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Syndemics and health disparities: a methodological note

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Abstract

In the theory of syndemics, diseases are hypothesized to co-occur in particular temporal or geographical contexts due to harmful social conditions (*disease concentration*) and to interact at the level of populations and individuals, with mutually enhancing deleterious consequences for HIV risk (*disease interaction*). Since its original elaboration more than 20 years ago, the epidemiological literature on syndemic problems has followed a questionable trajectory, stemming from the use of a specific type of regression model specification that conveys very little information about the theory of syndemics. In this essay we critically review the dominant approaches to modeling in the literature on syndemics; highlight the stringent assumptions implicit in these models; and describe some meaningful public health implications of the resulting analytical ambiguities. We conclude with specific recommendations for empirical work in this area moving forward.

Keywords

AIDS/HIV; social determinants

Introduction

In Singer's [1–3] theory of syndemics, diseases are hypothesized to co-occur in particular temporal or geographical contexts due to harmful social conditions (*disease concentration*) and to interact at the level of populations and individuals, with mutually enhancing deleterious consequences for HIV risk (*disease interaction*). This theory follows in the same vein as those deployed to explain the social patterning of co-occurring health risks among the marginalized and dispossessed [4] and the ways in which these historically ingrained forces exert conjoint influences on health [5,6]. Separately, the literature on multimorbidity [7,8] and dual diagnosis [9,10] have also highlighted the adverse health consequences of mutually enhancing and/or mutually causal psychosocial problems.

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Since its original elaboration more than 20 years ago, the epidemiological literature on syndemics can best be characterized as following a problematic trajectory. While psychosocial and structural problems commonly and undoubtedly do cluster among vulnerable populations [5,6], it remains unclear whether they co-occur independently, whether they co-occur and are mutually enhancing (i.e., interact with each other), or whether they co-occur and are mutually causal (i.e., cause each other). For this reason, in the remainder of this essay we use the term "syndemic problems" to refer specifically to co-occurring and mutually enhancing psychosocial and structural problems, while retaining the more cumbersome term "psychosocial and structural problems" to refer to settings in which these problems have not necessarily been shown to be mutually enhancing or mutually causal. Most studies that have been conducted with the expressed aim of generating empirical support for the theory of syndemics have not operationalized the concept of disease interaction in a way that actually supports the theory's predictions about mutually enhancing epidemics [11]. These findings are then frequently leveraged to argue that there is an evidence-based need for multi-component interventions that address multiple co-occurring psychosocial and structural problems in order to effectively address or prevent HIV-related health disparities [12].

The co-occurrence of psychosocial and structural problems, and the excess disease burden experienced by persons in vulnerable subgroups (e.g., homeless and marginally housed women [13–15]), requires our urgent attention. However, this objective would be most effectively undertaken if informed by an analytically clear approach. Therefore, the purpose of our essay is twofold: (a) to mathematically highlight the assumptions implicit in much of the empirical work on syndemics; and (b) to describe some meaningful public health implications of the resulting analytical ambiguities.

Modeling Interactions between Co-Occurring Psychosocial and Structural Problems

For the sake of illustration, we will consider a hypothetical study of homeless and marginally housed women, a vulnerable population in which violence, food insecurity, and mental illness frequently co-occur [13–15]. The extent to which these and other psychosocial and structural problems co-occur has typically been represented in the literature with the aid of Venn diagrams [13]; correlation matrices demonstrating nonzero, statistically significant values on the off-diagonals [16]; or similar matrices of unadjusted odds ratios [17]. Among the 40 studies included in the systematic review by Tsai & Burns [11], 27 (68%) demonstrated the co-occurrence of psychosocial and structural problems using one of these representations. Such analyses demonstrate that psychosocial and structural problems co-occur in at-risk populations -- thereby supporting one aspect of the theory of syndemics -- but do not necessarily implicate synergy or mutual causality.

We might fit the below linear regression model to the data:

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3 \quad (1)$$

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where Y represents a binary adverse HIV-related outcome such as HIV infection or HIV transmission risk behavior, X_1 represents violent victimization, X_2 represents food insecurity, and X_3 represents mental illness. Although the outcome is binary, the linear regression model is suitable for our purposes because: (a) the estimated regression coefficients are of primary interest and can be straightforwardly interpreted as marginal effects in a linear model [18,19]; (b) the predicted outcome probabilities are of secondary interest, so predicted probabilities lying outside of the [0,1] interval are not particularly troubling [18,19]; and (c) robust estimates of variance can be used to correct the standard errors for heteroskedasticity [20,21]. With the strong assumption of no observed confounding, which is commonly and implicitly invoked in this literature, this regression model estimates the causal relationship between the psychosocial and structural problems and HIV risk.

By definition, the covariates in Eq. (1) are said to have "additive" associations with the outcome. If b_1, b_2, and b_3 (i.e., the estimates of β_1, β_2, and β_3) are positive and statistically significant, then maximizing HIV risk reduction in this population would require addressing violence, food insecurity, and mental illness -- either through three separate interventions or through a single multi-component intervention. Because the effects of these co-occurring epidemics are simply additive, Eq. (1) does not implicate a syndemic: all three epidemics need not be addressed jointly in order to reduce HIV risk. Rather, one could (for example) implement a food security intervention with some reasonable expectation of achieving some degree of HIV risk reduction even if violence and mental illness continued unabated.

For many reasons, one might suspect that violence, food insecurity, and mental illness may serve as effect modifiers for each other. Evidence from a variety of contexts worldwide suggests, for example, that food insecurity is associated with HIV risk among women [22], but the estimated association between food insecurity and HIV risk could be even greater among women who are subjected to violence (which is itself independently associated with HIV risk [23,24]). A fully saturated linear regression model that captured the potential interactions between these psychosocial and structural problems could be represented as follows:

$$Y=\alpha+\beta_1X_1+\beta_2X_2+\beta_3X_3+\beta_4X_1X_2+\beta_5X_1X_3+\beta_6X_2X_3+\beta_7X_1X_2X_3 \quad (2)$$

If, for example, b_1, b_2, and b_4 are positive and statistically significant, then one could achieve some degree of HIV risk reduction by implementing a food security intervention in isolation, even if violence and mental illness continued unabated. However, an intervention to enhance food security would be predicted to have a greater preventive impact if bundled with an intervention to reduce violence than would otherwise be predicted by Eq. (1) where no synergistic effects are observed. Eq. (2) also makes it clear that if b_1, b_2, b_3, b_4, b_5, and b_6 are estimated to be close to zero, and b_7 is positive and statistically significant, then the syndemic of X_1, X_2, and X_3 *must* be jointly addressed in order to reduce HIV risk. That is, because the main effects are all null, public health interventions designed to eliminate the syndemic of X_1, X_2, and X_3 are perfect complements -- implying that no single intervention would be effective if implemented in isolation.

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These examples clearly demonstrate the potential utility of the saturated regression model in describing how psychosocial and structural problems potentially interact with each other to worsen HIV risk. The manner in which they interact (or not) has implications for the types of interventions needed to reduce HIV risk, and whether these interventions necessarily need to be bundled to maximize their effectiveness. Clearly the simple additivity of Eq. (1) does not obviate the need to address all three epidemics. Those interested in maximizing HIV risk reduction in this vulnerable population should still be motivated to address violence, food insecurity, and mental illness, whether or not they interact with each other.

Dominant Approaches to Modeling in the Literature on Syndemics

As summarized by Tsai & Burns [11], most studies in the syndemics literature have not subjected their data to the empirical test described in Eq. (2). Instead, in 31 of the 40 studies (78%) reviewed, the analysis was based on an ordinal variable created as follows:

$$X_4 = \sum_{i=1}^{3} X_i \quad (3)$$

Here, X_4 represents the total number i of psychosocial and structural problems experienced by each individual. Again following our illustration, a woman subjected to violent victimization and food insecurity, but not mental illness, would be assigned $X_4 = 2$. In many ways, this "sum score," or "count variable," resembles the comorbidity indices frequently used in health services research [25,26], but without the more sophisticated weighting procedures that typically accompany the development of such indices. The sum score is often included in regression models as a continuous variable (e.g., Mustanski et al. [27]):

$$Y = \alpha + \beta_8 X_4 \quad (4)$$

When b_8 is positive and statistically significant, the data are interpreted as demonstrating "interplay" (p.1269) between the psychosocial and structural problems [28].

Alternatively, the sum score has been specified as an ordered categorical variable (e.g., Mimiaga et al. [29]):

$$Y = \alpha + \beta_9 X_{4,n=1} + \beta_{10} X_{4,n=2} + \beta_{11} X_{4,n=3} \quad (5)$$

where $X_{4,n=i} = 1$ if $n = i$, and zero otherwise, denoting the presence of 1, 2, or 3 psychosocial and structural problems (with 0 problems serving as the reference category). By construction, $X_{4,n=1} + X_{4,n=2} + X_{4,n=3} = 1$. When b_9, b_{10}, and b_{11} are positive and statistically significant, and $b_{11} > b_{10} > b_9$, this pattern of estimates is also interpreted as evidence of "additive interplay" (p.941) between psychosocial and structural problems that magnifies vulnerability to HIV risk [30].

These interpretations of the sum score neglect several critical assumptions. Substituting for β_2 and β_3 in Eq. (1),

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$$Y=\beta_0+\beta_1X_1+\beta_1X_2+\beta_1X_3=\beta_0+\beta_1(X_1+X_2+X_3)=\alpha+\beta_1X_4 \quad (6)$$

it becomes apparent that b_8 does not provide evidence of synergy but rather simply encodes the assumptions that that $\beta_1 = \beta_2 = \beta_3$. However, these assumptions are unnecessary because they can be empirically proven (or disproven) using Eq. (1) to show that $b_1 = b_2 = b_3$. This is indeed the approach that some investigators have followed. For example, in the Adverse Childhood Experiences study, Anda et al. [31] first estimated Eq. (1) and then, *once it was empirically demonstrated that* b_1, b_2, *and* b_3 *were comparable*, created the sum score and estimated Eq. (4). The literature on early childhood adversities is rife with similar examples [32–37]. These studies often bear a striking resemblance to studies in the literature on syndemics: the co-occurrence of adverse childhood experiences is represented in matrix format, and the sum score is specified as a continuous variable in a regression model like Eq. (4) or as an ordered categorical variable in a regression model like Eq. (5). The methodological advantages and disadvantages of this approach have been comprehensively discussed [38]. A critical point of departure, however, is that while b_8 may provide important information about the effects of cumulative adversities, it does not provide information about synergistic interactions between these adversities. Stated simply, sum scores can help to demonstrate that being subjected to multiple psychosocial and structural problems is associated with adverse health outcomes -- not that they *interact* with each other to worsen health outcomes.

To provide a clearer illustration, consider a scenario in which a syndemic is known with certainty not to exist, i.e., the data are generated through the *additive* process of Eq. (1). Assuming, with no loss of generality, that all three psychosocial and structural problems are equally prevalent in the sample population, the expected value of Y for each value of the sum score is as follows:

$$\begin{array}{lll} X_4=0 & \text{implies} & Y \quad =b_0 \\ X_4=1 & \text{implies} & Y \quad =\frac{1}{3}[(b_0+b_1)+(b_0+b_2)+(b_0+b_3)] \\ & & \quad =b_0+\frac{1}{3}(b_1+b_2+b_3) \\ X_4=2 & \text{implies} & Y \quad =\frac{1}{3}[(b_0+b_1+b_2)+(b_0+b_1+b_3)+(b_0+b_2+b_3)] \\ & & \quad =b_0+\frac{2}{3}(b_1+b_2+b_3) \\ X_4=3 & \text{implies} & Y \quad =b_0+\frac{3}{3}(b_1+b_2+b_3) \end{array} \quad (7)$$

It is clear from Eq. (7) that Y is increasing in X_4. Thus, when b_1, b_2, and b_3 are positive, the estimated coefficient on the sum score covariate (b_8) in Eq. (4) will also be positive, as the implied effect on Y increases as each additional psychosocial and/or structural problem is added to the model. In the literature on syndemics, when b_8 in Eq. (4) is positive and statistically significant, the data are interpreted as demonstrating “interplay” (p.1269) between the psychosocial and structural problems [28]. But such an interpretation of the coefficient in our hypothetical example would be inconsistent with the data-generating process (which is known with certainty in this example to be additive). Therefore, if evidence in support of additivity is being sought, there is no mathematical reason to prefer Eqs. (4) or (5) over Eq. (1).

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It is worth noting that if b_9 and b_{10} are estimated to be close to zero and b_{11} is positive and statistically significant, then the results obtained using Eq. (5) are identical to those that would be obtained using Eq. (2) when b_1, b_2, b_3, b_4, b_5, and b_6 are estimated to be close to zero, and b_7 is positive and statistically significant. Given such a pattern of estimates from Eq. (5), the data imply that interventions designed to eliminate the syndemic of X_1, X_2, and X_3 are perfect complements and *must* be implemented jointly in order to reduce HIV risk. However, Eq. (5) still imposes a number of strong assumptions on several of the product terms in Eq. (2), namely that $\beta_4 = \beta_5 = \beta_6 = 0$. These assumptions could potentially be justified on the basis of prior theory, but we are unaware of any studies in the literature that have made such appeals to theory. Furthermore, in the event that other patterns of findings are obtained for b_9 and b_{10} (even assuming $\beta_4 = \beta_5 = \beta_6 = 0$), it is unclear whether the sum score specification can provide evidence in support of the theory of syndemics [11].

To summarize, the sum score conveys very little information about the theory of syndemics: given a known data-generating process that *explicitly excludes* the possibility of interactions between the covariates, the estimated coefficient b_8 on the sum score in Eq. (4) can nonetheless be positive and statistically significant. More flexibly specifying the sum score as a categorical variable does not resolve this problem or other ambiguities.

The Public Health Case for Analytical Clarity

A close reading of Singer's [1–3] work yields an understanding in which Eq. (2) should be regarded as the preferred approach to empirical modeling in this literature: "At the population level, the term syndemic refers to two or more epidemics *interacting synergistically* and contributing as a result to excess disease load in a population... At the individual level, the term syndemic refers to the health consequences of the biological *interactions* that occur when two or more diseases or health conditions are co-present in multiple individuals within a population" [3] (pp.39–40, emphases added). Moreover, his own work specifically excludes the sum score specification as an adequate test of his theory. For example, in reporting data on disease counts among persons who inject drugs, Singer & Clair [39] explicitly noted, "While the data *do not enable an assessment of disease interaction*, collecting biological and health data that would allow such an assessment with this population seems warranted" (p.433, emphasis added).

The sum score approach to modeling, which currently dominates the literature [11], does not generate estimates with clear programmatic implications for public health policy to address syndemics. The public health implications of these ambiguities are threefold. First, while it is clear that independently co-occurring epidemics of psychosocial and structural problems would present an occasion for public health concern, it is empirically much less clear *how much more* concern is warranted for truly syndemic problems. Again following our illustration above, researchers and program implementers would agree that an epidemic of violence among homeless and marginally housed women is undesirable [40], and that an independently co-occurring epidemic of food insecurity in the same population is undesirable [41]. But if violence and food insecurity co-occur and are mutually enhancing, how much *more* undesirable (in terms of their impact on HIV-related outcomes) is such a syndemic compared to a scenario in which these epidemics of violence and food insecurity

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co-occur independently of each other? The answer to this question remains unanswered by Eqs. (4) and (5).

Second, if syndemic problems actually do interact in ways that synergistically elevate HIV risk, but Eqs. (4) and (5) continue to dominate the literature, then the field is missing critical opportunities to identify these synergies and support the development of appropriately targeted interventions. For example, if Eq. (2) suggests that intimate partner violence and food insecurity interact synergistically to magnify HIV acquisition risk among homeless and marginally housed women, then an intervention to enhance food security would be predicted to have a greater impact on reducing HIV risk if bundled with an intervention to reduce violence than would otherwise be predicted in a model where no synergistic effects were observed. But this finding also implies that a food security intervention administered in isolation would have a greater impact on reducing HIV risk if provided to women experiencing intimate partner violence compared with a food security intervention provided to women not experiencing violence. In the setting of scarce resources, food security interventions might be preferentially deployed in order to maximize HIV prevention efforts. Such investigations are particularly warranted when budgetary considerations may preclude larger interventions but still allow for effective interventions targeting specific domains or specific populations. Recommendations of this nature, however, are rarely issued in the syndemics literature, perhaps owing to the empirical ambiguities described above.

Third, although estimates from Eqs. (4) and (5) are typically interpreted as supporting calls for multi-component interventions that address multiple co-occurring psychosocial and structural problems [12], it is not immediately apparent that an intervention ought to *simultaneously* target each of the co-occurring psychosocial and structural problems (classically described as the “treatment package strategy” [42]). The optimal strategy should depend on their causal structure. For example, an alternative strategy might be to target the problems *sequentially*, particularly if improvement in one domain increases the probability of response to an unrelated intervention targeting another domain [43,44]. Another possible strategy would be to target one problem with the expectation of observing collateral intervention effects in other *untreated* domains of health or wellbeing (e.g., treating depression to improve HIV treatment adherence and reduce stigma [45,46]). A third option would be to adopt the fractional factorial design approach, in which inactive components are screened out of a multi-component intervention so that a costly, full factorial randomized controlled trial can be avoided [47–50]. Doing so may result in an intervention that leaves some aspects of the syndemic unaddressed, but that may be an acceptable price to pay for the ability to gain some traction on the other aspects of the syndemic (especially if observational studies have not conclusively demonstrated that the different intervention components are indeed perfect complements). While the literature on multiple health behavior change interventions has explored these and other types of configurations in the context of primary care and preventive cardiology [51–53], the findings and lessons learned from this body of work are rarely invoked (see Wim et al. [54] for a recent example) by investigators seeking feasible entry points to effectively address syndemics in vulnerable populations.

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Addressing Concerns about Sample Size

As noted by Stall et al. [55], small sample sizes may preclude full elucidation of all of the interaction effects in Eq. (2), potentially resulting in wide confidence intervals for the parameters of interest. The issue of statistical imprecision is exacerbated by potential collinearity between the psychosocial and structural problems of interest (which is likely to occur given the very hypothesis motivating research on syndemics, i.e., that these problems frequently co-occur) [11]. The public health implications of this type II error are not insubstantial. Interaction terms that are not statistically significant may leave investigators unable to precisely identify syndemics that truly exist. Investigators may also falsely conclude that a syndemic consists of the co-occurrence and synergistic interaction of fewer epidemics than is actually the case. While concerns about type II error are valid, they may be overstated. Tsai & Burns [11] showed that nearly half of the studies included in their review would have permitted fully saturated regression models given the sample sizes and conventional rules of thumb.

Despite these reassurances, concerns about statistical power may remain. Researchers limited by statistical power may be able to mitigate these concerns in several ways. First, Eq. (2) can be fitted subject to linear equality restrictions, which would reduce the number of parameters to be estimated [56,57]. As is apparent in the equations above, these linear restrictions simply encode the assumptions that already predominate in the syndemics literature but which should be formally motivated on the basis of conceptual considerations or previously published empirical work. For example, researchers investigating a candidate pool of six psychosocial and structural problems may restrict the coefficients on some of the two-, three-, four-, and five-way product terms to be equal to zero. To promote transparency, the hypotheses motivating these linear restrictions can be prospectively registered in prespecified analysis plans [58–60] and/or the data and statistical code uploaded to an online archive [61,62].

Second, researchers can group some of the variables into broader clusters (e.g., mental health, socioeconomic, etc) [32,63], especially for variables whose correlation approaches unity [64]. This maneuver can reduce the number of parameters to be estimated in Eq. (2).

Third, even if valid concerns persist about statistical power to reject the null hypothesis for any specific regression coefficient, researchers could still estimate Eq. (2) while employing joint significance tests to determine whether some of the product terms are collectively important. Demonstrating the joint statistical significance of a series of two- or three-way product terms could provide concrete evidence to motivate the need for studies with larger sample sizes.

Fourth, researchers who still seek to estimate Eq. (5) on the basis of concerns about statistical power should use statistical tests for nested models to test for differences in explanatory power between Eq. (2) and Eq. (5). For example, in the setting of regression models fitted using the method of maximum likelihood, researchers could estimate Eq. (2) and Eq. (5) and then perform a likelihood ratio test of the null hypothesis that the parameter vector satisfies the constraints implied in the decision to estimate Eq. (5). Failure to reject

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the null could support the use of the more restricted specification. However, rejection of the null would speak to important differences in the lower-order product terms that are obfuscated in Eq. (5), and researchers would still be provided with valuable information about the true underlying structure of the model.

Recommendations

Our recommendations for empirical research on syndemics can be summarized as follows:

1. If the primary analytic objective is to show that psychosocial and structural problems are additively associated with HIV risk, then Eq. (1) should be used.
2. If the primary analytic objective is to understand the health and mental health impacts of cumulative adversities, then Eq. (4) can be used, but the comparability of the individual adversities should first be empirically demonstrated using Eq. (1) to justify the use of Eq. (4).
3. If the primary analytic objective is to provide evidence of disease interaction, then Eq. (2) should be used, because it is the only specification that fully and flexibly conveys important information about how syndemic problems interact to worsen HIV risk.
4. Eq. (4) cannot convey meaningful information about interactive effects and should be abandoned entirely in the literature on syndemics.
5. Eq. (5) may, under certain conditions, provide more information than Eq. (4), but the strong assumptions required of the data suggest Eq. (2) is still to be preferred.

We hope these recommendations, if followed, will maximize study resources toward understanding how syndemics adversely affect HIV risk in vulnerable populations and how interventions can best be deployed to mitigate these risks [65].

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