emotional, physical, and police-based violence [55] and typologies of interpersonal, community, and institutional assets [56] on mental health, substance use and HIV continuum of care outcomes. Violence and asset-based class memberships differentially impacted health outcomes.

As all of these studies indicate, there is significant inconsistency in the application of syndemic theory. Boateng et al. [33] utilize experiences with health conditions rather than clearly defined diseases and Hatcher et al. [35] assess the interactions of behaviors rather than diseases on a behavioral rather than disease outcome. Neither clearly assesses biological-biological interactions as outlined in syndemics theory. The studies that use LCA analyses to determine classes of shared experience (be it diseases, exposures, biomarkers, or causes of disease), similarly fail to clearly articulate disease-disease clustering and interactions. None of the 24 studies using LCA to identify classes of syndemic determinants tested the nature of the interaction between these factors to determine synergy as opposed to comorbidity. All syndemics studies, particularly those that draw on large datasets, must be cautious in selecting for patterns of disease clustering that are based on theories of etiology and clinical epidemiology rather than statistical technology to ensure relevance for clinical and public health practice.

2. Method

The example dataset. The empirical data set used for illustration was the South Africa Demographic and Health Survey (DHS) 2016. The sample population included 8514 females and 3618 males aged 15–59. HIV testing was conducted on a random sample of selected households, with 6591 individuals tested. Among these, 34 participants had undetermined HIV test results and a further 242 had missing data and were removed from the dataset. The final sample consisted of 6315 individuals. All data were weighted (using a provided HIV weight) to be representative of the national population. Complete details of fieldwork procedures, questionnaire content, survey methodology, and laboratory testing procedures are available at https://dhsprogram.com/methodology/survey/survey-display-390.cfm.

The DHS is a large data set thus it serves as a useful tool to illustrate the recommended approach. However, there is only limited inclusion of critical factors in the HIV/CVD syndemic. The South Africa 2016 DHS does not offer robust biometrics such as viral loads, CD4 counts, and cholesterol levels. In addition, reported risk behaviors are limited in number and do not include physical activity levels. The DHS is cross-sectional, offering no indication of the timing of events. As such, the analysis presented here serves only as an illustration of an analytical approach, it does not offer conclusions on a syndemic of HIV/CVD in South Africa.

HIV/CVD interactions. It has been observed that people living with HIV are at higher risk of CVD and hypothesized that this may be due to synergistic disease interactions, supported by local social and structural conditions that allow diseases to cluster.

Emergent biological risk factors include obesity, antiretroviral drug (ARV) toxicity, substance use, and other disease comorbidities. Common components of ARVs can elevate serum lipids by over 25 % and increase truncal fat [57–60], accelerating progression toward cardiovascular events [61]. Several substances with known CVD risks including tobacco and alcohol are used more often in people living with HIV (PLWH), as noted in prior studies using syndemic models [62–66]. Disease comorbidities including tuberculosis (TB) and diabetes, observed to cluster in PLWH, may heighten CVD risk [67,68]. HIV disease itself is responsible for persistent immune activation, inflammation, and immune system dysfunction which influence the onset and subsequent progression of hypertension (HTN), subclinical atherosclerosis, and other cardiovascular events like heart failure.

The mechanism of action of key social and structural factors impacting CVD risk in PLWH is less well understood and likely specific to context and community [69]. In the general population, lower socioeconomic status is associated with CVD [70]. Recent studies indicate that neighborhood socioeconomic environments predict CVD outcomes [71–73]. For PLWH, these factors may contribute to disparities in healthcare access resulting in delayed CVD or HIV treatment and health outcome disparities [74], or contribute to diets that increase levels of obesity or HTN. Fig. 1 offers a theoretical model of an HIV/CVD syndemic considering specific social and structural mediators of risk in South Africa.

Guided by the syndemic framework the following four research questions are addressed.

(1) What diseases cluster together in this population?
(2) What social and structural factors support this clustering of diseases?
(3) Are these disease clusters distinct by demographic group?
(4) Do disease clusters contribute to worse health outcomes?
(5) Are these diseases adversely interacting?

Measures. To identify disease profiles, five indicator variables were included: HTN, HIV, high cholesterol, diabetes, and tuberculosis (TB). Adverse disease outcomes were measured by a 'severe cardiovascular disease' variable, which included individuals who reported either having a stroke or a heart attack. Consistent with scholarship exploring HIV disease comorbidities, known associated social determinants of health and risk behaviors are included: private health insurance, ever smoked, alcohol consumption in the past 12 months, routine diet including fried foods, fast foods, salty foods, and processed meats. Additional variables used in this illustrative example include age, gender, race/ethnicity, education level, literacy level, employment status, and household wealth status. SAS version 9.4 was used to conduct all analyses.

(1) *What diseases cluster together in this population?* In other words, is there a latent class structure that adequately represents the heterogeneity in disease status among members of the community? If so, what are the diseases and their corresponding prevalence?

To answer question 1, a latent class analysis (LCA) was implemented (SAS PROC LCA) to identify a set of discrete, mutually exclusive latent classes of individuals based on their disease status [75]. In the language of syndemic theory, LCA describes common combinations of observed diseases, which are related via unobserved experiences and patterns of concentration and interaction [41]. A one-class model was first considered, and then additional classes were added until a model with the best fit was identified. Model fit is determined based on a theoretical understanding of the associations between HIV comorbidities and the following statistical criteria: (a) the AIC, with lower AIC indicating better model fit; (b) the BIC, with lower BIC indicating better model fit; and (c) likelihood-ratio G^2 statistic. Weller, Bowen [43], Lanza, Collins [75], and Sinha, Calfee [44] provide detailed guidance and discussion on the standards being followed regarding LCA model fit parameters. Other fit statistics that were considered but not relied upon to determine a final class model included an entropy above 0.6. Entropy indicates how accurately the model defines classes. In general, an entropy value close to 1 is ideal [76], and above 0.6 is acceptable, although there is no agreed-upon cutoff criterion for entropy [77]. The interpretability of the model was also considered including distinguishing class features, the possibility of assigning a meaningful label to each class, and class size (no class with fewer than 50 cases and no class with less than 5 % of the sample).

(2) *What social and structural factors support this clustering of diseases?* In other words, are demographics or social determinants of disease predictive of latent class membership?

The maximum probability assignment rule was used to assign individuals to a latent class. Individuals were assigned to the latent class with the highest posterior probability of membership. Following Lanza, Collins [75] guidance on the use of PROC LCA, posterior probabilities were calculated as part of the program and individuals were automatically assigned to the best class [74]. The association of key sociodemographic and health-related indicators with latent class membership was examined using chi-square test statistics. All

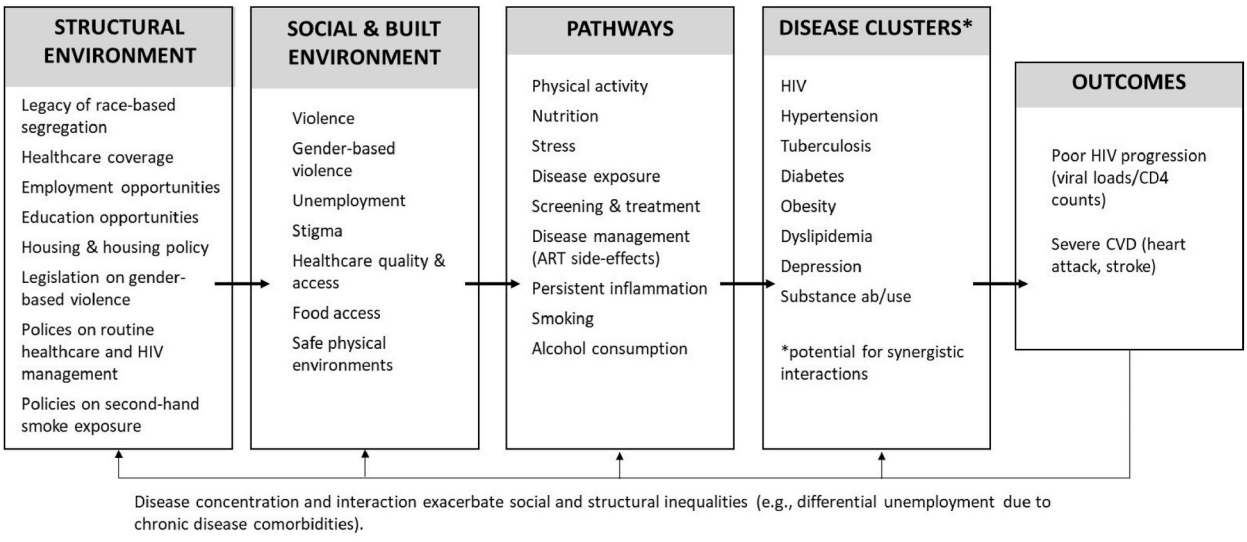

Fig. 1. A tentative syndemics model of HIV/CVD in South Africa.

demographics were collapsed into binaries for statistical power.

(3) *Are these disease clusters distinct by demographic group?* For example, do genders experience different latent class structures?

Once a baseline latent class model was selected, the impact of specific demographic grouping variables was assessed assuming that disease clusters may appear distinct by group. To test whether measurement is invariant across the demographic group (e.g., gender) the models were run with all parameters freely estimated and again with item-response probabilities constrained equal across groups. The G^2 statistics for each model were compared to determine if the models measured disease clusters the same by each demographic.

(4) *Do disease clusters contribute to worse health outcomes?* In other words, is there an association between classes and disease onset, progression, or severity?

Pairwise Wald test results were used to examine whether profiles of disease (class membership) were associated with adverse health outcomes. In this example, if individuals in latent class 1 had more severe CVD, measured as experiencing a stroke and/or heart attack, than individuals in latent class 2 or 3.

(5) *Are these diseases adversely interacting?* In other words, what is the relationship between the diseases that are observed to cluster? Are they interacting in a synergistic manner that would indicate that their combined effect is greater than the sum of their individual effects?

To assess the interaction between the diseases co-occurring in an identified disease cluster (or latent class) associated with an adverse health outcome, three surrogate measures of additive interaction based on the parameters of logistic regression have been proposed: the relative excess risk due to interaction (RERI) [78], the attributable proportion due to interaction (AP), and the synergy index (SI) [78,79]. RERI captures the additional, additive risk from the interaction between the two variables (Relative $Risk_{ALL}$ – Relative $Risk_{Synergy\ factor1}$ – Relative $Risk_{Synergy\ factor2}$ – Relative $Risk_{Synergy\ factor3}$ … +1). AP standardizes this value as a proportion of the combined effect ($RERI/OR_{ALL}$). SI is the ratio of the risk of the combined effect (Relative $Risk_{ALL}$-1) to the sum of the individual effects [(Relative $Risk_{Synergy\ factor1}$-1)+(Relative Risk $_{Synergy\ factor2}$-1) + …]. In each case, the additional risk presented by the combination of factors is assessed relative to the risk presented by each factor on its own. Lack of interaction is reflected by RERI, AP = 0 and SI = 1. In this paper RERI is calculated using the published SAS code for binary factors [80].

Table 1
Sample Characteristics of a weighted sample of DHS participants (aged 15–59 years), in South Africa, 2016 (N = 6315).

Sociodemographics	*n* (%)
Age (mean, SD)	39 (17.66)
Gender	
Female	3838 (60.65)
Male	2490 (39.35)
Race/Ethnicity	
Black	5373 (84.91)
Coloured	360 (5.69)
White	506 (7.99)
Asian/Indian	85 (1.35)
Highest level of Education (none/primary)	1509 (23.85)
Literacy (limited)	1442 (22.79)
Currently Unemployed	4110 (64.94)
Household Wealth Index (poor)	2482 (39.22)
Disease status	
HIV Status (positive)	1197 (19.05)
Hypertension	1201 (19.06)
Diabetes	272 (4.32)
High Cholesterol	236 (3.74)
Tuberculosis	316 (5.02)
Stroke	72 (1.13)
Heart Attack	220 (3.49)
Social determinants of health & CVD risk behaviors	
Private Health Insurance Coverage	972 (15.36)
Currently taking medication	1668 (26.35)
Ever smoked tobacco	5083 (80.32)
Consumed alcohol in past 12 months	455 (18.33)
Eat fried foods	5295 (83.66)
Eat fast foods	5523 (87.27)
Eat salty snacks	4882 (77.15)
Eat processed meats	4863 (76.84)

3. Results

Table 1 presents sample characteristics and responses to indicator variables. The mean age was 39 years (std dev = 17.66). As shown, 60.7 % of the population was female, 84.9 % Black, 64.9 % currently unemployed, and 39.2 % in the lowest measures of the household wealth index. Nineteen percent of the sample had a confirmed positive HIV test, 19.1 % reported an HTN diagnosis. An additional 5 % had a confirmed TB diagnosis, 4.3 % reported having diabetes, and 3.7 % indicated having a high cholesterol diagnosis. Only 3.5 % and 1.1 % had a severe CVD outcome of a heart attack or stroke, respectively, with 4.4 % reporting either a stroke or heart attack. Only 15.4 % of the sample had private health insurance coverage, the remainder receiving care through the public health system; 26.4 % were taking medications. The majority had smoked tobacco at some time (80.3 %), and routinely consumed a diet that included fried foods (83.7 %), fast foods (87.3 %), salty snacks (77.2 %), and processed meats (76.8 %).

3.1. Identify latent profiles of disease (Question 1)

LCA supported the existence of disease clusters. Table 2 presents LCA results for different class models with the AIC, BIC, class count sizes and percentages, and an acceptable entropy (above 0.6) suggesting a three-class model (bolded).

Fig. 2 shows a graphic representation of the three-class model (classes were described by the investigator as: *No Disease, HIV,* and *All Disease*). The x-axis lists the names of the diseases. The y-axis provides the average probability of class membership for each of the indicators; as the number approaches 1, the probability of class membership is higher. All indicators were coded with higher scores reflecting disease diagnosis (1 = no disease, 2 = disease, a condition of PROC LCA that requires sequential integer values from 1 to R); therefore, probabilities closer to 1 are indicative of disease. Most of the population (62.1 %) were in the *No Disease* class. Conversely, the *All Disease* class comprised only 12.9 % of the population, and 25 % of the population made up the *HIV* class. Note that 10 % of the designated *HIV* class had HTN, equivalent to the HTN in the *No Disease* class. The distinction between the classes is HIV status. The association between class membership and adverse health outcomes will be determined in Step 4.

3.2. Determining the impact of social and structural factors on class membership (Question 2)

As shown in Table 3, Black participants comprised the majority of both the *No Disease* (84.1 %) and the *HIV* (95.8 %) classes. Females comprised more than half of all the classes. Individuals under the age of 50 years comprised most of the *HIV* (83.3 %) and *No Diseases* (75.3 %) classes. The *HIV* class was characterized by individuals with low household wealth indices, the lowest levels of private health insurance, and lower than anticipated medication use (29.5 %). The majority of individuals in the *All Disease* class were currently using medication (82.0 %).

3.3. Assessing for group differences (Question 3)

Given these predictors of class membership, classes can differ by demographic group. For illustrative purposes only, an assessment of gender is shown here. Additional socio-demographic variables of concern should also be evaluated. The G^2 statistic was 35.22 (df = 29) for the freely estimated model and 86.43 (df = 44) for the constrained model, resulting in a likelihood-ratio difference test statistic of 51.21 (df = 15). This difference is not statistically significant, providing evidence that measurement invariance across gender holds.

Because measurement invariance held, gender differences in class membership probabilities (γ parameters) could be interpreted with confidence that the classes have the same meaning for males and females. Males and females were equally likely to belong to the *No Disease* class (13.2 % of males, 11.1 % of females). More females than males were likely to belong to the *All Disease* class (54.9 % of males, 68.7 % of females), and more males than females were likely to belong to the *HIV* class (34.0 % of males, 18.0 % of females). These results do not suggest that the social and structural determinants influencing class membership are not distinct by gender. As shown in Table 3, there are likely many distinct social and structural mediators on class membership, however, the classes remain constant relative to gender. In other words, among both males and females, there are the same three distinct classes.

3.4. Association between classes and severe disease outcomes (Question 4)

Table 4 shows the odds of severe CVD outcomes based on individual disease states. In this measure, individuals with one disease

Table 2
Model fit and diagnostic criteria for evaluating class solutions. Note: N = 6315 (weighted). Bold text indicates model met fit criteria. LL = log-likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; A-BIC = sample-size adjusted BIC; G^2 = likelihood-ratio G-squared statistic; CAIC = consistent Akaike information criterion; DF = Degrees of Freedom.

Model	LL	AIC	BIC	A-BIC	G^2	CAIC	DF	Smallest class count (n)	Smallest class size (%)	Entropy
1 class	−9490.37	1000.26	1034.02	1018.13	990.26	1039.02	26	6315	100	1
2 class	−9024.91	81.33	155.59	120.63	59.33	166.59	20	1010.4	16	0.71
3 class	−9005.83	**55.17**	**169.93**	115.81	21.04	186.81	14	820.95	13	**0.63**
4 class	−9002.34	60.19	215.46	142.37	14.19	238.46	8	252.6	4	0.54
5 class	−8997.42	62.36	258.13	164.84	3.23	287.13	2	252.6	4	0.54
6 class	−8997.35	74.22	310.49	199.11	4.06	345.49	−4	252.6	4	0.46

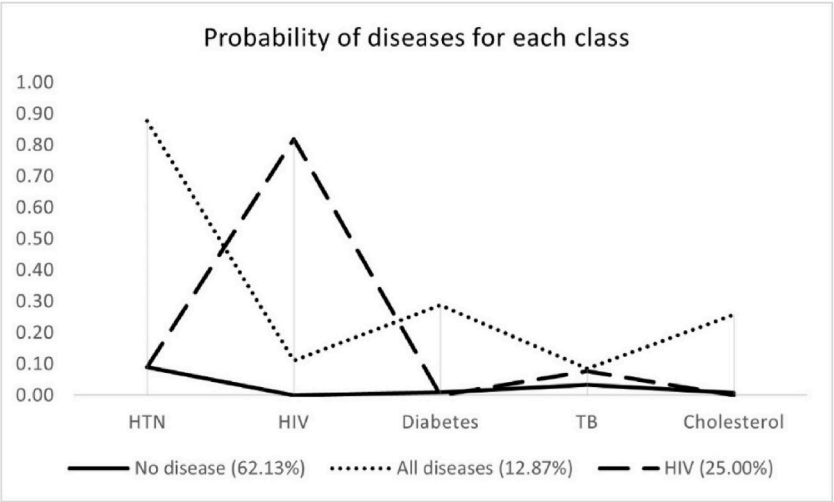

Fig. 2. Latent profiles of diseases. Note: $N = 6315$. Figure illustrates the characteristics of the three classes based on responses to the five disease indicators.

Table 3
The proportion (frequency) of each demographic, social determinant, or risk behavior comprising each latent class.

	No Disease	All Diseases	HIV	*p*
Race (Black)	84.01	64.78	95.76	<0.0001
Gender (Female)	60.39	67.06	59.46	0.0193
Age (<50 years)	75.26	19.61	83.35	<0.0001
Household Wealth Index (lowest quintiles)	39.21	21.87	45.45	<0.0001
Highest Level of Education (none/primary)	22.89	37.05	23.14	<0.0001
Literacy (limited)	21.85	29.49	24.28	0.0008
Currently unemployed	65.37	71.05	61.01	0.0006
Private Health Insurance	15.32	29.65	10.42	<0.0001
Current medication use	20.81	82.01	29.48	<0.0001
Routine fast-food consumption	87.56	82.34	87.81	0.008
Smoker	19.34	17.03	22.04	0.0442
Alcohol consumption in past 12 months	81.33	77.47	84.7	0.1043

could have multiple diseases, but they are assessed by one disease at a time. Individuals with HTN are 6.8 times more likely to experience severe CVD than someone without HTN (OR = 6.78, 95%CI 5.07–9.07). Individuals with diabetes, TB, and cholesterol are also more likely to experience a severe CVD outcome than individuals without those diseases. Individuals with HIV are not at higher risk for severe CVD outcomes (OR = 0.97, CI95 % 0.92–1.02).

Pairwise Wald tests assessed if having multiple diseases simultaneously (measured as class membership) may be differentially associated with the likelihood of severe disease outcomes (Table 5). As shown, the odds ratio for the *All Disease* class having severe CVD was 6.50 (or 650 % higher) compared with the *No Disease* class. The *HIV* class showed no statistically significant association with severe CVD outcomes.

3.5. Assessing synergy (Question 5)

The LCA indicates that diseases do cluster and that the clustering of diseases are predictive of severe disease outcomes. RERI calculations offer an indication of additive risk of having multiple health conditions simultaneously. As RERI is calculated from relative risk, only two diseases can be assessed simultaneously. Using weighted case-counts, Table 6 lists RERI calculations for all combinations

Table 4
Severe CVD outcomes (heart attack or stroke) by disease.

Disease	OR	[95 % CI]		*p*
HTN	6.78	[5.07 -	9.07]	<0.0001
HIV	0.97	[0.68 -	1.39]	0.8725
Diabetes	1.99	[1.37 -	2.89]	0.0003
TB	3.22	[2.15 -	4.82]	<0.0001
Cholesterol	3.40	[2.39 -	4.84]	<0.0001

Table 5
Severe CVD outcomes (heart attack or stroke) by class membership.

Latent class	OR	[95 % CI]		*P*
No Disease (reference)	–	–	–	
All Disease	6.469	[4.81 -	8.70]	<0.0001
HIV	0.981	[0.70 -	1.38]	0.9143

of two diseases with all other diseases added as covariates. Any RERI not equal to zero indicates additive interaction. HIV and HTN show an additive interaction (RERI >0), but given that the confidence interval spans zero, it is not statistically significant (RERI = −0.17, CI95 % −3.36-3.02). Although RERI gives the direction (positive, negative, or zero) of the additive interaction, we cannot in general use these estimates to make statements about the relative magnitude of the underlying additive interaction for risks [80]. However, stronger magnitude RERI has been presented as indicative of synergism or sufficient cause interaction [80], as indicated with HIV and TB, HTN and TB, high cholesterol, and diabetes, and TB and high cholesterol. These findings suggest that there are strong interactions between the diseases although not necessarily between HIV and HTN, indicating that HTN may have a moderating relationship. Given the self-reported nature of the dataset, these findings are not conclusive of an HIV/CVD syndemic, rather illustrative of the process of evidencing a syndemic.Van der Weele and Knol [80] offer a detailed tutorial on assessing interactions.

4. Discussion

The empirical approach presented here begins with a definition of syndemics that considers adverse disease interactions supported by social constructs. This definition is supported by two assumptions. First, diseases co-occur as a consequence of unique social arrangements. Second, the diseases interact to worsen specified health outcomes. Outcomes may be defined as the onset of a new disease or the worsening of an existing health condition. As indicated, not all syndemics literature has consistently assessed biological interactions in terms of disease-disease relationships, extending syndemics theory to include interactions of disease exposures, risk behaviors, biomarkers, and social conditions. Intersectionality theory indicates that there are relevant interactions among the social conditions that drive disease. Given that syndemic theory aims to present a holistic understanding of disease, it is important to include all clinical and public health practice relevant aspects in an analysis. However, inherent in a syndemic analysis is disease-disease interaction. Context and intention may predicate how “disease” is measured, as case-counts or prevalence, biomarkers, experiences, or behavioral risk predictors.

In this approach, step 1 identifies clustered disease arrangments using LCA to define disease classes. Step 2 assesses mediators of class membership to determine if specific social and structural factors support disease clustering. These analyses do not explain the dynamics present. Robust qualitative analyses are necessary to inform those associations, but the analysis does indicate what unique social conditions may support disease co-occurrence. It may also suggest that there are distinct syndemic arrangments (both disease classes and social contexts) by social groups that should be examined independently. Step 3 determines if class membership is unique by social group. This does not prove or disprove that there are unique syndemic arrangements by group, it only determines if there are unique disease classes by group. The social constructs supporting disease classes may vary by group and warrant further exploration. Step 4 determines the association between disease classes and adverse health outcomes. At this point, synergistic interactions of diseases have not yet been determined. The relationship to adverse health outcomes may be a consequence of co-occurrence alone. Step 5 evaluates if the relationship between clustering diseases is synergistic. Given that this is a cross-sectional analysis, serial causality cannot be assessed. As a final step, interactions between social environment variables and interacting diseases should be assessed to complete the syndemics model. This is not shown here as the aim of the paper was not to present a complete model of a syndemic (given the limitations of the dataset and the lack of qualitative data to guide additional analyses), but rather to present a tutorial on how to conduct a series of analyses consistent with syndemics theory. Completing this series of analyses ensures a thorough quantitative assessment of a syndemic. A robust syndemic analysis requires a mixed-methods approach to fully understand, operationalize, and interpret any measured syndemic arrangement.

There are two key limitations in this recommended approach to empirical assessments of syndemic arrangements. First, LCA may not be regarded as the most robust method to establish clustering. However, it aligns more closely with syndemic theory than other clustering analyses. If a large enough dataset is available and disease prevalence is high, individuals can be categorized into observed disease clusters using case-counts rather than the probability classes calculated by LCA. Second, as with any assessment of cross-sectional data, this approach can only begin to explore interactions and cannot ascertain causality.

5. Conclusion

While syndemics theory has proven valuable in guiding public health interventions and policy, progressive improvement must be made in the application of the theory to ensure that it continues to effectively inform comprehensive practice. This guide provides valuable information to researchers utilizing the syndemic framework. LCA analysis to identify disease classes, combined with Wald analyses to measure associations between classes and adverse health outcomes, and measures of interaction provide evidence of a syndemic arrangement. Further assessments of the impact of social, environmental, and structural factors on disease classes are supported by robust qualitative analyses of unique social contexts. Ensuring rigor in our assessments of syndemics will improve the applicability of results on public health interventions and policy.

Table 6
RERI (relative risk) calculations for all disease combinations, with other diseases included as covariates.

Disease combination	RERI	[95 % CI]	
HIV*HTN	−0.17	[-3.36 -	3.02]
HIV*TB	−2.24	[-4.58 -	0.10]
HIV*Cholesterol	−1.45	[-3.94 -	1.03]
HIV*Diabetes	0.15	[-1.87 -	2.17]
HTN*TB	2.50	[-6.20 -	11.21]
HTN*Cholesterol	12.80	[3.76 -	21.84]
HTN*Diabetes	3.57	[-2.32 -	9.46]
Diabetes*Cholesterol	−0.17	[-3.56 -	3.22]
Diabetes*TB	1.11	[-7.12 -	9.34]
TB*Cholesterol	9.66	[-3.57 -	22.89]

Data availability statement

All data used in this article are available via the Demographic and Health Surveys Program public repository at https://dhsprogram.com/methodology/survey/survey-display-390.cfm.

CRediT authorship contribution statement

Nicola Bulled: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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