Mapping the current knowledge in syndemic research applied to Men who have Sex with Men : a Scoping Review

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# Abstract

# Introduction

# Methodology

# Results

This section summarizes the findings relevant to our aforementioned research questions. [Table 1](#RefTabQuant), [Table 2](#RefTabQual) and [Table 3](#RefTabRev) in our supplementary material, summarize every reference identified and the variables extracted to answer our research questions for quantitative studies, qualitative studies and reviews, respectively.

## Literature search

The electronic search identified 769 references and our handsearch of reference lists resulted in the addition of the seminal study by Stall and colleague [Stall et al.](#ref-Stall2003) ([2003](#ref-Stall2003)) . After removing duplicates, 277 records were screened for inclusion.

After screening the title and abstract, 109 records were excluded. The two main reasons for exclusion at this stage were that MSM was not the main study population (n=46) and that syndemic was not the main focus of the paper (n=34). 29 studies were excluded because the type of publication did not meet our inclusion criteria.

The full texts of the 168 remaining references were obtained and read; 59 were excluded after this phase. During the previous step, we had decided to tentatively include papers in which the sample was not entirely comprised of MSM. After reviewing the full paper, we decided to exclude studies if the MSM data was aggregated with data from another population (n=9), most commonly transgender women. The rationale for this decision was to keep the focus clearly on MSM.

The PRISMA flowchart generated by DistillerSR can be found in Figure [1](#PRISMA)

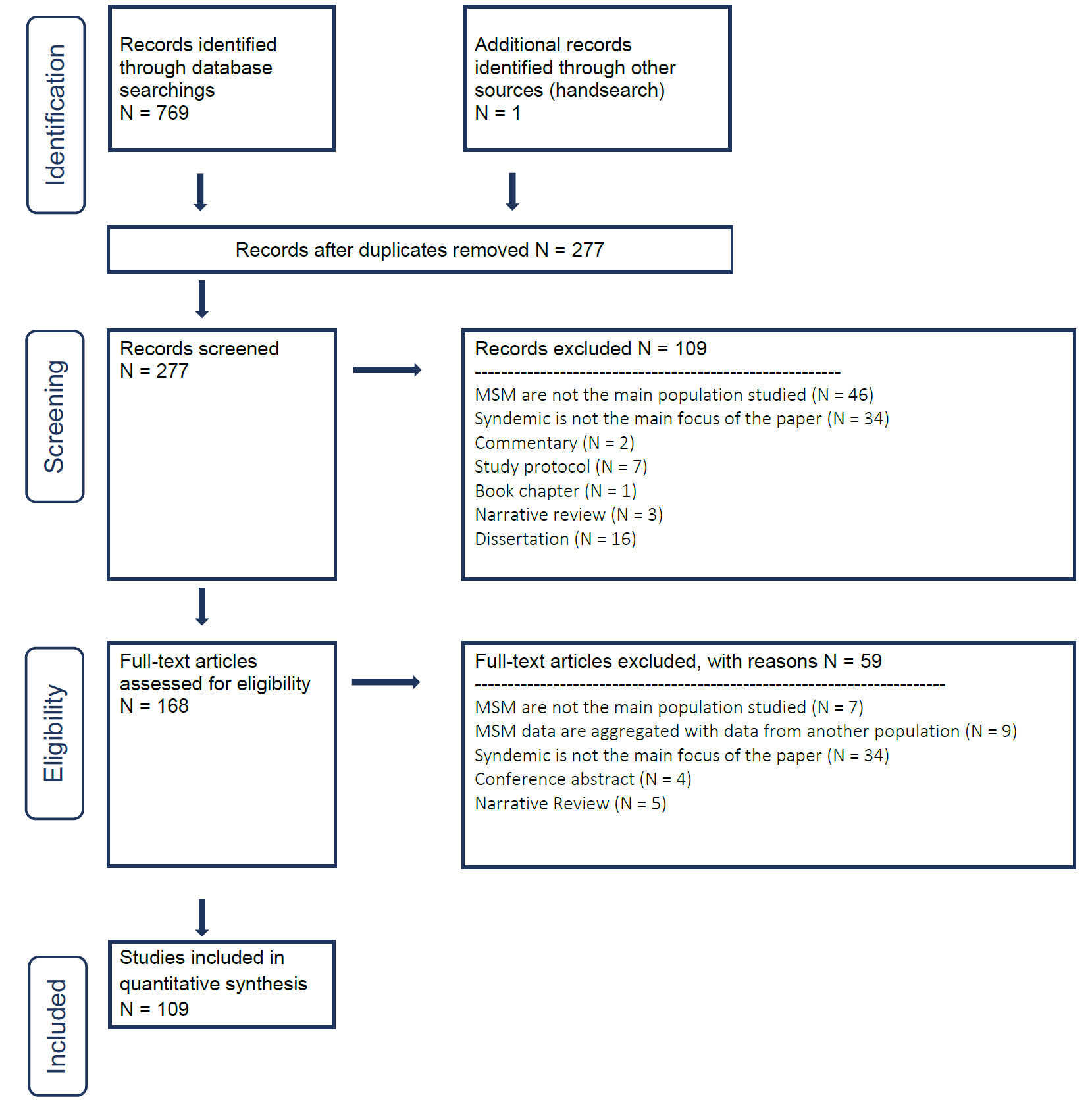


Figure 1: PRISMA flowchart of the search strategy

## How are studies concerning Syndemic Theory applied to MSM conducted?

### General characteristics of included studies

The publication date of the studies ranges from 2003 to 2021 with a marked increase in the number papers published annually from 2013 onward as illustrated in Figure [2](#PlotYear). There is also an increase in the diversity of the studies, both in the study design used and the continents where the studies were conducted.

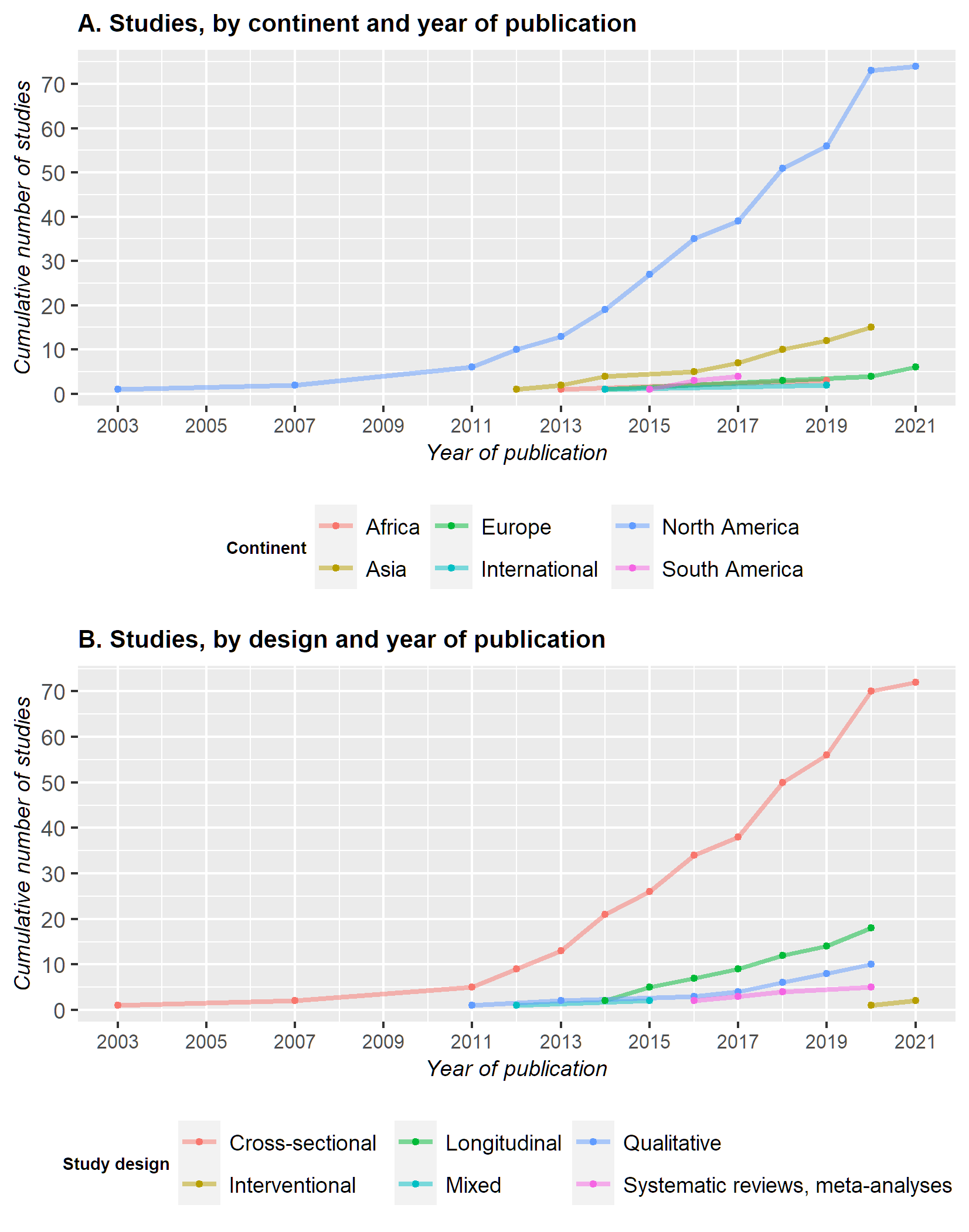


Figure 2: Plot of the cumulative number of studies published yearly

However, despite the increasing diversity, the vast majority of the studies were conducted in North America (N = 74), with a large predominance of studies in the United States of America (N= 62). The majority of the remaining studies were then located in Asia (N = 15) or in Europe (N = 6). South America (N = 4) and Africa (N = 3)were the least represented continents.

In terms of design, a similar pattern appears, with most of the studies employing a cross-sectional design (N = 72). The number of longitudinal studies has grown steadily since 2014 and represents 17% of the papers. The duration of longitudinal studies ranged from 6 to 78 months.

Compared to quantitative studies, qualitative studies are under-represented, with only 10 papers. In terms of analysis method, the most common was thematic (content) analysis (N= 5). The rest of the studies consisted in framework analysis (N = 2), grounded theory (N = 1), analytic induction (N = 1) and constant comparative analysis (N = 1).

We only identified 2 papers employing mixed methods design ([Buttram and Kurtz, 2015](#ref-buttram2015); [Halkitis et al., 2012](#ref-Halkitis2012)); Buttram et al. used a cross-sectional design for the quantitative part and in-depth interviews analyzed through grounded theory for the qualitative part while Halkitis et al used a cross-sectional quantitative survey and in-depth discovery interviews.

The first systematic reviews and meta-analyses were published, in 2016, while the first interventional studies were published in 2020.

Finally, the median sample size of the studies was 450 (range : 15 - 24 274) and the mean age of the participants, when reported, ranged from 16 to 58 years.

### Subpopulations studied

Fewer than half of the studies (N = 48 ) focused on a subpopulation of MSM, of those, we identified 7 types of MSM subpopulations : (a) young MSM ; (b) older MSM ; (c) MSM from a racial/ethnic minority ; (d) MSM living with HIV ; (e) MSM engaged in sex work ; (f) Men who have Sex with Men and Women (MSMW) ; and (g) transgender MSM.

Among studies focusing on a specific age group, 12 studies focus on young adults, 2 studies focus on older MSM([Halkitis et al., 2012](#ref-Halkitis2012); [Zepf et al., 2020](#ref-zepf2020)) and 1 study focuses on adolescents([Perry et al., 2019](#ref-Perry)). Of note, the two studies on older MSM are both entirely composed of a sample of older MSM living with HIV.

Black MSM (BMSM) are the most studied MSM from a racial/ethnic minority (N= 14) but studies focusing on them still represent only 13% of our sample. Among these studies, 2 studies are composed of young BMSM([Maiorana et al., 2020](#ref-Maiorana); [Reed and Miller, 2016](#ref-Reed2016)) and 1 study focuses on Black MSM engaged in sex work([Cristian J. Chandler et al., 2020c](#ref-chandler2020)).  
7 studies focus on Latino MSM (LMSM) and 1 of these studies focus on Latino MSMW([Muñoz-Laboy et al., 2018](#ref-Munoz-Laboy2018)). Furthermore, 1 study focus on both BMSM and LMSM([Cassels et al., 2020](#ref-cassels2020)).

Concerning the serologic status of MSM in syndemic literature, 13 studies are entirely comprised of a sample of MSM living with HIV. Apart from the studies mentioned above on older MSM living with HIV, 2 studies focus on young MSM living with HIV([Bruce et al., 2011](#ref-Bruce2011); [Lyons et al., 2013](#ref-Lyons2013)) . Notably, we didn’t identify any studies focusing on racial minority MSM living with HIV.

Finally, the least represented subpopulation of MSM in this review are MSMW (N = 2), MSM engaged in sex work (N = 2) and transgender MSM (N = 1). Strikingly, transgender MSM, in addition to being the focus of only one study ([Reisner et al., 2016](#ref-Reisner2016a)) are, by design, excluded from every other study whereas other MSM subpopulation are at least partially represented in most of the samples.

Figure [3](#PlotPop) gives a visual representation of MSM subpopulation’s representation in the studies included in this paper.

In order to obtain the most comprehensive knowledge of the representation of MSM subpopulations in syndemic literature, we also took into account studies that did not focus on any subpopulation in particular but who presented disaggregated data and analyses for one or more MSM subpopulations.  
8 studies presented such data : 1 for Black MSMW([Dyer et al., 2020](#ref-dyer2020)), 4 for MSMW([Branstrom and Pachankis, n.d.](#ref-branstrom); [Ferlatte et al., 2018b](#ref-ferlatte2018); [Friedman et al., 2014](#ref-friedman2014); [Mustanski et al., 2014](#ref-Mustanski2014)), 2 for MSM living with HIV([Kurtz et al., 2012](#ref-Kurtz2012); [Ng et al., 2020](#ref-ng2020)) and 1 for Latino and Black MSM([Mustanski et al., 2017](#ref-Mustanski2017)).

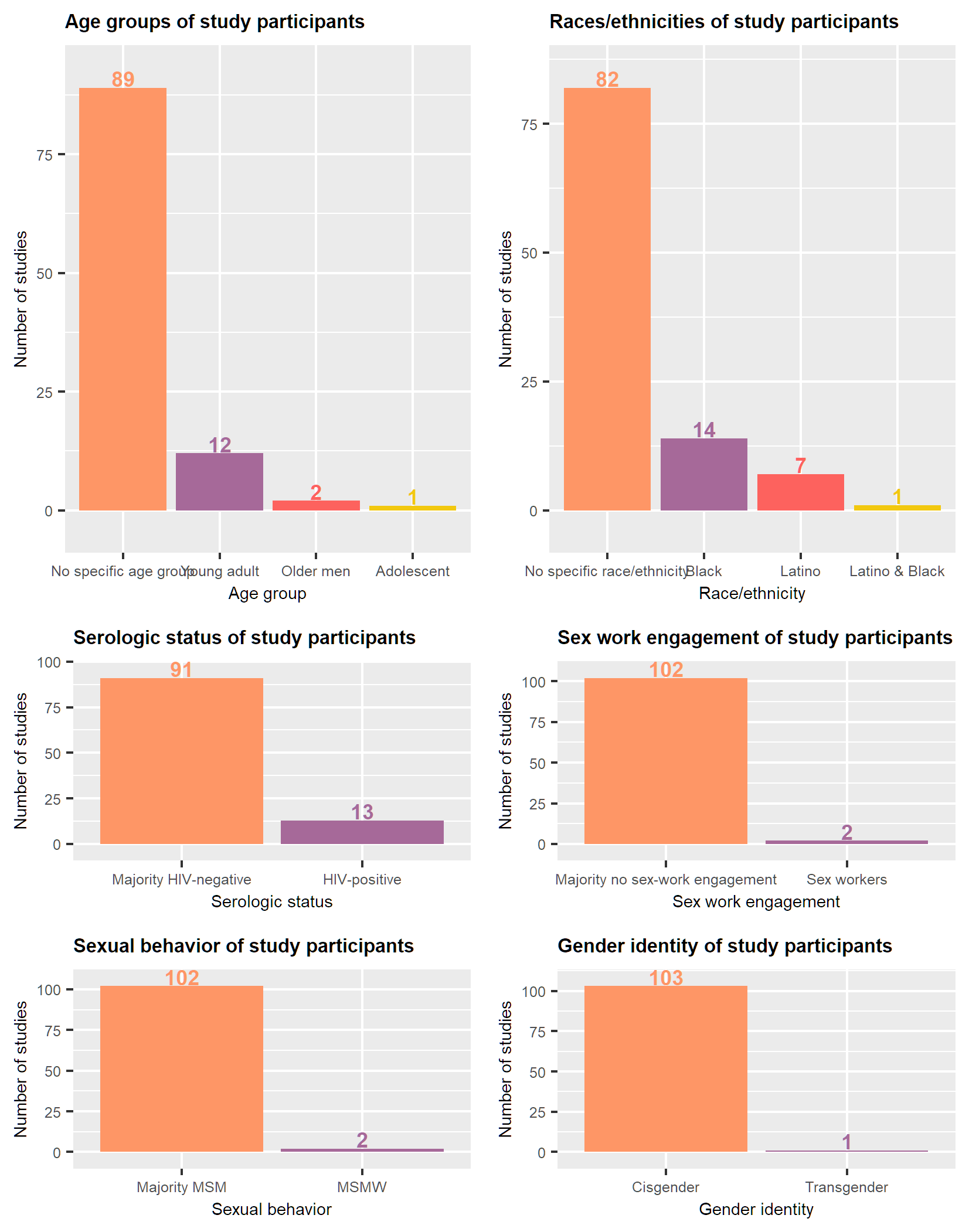


Figure 3: Number of studies focusing on a MSM subpopulation

### Syndemic conditions and their measurement

#### Number and type of syndemic conditions identified

We identified 46 different syndemic conditions in the 94 quantitative studies we included : depression or depressive symptoms (N = 76), intimate partner violence [IPV] (N = 45), substance use (N = 43), childhood sexual abuse [CSA] (N = 34), polysubstance use (N = 26) , binge drinking (N = 22), sexual compulsivity (N = 19), alcohol use disorder [AUD] (N = 18), suicidal thoughts and/or attempts (N = 16), sexual risk behaviors (N = 15), experiences of violence (N = 15), anxiety (N = 14), substance use disorder [SUD] (N = 13), alcohol use (N = 12), discrimination (N = 10), post-traumatic stress disorder [PTSD] (N = 34), chemsex (N = 7), loneliness (N = 6), incarceration (N = 5), unstable housing (N = 5), tobacco use (N = 5), general mental distress (N = 5), low social support (N = 4), low self-esteem (N = 4), internalised homophobia (N = 3), exchange sex (N = 3), sexually transmitted infections [STI] (N = 3), childhood abuse (N = 3), intravenous drug use [IDU] (N = 2), poverty (N = 2), unemployment (N = 2), poor healthcare access (N = 2), involuntary subordination (N = 2), HIV diagnosis (N = 2), hostility (N = 2), stress (N = 2), experience of trauma (N = 2), alexithymia (N = 1), attention deficit hyperactivity disorder [ADHD] (N = 1), cognitive escape (N = 1), frequenting gay social venues (N = 1), hypersexuality (N = 1), impulsivity (N = 1), poor physical health (N = 1), school bullying (N = 1), and sleep disturbance (N = 1).

We chose to distinguish between alcohol use disorder, binge drinking and alcohol use instead of merging them into a broad “alcohol-related syndemic condition.” Some authors also considered “heavy drinking” ([Martinez et al., 2020](#ref-martinez2020); [Martinez et al., 2016](#ref-Martinez2016a)) or “heavy alcohol use”([Mimiaga et al., 2015](#ref-Mimiaga2015b)) but we chose to aggregate these conditions under “binge drinking” for clarity. Similarly, we distinguish between substance use, substance use disorder, intravenous drug use, polysubstance use, marijuana use, tobacco use and chemsex since they differ in terms of potential harm and the context of use.

Despite the high number of syndemic conditions studied in the literature, the impact of the seminal study by Stall et al.([Stall et al., 2003](#ref-Stall2003)) is striking. The conditions studied in that paper (depression, IPV, CSA and polysubstance use) are among the five most studied conditions in the field. Furthermore, 91% of the quantitative studies included in our review consider at least one of the four conditions studied by Stall and colleagues as part of a syndemic.

#### Network analysis of the syndemic conditions

In order to better understand the connections between the syndemic conditions in the studies we elaborated a network plot (Figure [4](#SyndemicNetwork)). Nodes represent the syndemic conditions studied in the literature and edges (connectors) are drawn between two nodes when two conditions are studied in the same research paper. Furthermore, edges between nodes are thicker if the two conditions are frequently studied together. Furthermore, the outline of the nodes represent pie chart of their frequency in syndemic literature. For example, depression, the most studied condition, appears in 81% of our sample. As such, the node is circled by a chart representing this proportion. Moreover, as a force-directed graph, the location of the nodes gives an indication regarding their importance in terms of frequency and linkage to other conditions. As such, depression occupies a more central position than ADHD which was only studied once.

In this figure, we divided the conditions studied into 4 categories : mental health (e.g. depression, anxiety, PTSD) in blue, social conditions (e.g. substance use, loneliness) in teal, structural conditions (e.g. unemployment, healthcare access) in orange and physical health (e.g. STI, HIV) in red . The figure shows that structural syndemic conditions and physical health-related syndemic conditions are much less central, therefore much less studied, than social syndemic conditions and mental health-related syndemic conditions which are located towards the center of the figure.

Regarding the edges of the network, we identified 337 pairs of syndemic conditions. However, nearly half of these pairs of conditions (N = 157) appear in only one research paper. On the other hand , the most studied pairs of syndemic conditions were depression and IPV (N = 37), depression and substance use (N = (N = 33), depression and CSA (N = 29), depression and polysubstance use (N = 24) and IPV and CSA (N = 24).

In order to obtain a deeper understanding of the relation between the syndemic conditions, we also computed centrality indices for this network, namely degree centrality, the sum of weight in the network, closeness centrality, the inverse of the total length of the paths from a node to all other nodes, and betweenness, the number of shortest path passing through a node([Opsahl et al., 2010](#ref-opsahl2010)).  
Because the weight of the nodes in this network corresponds to the number of studies in which the syndemic conditions appear, degree centrality of each node is nearly perfectly correlated to the number of studies in which the syndemic condition was studied (r(44) = 0.99, p<0.01).  
Closeness centrality and betweenness centrality are also strongly correlated to the number of studies (r(44) = 0.8, p<0.01 and r(44) = 0.76, p<0.01 respectively). Interestingly, the betweenness centrality of unstable housing is notably high given the low number of studies focusing on this syndemic condition (N = 5). Betweenness centrality can be seen as the extent of brokerage a node can exert on a network ([Zweig, 2016](#ref-zweig2016)). Moreover in [4](#SyndemicNetwork) we see that the three structural syndemic conditions “unstable housing,” “incarceration” and “poverty” are grouped together, indicating that they are frequently studied together. In other words, in syndemic literature, unstable housing seems to act as a bridge between the two aforementioned structural syndemic conditions and the rest of the syndemic conditions. Indeed, unstable housing has been studied alongside 15 other syndemic conditions : depression, substance use, IPV, binge drinking, sexual compulsivity, IDU, CSA, polysubstance use, incarceration, poverty, unemployment, discrimination, poor healthcare access, alcohol use and violence.

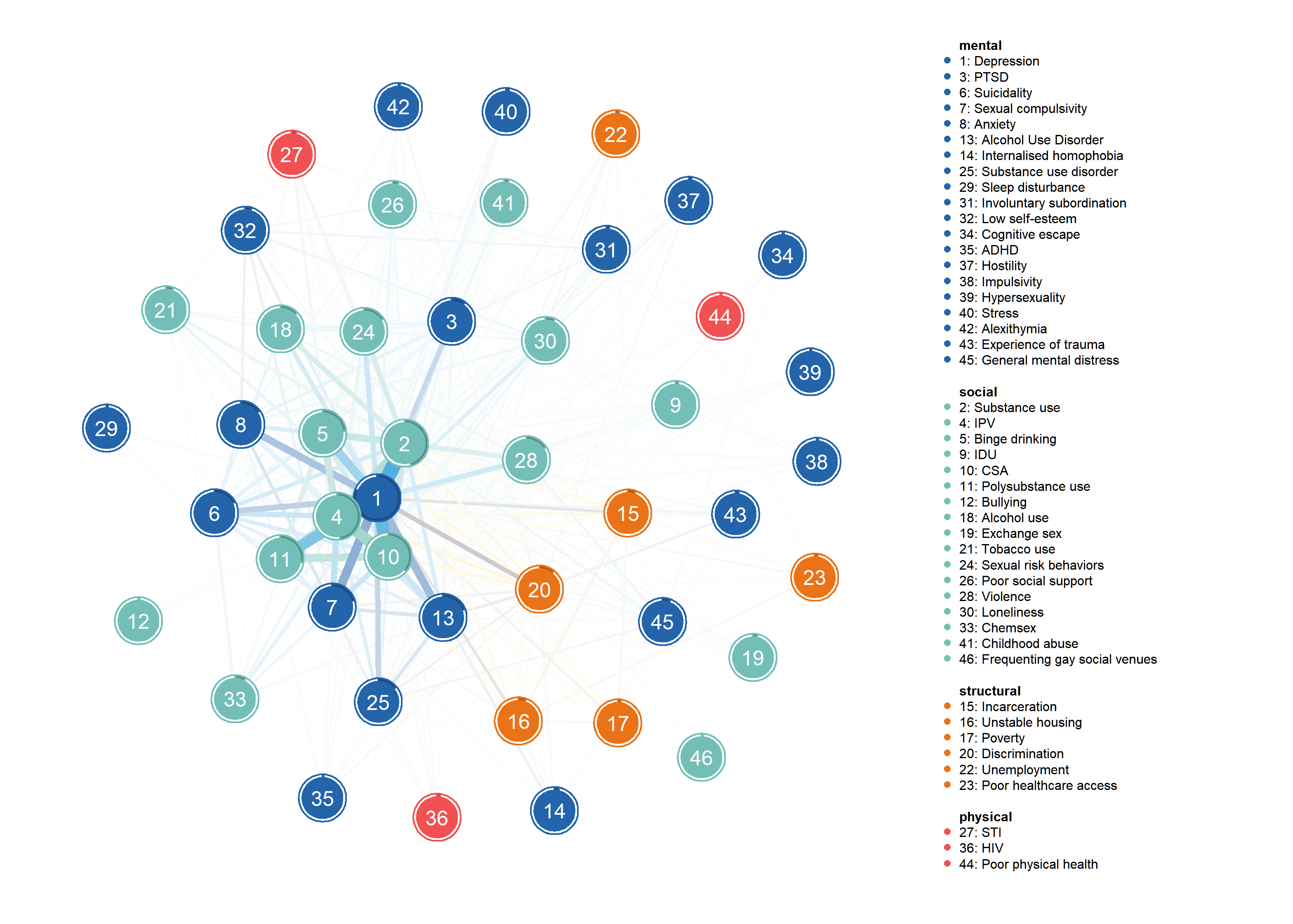


Figure 4: Network of the syndemic conditions studied in quantitative research. As a force-directed network, the most studied and interconnected conditions are the most central. Moreover, each node is circled by a pie chart of their frequency in the review. The thickness of the edges linking two nodes reflects the number of studies in which the two conditions were studied together.

#### Measurement of the syndemic conditions

The next part of our research question was to examine the way the syndemic conditions were studied in the literature. For the most often studied syndemic conditions, we found a high degree of variability in their measurement. Different authors used different scales or criteria and, even when the same scale or criteria was used, the cutoff or reference period differed among studies. For the sake of brevity, we will not provide a detailed description of the measurement method of the syndemic conditions studied in fewer than 10% of our sample. Detailed information about each of the papers included is presented in the supplementary material, part B ( [Table 4](#DepressionTab) to [Table 11](#AnxietyTab)).

For depression, 20 different scales or criteria were used among the 76 studies in which this condition was studied.  
66 studies used scales while 10 studies used criteria to assess the presence of depression or depressive symptoms among the participants. The most frequently used scales were the full Center for Epidemiologic Studies-Depression scale [CESD] (N = 24) and the 10-items version of this scale [CESD-10] (N=10), the 9-items version of the Patient Health Questionnaire [PHQ-9] (N=8) and the Beck Depression Inventory [BDI-II] (N = 5).  
Cutoff for these scales varied the most for the CESD (range : 16 to 27) and the PHQ-9 (range : 5 to 15).  
When a scale was not used, the most frequent criteria to assess the presence of depression was the participant being on medication for depression in the past 12 months (N = 4).

For IPV, 5 types of intimate partner violence were identified : physical violence (N = 36), sexual violence (N = 21), psychological violence (N = 23), gay-related violence (e.g. threats to reveal the partner’s sexual orientation ; N = 3) and HIV-related violence (e.g. threats to disclose the partner’s serologic status ; N = 1). Reference periods varied from past month to lifetime.  
Furthermore, 7 studies used a scale to assess the presence of IPV : the HITS scale (N = 3) the Revised Conflict Tactics Scale [CTS2] (N= 3) and a scale developed by the authors of the study, assessing physical and psychological violence([Yu et al., 2013](#ref-Yu2013)).

For substance use, we looked at the class of substances explicitly screened by the authors and the reference period used. The most frequently screened class of substance was stimulants (i.e. cocaine/crack, amphetamines ; N = 37), followed by depressants (i.e. GHB/GBL, benzodiazepines without prescriptions ; (N = 19), opioids (i.e. opioids misuse and ecstasy ; N = 19), marijuana (N = 17), ecstasy /MDMA (N = 17), hallucinogens (i.e. ketamine, psilocybine, phencyclidine ; N = 17), inhalants (nitrous oxyde, Popper ; N = 13) and new psychoactive substances (i.e. synthetic cannabinoids, cathinones ; N = 3).  
Reference period ranged from the past month to over the lifetime.

For CSA, we identified 13 different definitions and 3 scales among the 34 studies. The various definitions differed on the age at which the sexual intercourse occurred to be qualified as childhood sexual abuse, the age gap between the victim and the perpetrator and whether the sexual intercourse was unwanted. The most frequent definition was Finkelhor’s definition([Finkelhor, 1994](#ref-finkelhor1994)) : any sexual experience before 13 years old with someone at least 5 years older or any sexual experience between 13 and 17 years old with someone at least 10 years older (N = 7).

For polysubstance use, 17 studies considered that there was polysubstance use when 3 or more classes of substances were used while 9 studies defined polysubstance use as more than one class of substance being used. Furthermore, 4 studies excluded marijuana from the class of substances screened and 1 study excluded stimulants, because stimulants were already screened in another syndemic condition.

For binge drinking, we identified 6 different thresholds for binge drinking, differing on the number and frequency of binge drinking episodes. The threshold ranged from one episode in the past 12 months to more than one episode per week, every week in the past 12 months.

Measurement of sexual compulsivity was relatively standardized, compared to the rest of the syndemic conditions. Nearly every study used the Kalichman’s Sexual Compulsivity Scale, with cutoff ranging from 20 to 26, except for two studies using the Compulsive Sexual Behavior Inventory([Dyer et al., 2012](#ref-Dyer2012); [Herrick et al., 2013](#ref-Herrick2013)) and one study using a scale devised by the authors [Wang et al.](#ref-Wang2017) ([2017](#ref-Wang2017)).

For AUD, we identified 4 different definitions. 8 studies used the full Alcohol Use Disorder Identification Test (AUDIT-10), 4 studies used the 3-items version of this screening test (AUDIT-C), 5 studies used the CAGE questionnaire and one study used clinical diagnosis based on the DSM-IV criteria.

Regarding suicide, 6 studies considered only suicidal thoughts, 5 studies considered both suicidal thoughts and suicide attempts and 3 studies considered only suicide attempts. Furthermore, one study used the Positive and Negative Suicide Ideation scale (PANSI) and one study used the Suicide Behaviors Questionnaire-Revised (SBQ-R).

A number of behaviors have been used to define sexual risk behaviors as a syndemic condition. The most widely used of these criteria is condomless anal sex (N = 11), followed by the number of partners (N = 7). The condomless anal sex criteria has been refined in three studies, two of them taking into account the type of partner (regular versus casual) and one, the serologic status of both partners.  
Other criteria such as condomless oral sex, condomless vaginal sex, STI diagnosis, engagement in sex work and sexual intercourse with an HIV positive partner have been used. Finally, one study used the Kalichman’s Sexual Sensation Seeking Scale to assess the propensity of participants to engage in novel or risky sexual stimulation.

For violence 11 studies looked at sexual violence, 10, at physical violence and 5 at psychological violence. One Indian study also took into account sexual and physical harassment by the police.

Several types of anxiety disorder were studied : generalized anxiety disorder (N = 7), social phobia (N = 5) and panic disorder (N = 3). The type of anxiety disorder screened was not specified in 5 studies.  
8 different criteria were used to assess the presence of an anxiety disorder among the 14 studies considering anxiety as a syndemic condition. The most frequent criteria was a score equal or greater than 10 on the 7-items version of the Generalized Anxiety Disorder screening test (GAD-7 ; N = 4).

SUD was screened through a clinical diagnosis based on the DSM-IV, mention of substance abuse in the electronic medical record or the participant thinking he should reduce his substance use. Several screening test were also used : the Drug Use Disorder Identification Test (DUDIT), the Texas Christian University Drug Screen (TCUDS), the Mini International Neuropsychiatric Interview (MINI) and the 10-items Drug Abuse Screening Test (DAST-10).

Outside of binge drinking and alcohol use disorder, which represents two distinct syndemic conditions, we aggregated three aspects of alcohol use studied in syndemic literature to form a generic “alcohol use” syndemic condition : alcohol consumption, alcohol use until intoxication and early alcohol use.

Finally, for discrimination, there were as many criteria as there were research papers studying this condition. Most of the studies only considered discrimination based on sexual orientation, except for two studies examining racial discrimination, one study examining HIV-based discrimination and one study which did not distinguish between discrimination based on sexuality, race/ethnicity or any other factor.

### Outcomes and their measurement

We identified 20 different outcomes in our sample of quantitative studies. Sexual risk behaviors was the most frequently studied outcome, appearing in 57 research papers. The second most studied outcome was HIV diagnosis (N = 19), followed by STI diagnosis (N = 10), adherence to antiretroviral therapy (N = 6), pre-exposure prophylaxis (PrEP) use (N = 4), healthcare use (N = 4) and the syndemic conditions themselves (N = 4). Less often, researchers also used viral load (N = 3), suicidality (N = 3) or engaging in exchange sex (N = 2) as outcomes.

Every other outcome was only studied once : HIV screening([Cristian J. Chandler et al., 2020a](#ref-Chandler2019b)), physical activity([Zhang et al., 2019](#ref-Zhang2019)), hypothalamic-pituitary-adrenal (HPA) axis dysregulation([Carrico et al., 2018](#ref-carrico2018)), sexual violence([Semple et al., 2017](#ref-semple2017)), glycemic control([Byg et al., 2016](#ref-Byg2016)), engagement in HIV care([Biello et al., 2016](#ref-Biello2016)), engagement in chemsex([Friedman et al., 2014](#ref-friedman2014)), having sexual intercourse with both men and women([Eaton et al., 2013](#ref-eaton2013)) , help-seeking behaviors([Achterbergh et al., 2021](#ref-achterbergh2021)) and substance use([Turpin et al., 2020](#ref-turpin2020)).

There was a high degree of variability in the definition of what constitutes a sexual risk behaviors though the most frequently used proxy was, by far, condomless anal sex. Indeed, condomless anal sex was one of the criteria in 55 studies out of the 57 with sexual risk behaviors as an outcome. While 30 studies considered all form of condomless anal sex as a risk behavior, the other tried to refine the criteria. The most frequent of such refinement was to consider only serodiscordant condomless anal sex as a risk behavior (N = 16). Other options were to only consider condomless anal sex with casual partners (N = 4), condomless anal sex without PrEP or with a detectable viral load, if HIV-positive (N = 3), receptive condomless anal sex (N = 1) or condomless anal sex at first sexual intercourse with the current male partner (N = 1).

Used in conjunction with condomless anal sex, other proxies for sexual risk were number of partners (N = 11), substance use during sex (N = 2), condomless vaginal sex (N = 2), condomless oral sex (N = 1), sexual intercourse with female partners (N = 1) , engaging in group sex (N = 1) and non-disclosure of HIV serostatus before first sexual intercourse with current main partner (N = 1).

When HIV was used as an outcome, it was self-reported in nearly half of the studies (10 studies out of 19) Similarly, for STI diagnosis, self-reporting was used in 5 papers out of 10.

### Interventions

We identified only 2 interventional studies guided by syndemic theory ([Achterbergh et al., 2021](#ref-achterbergh2021); [Chakrapani et al., 2020](#ref-Chakrapani)). Chakrapani et al. used a pre-test/post-test non-equivalent group design and the intervention consisted of motivational-interviews. The goal of this intervention was to reduce condomless anal intercourse by enhancing condom self-efficacy and addressing co-occurring syndemic conditions.

Achterbergh et al. conducted a randomized controlled trial and the intervention consisted of tailored feedback and help-seeking advice on mental health screening. The primary endpoint was to increase help-seeking behaviors ; the secondary endpoints were reducing sexual risk behaviors and STI incidence.

The intervention lasted for 12 months in both studies.

In Chakrapani et al. the intervention was successful in reducing the psychosocial conditions investigated (depression, alcohol use and internalised homophobia) and improving condom use. Furthermore, synergy, as measured by interaction on the additive and multiplicative scales, was present for depression and alcohol use as well as for depression and internalised homophobia on inconsistent condom use. Finally, mediation analysis revealed that the improvement in consistent condom use was due to an improvement in condom self-efficacy caused by a reduction in alcohol use and internalised homophobia.

On the other hand, the RCT conducted by Achterbergh et al. failed to affect the primary endpoint nor the two secondary endpoints.

### Summary of reviews

We found 3 systematic reviews ([Lassiter and Parsons, 2016](#ref-Lassiter2016); [Lewis and Wilson, 2017](#ref-lewis2017); [Woodward et al., 2017](#ref-woodward2017)) and 2 meta-analysis ([Pantalone et al., 2020](#ref-Pantalone2020); [Rooney et al., 2018](#ref-Rooney2018a)) in our review.

Woodward et al. aimed to identify a set of resilience resources among MSM burdened with minority stress and psychosocial condition in order to improve HIV prevention ([Woodward et al., 2017](#ref-woodward2017)). They included 20 in their reviews and identified 31 resilience resources, with social support and incomes as the two most frequently cited. Of note, most of these resources were associated with a lower HIV risk.

Lassiter et al. aimed to propose a framework to include religion and spirituality into HIV research with MSM ([Lassiter and Parsons, 2016](#ref-Lassiter2016)). They found that religion and spirituality had mixed effect on syndemic conditions but could be more beneficial for MSM of color than for white MSM. Of note, they only included 9 studies as these two factors were very sparse in syndemic literature.

Lewis et al. sought to examine the HIV prevalence and associated risk behaviors among migrant and ethnic minority MSM in North America and Europe ([Lewis and Wilson, 2017](#ref-lewis2017)). They found high rates of HIV prevalence and associated risk factors and proposed that transnational migration could be part of a syndemic.

In their meta-analysis, Rooney et al. studied the syndemic conditions associated with sexual compulsivity among MSM and computed the mean effect size as well as whether this effect varied as a function of the type of syndemic conditions associated ([Rooney et al., 2018](#ref-Rooney2018a)). They included 36 papers and found that sexual compulsivity was significantly associated with 7 syndemic conditions (anxiety, depression, CSA, alcohol use, substance use, IPV and sexual risk behaviors). The two strongest associations were with depression and anxiety.

Finally, Pantalone et al. sought to have a better understanding of the state of interventions co-targeting interconnected syndemic conditions and HIV-related health behaviors of MSM ([Pantalone et al., 2020](#ref-Pantalone2020)). They included 43 studies and found a small significant positive effect of combined behavioral interventions to improve mental health, substance use, alcohol use and sexual risk behaviors, with significant heterogeneity. Interestingly, a greater number of sessions (at least 9) and individual rather than group interventions showed greater efficacy.

### Additional framework used in the studies

19 studies used an additional framework alongside syndemic theory. The most widely used was resilience theory (N = 10), followed by minority stress model (N = 5), intersectionality (N=2), social-cognitive theory (N=2) and salutogenesis (N=1).

## How is the concept of interaction explored in syndemic research applied to MSM?

### Statistics used to show an interaction

It should be stated that, when we speak of interaction between syndemic conditions we don’t necessarily mean “synergy,” though synergy is indeed one of the interaction we consider. Drawing from the works of authors such as Tsai and Chakrapani, we consider three types of interaction : synergistically interacting epidemics, serially causal epidemics and mutually causal epidemics ([Chakrapani et al., 2019b](#ref-Chakrapani2019); [Tsai, 2018](#ref-Tsai2018a)). As such, statistical methods such as mediation analysis, path analysis or structural equation modeling are also considered.

Our review revealed a high degree of variability in the statistic analyses. The most frequently used statistical method was to conduct regression analysis using a summation score of the syndemic conditions (N = 64). Among studies employing this method, 42 did not use any other method to determine the degree of interaction between syndemic conditions.

In comparison, only 11 studies tried to evaluate departure from additivity on the additive and/or multiplicative scales, as recommended by Tsai ([Tsai and Burns, 2015](#ref-tsai2015)) to demonstrate synergy between syndemic conditions.

Furthermore, some studies sought to get a better understanding on the mechanism of interaction between the syndemic conditions and the outcome by using mediation analysis (N = 12), moderation analysis (N = 8), Structural Equation Modeling (N = 6) or path analysis (N = 1).

Moreover, 8 studies used latent variables modeling such as Exploratory/Confirmatory Factor Analysis, Latent Profile Analysis, Latent Class Analysis or Latent Transition Analysis.

Using a different approach, 2 studies conducted by Lee and colleagues ([J. S. Lee et al., 2020](#ref-lee2020); [Jasper S. Lee et al., 2020](#ref-Lee)) used network analysis, in which syndemic is conceptualized as a network and the syndemic conditions as interconnected nodes reinforcing each others.

Finally, other statistic analysis used to assess interaction were observed/expected ratio (N = 2), cluster analysis (N = 1) and point-biserial correlation matrix (N= 1).

### Proposed mechanisms of interaction

In our sample of quantitative studies, we found only one study offering a mechanism of biological interaction [Carrico et al.](#ref-carrico2018) ([2018](#ref-carrico2018)) and one study offering a mechanism of bio-social interaction ([Klein, 2011](#ref-Klein2011)).

Carrico et al. showed that the combined effects of HIV infection and methamphetamine use were detrimental for the functioning of the Hypothalamic-Pituitary-Adrenal axis which is thought to play an important part in the reinforcing effect of stimulants.

Klein proposed that attitudes towards condom was one of the key factor contributing to condomless sex and, subsequently, HIV infection. In their study, attitudes toward condoms was predicted by low self-esteem, as condom use represents a self-protecting mechanism, as well as by sexual preferences, substance use, race and education. Furthermore, childhood emotional neglect had a negative influence on self esteem thus indirectly contributing to sexual risk taking.

Qualitative studies proposed mechanisms of bio-social interaction more often than quantitative studies as we identified 5 papers with such hypothesis of interaction. On the other hand, we did not find any qualitative paper exploring biological interaction.

Stigma and structural inequalities were indicated by the 5 papers as the root causes of syndemic conditions and HIV risk behaviors. Maionara et al. showed that economic dependency and fear of violence may maintain YBMSM in dysfunctional relationships plagued by IPV and substance abuse which increase their odds of incarceration and HIV infection ([Maiorana et al., 2020](#ref-Maiorana)). Furthermore, methamphetamine is used as a coping strategy while simultaneously representing a potential factor in acquiring or transmitting HIV to others, notably during sex parties.  
This finding of substance use as a coping mechanism was supported by the study by Pollard et al. who found that maladaptive coping strategies to minority stress and the performative resistant space of the gay scene contributed to chemsex use ([Pollard et al., 2018](#ref-Pollard2018a)).

For Black MSM, other sources of structural violence such as racial neighborhood segregation contributed, alongside poverty, unemployment, violence, unstable housing, incarceration and poor healthcare access to expectations surrounding masculinity which may conflict with the sexual orientation of BMSM, leading to internalised homophobia ([Quinn, 2019](#ref-Quinn)). Internalised homophobia, in turn, may lead to poor mental health as well as to substance abuse and sexual risk taking as coping mechanisms. Moreover, the use of PrEP, perceived as a “gay pill” may negatively impact the use of PrEP in this community. Lyons et al. also showed that the marginalization of YMSM within their school, communities of origin and families resulted in a lack of gay-specific HIV prevention education, role-model and productive goal-related activities ([Lyons et al., 2013](#ref-Lyons2013)). The HIV-positive MSM youth in this study linked these factors to their HIV acquisition. Finally, ([Chakrapani et al., 2019a](#ref-Chakrapani2019a)) showed the role of family support and communities of MSM to serve as resilience resource to counteract the negative effects of stigma and syndemic conditions.

## What were the key findings of these studies?

In nearly all of the quantitative studies, the syndemic conditions chosen by the authors were found to be associated to the outcomes of interest.

However, some interesting discrepancies in the findings were found. On the topic of synergy, results were conflicting between studies. Chakrapani and colleagues found support for the three models of interacting epidemics (synergistically interacting epidemics, serially causal epidemics and mutually causal epidemics) with the strongest support for the model of synergistically interacting epidemics ([Chakrapani et al., 2019b](#ref-Chakrapani2019)). These findings were supported by other studies who found synergy when using significant product terms in the additive and/or multiplicative scales ([Chakrapani et al., 2020](#ref-Chakrapani); [Cristian J. Chandler et al., 2020c](#ref-chandler2020); [Cristian J. Chandler et al., 2020b](#ref-Chandler2019); [Tomori et al., 2018](#ref-tomori2018)). However, other studies found no synergy between the syndemic conditions using the same statistical approach ([Batchelder et al., 2019](#ref-Batchelder2019); [Ferlatte et al., 2018a](#ref-Ferlatte2018a); [Shuper et al., 2020](#ref-shuper2020)).

Conflicting results were also found for MSMW. Brandstrom and Pachankis found no clustering of syndemic conditions for MSMW ([Bränström and Pachankis, 2018](#ref-Branstrom2018)) while Mustanski et al. found a stronger clustering of syndemic conditions in YMSMW compared to YMSM([Mustanski et al., 2014](#ref-Mustanski2014)). Furthermore, Dyer et al. found more STI in the Black MSM compared to the Black MSMW ([Dyer et al., 2020](#ref-dyer2020)) and Ferlatte found more syndemic conditions in the MSM compared to the MSM ([Ferlatte et al., 2018b](#ref-ferlatte2018)), mainly driven by party drug use and treatment for depression or anxiety. Finally, in a sample of Latino MSMW, having two syndemic conditions predicted receptive condomless anal sex and STI diagnosis but not insertive nor vaginal condomless sex ([Muñoz-Laboy et al., 2018](#ref-Munoz-Laboy2018)).

While condomless anal sex is often used as a proxy for the risk of acquiring HIV or another STI, the findings of some studies tend to show some limitation of this proxy. For example, Moeller et al. found an association between syndemic conditions and condomless anal sex but not with HIV diagnosis ([Moeller et al., n.d.](#ref-moeller)). A similar pattern was found in a longitudinal study that found an association between syndemic conditions and sexual risk behaviors but not with HIV or STI incidence ([Mustanski et al., 2017](#ref-Mustanski2017)). On the other hand, some authors found an association between syndemic conditions and HIV but not with condom use ([Chuang et al., 2018](#ref-chuang2018)).

Alcohol misuse was inconsistently linked to risk taking. Card et al found no association between the AUDIT score and sexual risk behaviors ([Card et al., 2018](#ref-Card2018)) while another study using latent class analysis found that the class with alcohol misuse had a lower level of risk behaviors ([Scheer et al., 2021](#ref-scheer2021)). Nonetheless, alcohol misuse was found to be associated with PrEP non-adherence ([Shuper et al., 2020](#ref-shuper2020)).

In a longitudinal study ([Mustanski et al., 2017](#ref-Mustanski2017)) Black MSM were found to have the highest HIV incidence while having a lower burden of syndemic condition than White MSM, raising the question of the need to focus on syndemic conditions specific to Black MSM.

# Discussion

What stands out the most when we consider syndemic literature applied to MSM is that it is both too homogeneous in some aspects while being not focused enough in other parts. As we will discuss in more depth below, the location, design, subpopulation and outcomes should be more diverse that it currently is. On the other hand, the syndemic conditions and ways of measurement should be more focused to improve the robustness and reproducibility of the findings.

More concerning, maybe, is the fact that a substantial part of the literature doesn’t provide empirical data to support one of the core tenets of syndemic theory - namely disease interaction- as was already pointed out in a previous review ([Tsai and Burns, 2015](#ref-tsai2015)).

## Location

The location of study is an aspect of syndemic literature suffering from too much homogeneity. Indeed 71% of studies are conducted in North America alone while all studies conducted in the Global South represents only 21% of our sample.

Three issues arise from this. First, under-representation of the Global South is inherently an issue as it precludes us to better understand the health of MSM living in these countries. Furthermore, as aptly pointed out by [Weaver and Kaiser](#ref-weaver2020) ([2020](#ref-weaver2020)), the screening tool used to assess the presence of a syndemic condition in the Western context may not be efficient in another sociocultural setting, especially in regard to mental health. As syndemics are driven by the sociocultural forces of a given place at a given time, these potential biases need to be addressed in order to conduct meaningful research outside Europe and North America.

Moreover, even for studies conducted in Europe and North America, a large portion of the studies conflate data from different cities, counties, states or even countries in order to obtain a sample big enough to conduct statistical analyses. However, geographical variations in syndemic burden are likely to be missed. Migration of MSM to larger cities is a well-known phenomenon and thought to be an important part of syndemic production among MSM as well as a source of resilience ([Bruce et al., 2011](#ref-Bruce2011); [Wolitski et al., 2007](#ref-stall2007)). Differences in the density of gay social venues and peer organizations as well as exposure to discrimination and violence or an easier access to substances need to be taken into account when studying a syndemic. Thus, as [Shrestha et al.](#ref-shrestha2020) ([2020](#ref-shrestha2020)) suggested, syndemic research needs to incorporate data from spatial epidemiology to better understand the interactions of socioeconomic forces in the physical space and how these forces can influence the health of MSM.

## Design

The design of syndemic studies is another point suffering from a lack of diversity. The field is dominated by quantitative studies as qualitative papers represent only 9% of our sample. Quantitative studies, on their part, employ a cross-sectional design in 69% of the papers. As vulnerability to syndemic conditions is suspected to arise from early adverse experience [Wolitski et al.](#ref-stall2007) ([2007](#ref-stall2007)) longitudinal studies running on a long period of time are probably needed to study syndemic production among MSM.

Moreover, as shown in our result, qualitative paper are more prone to discuss the potential interactions between syndemic conditions. Some concepts and experiences needed to understand syndemic production in MSM can only be studied through a qualitative lens. For example, the complex narratives surrounding drug use and its link to loneliness, marginalization, personal affirmation, resistance and lack of meaningful emotional connections [Pollard et al.](#ref-Pollard2018a) ([2018](#ref-Pollard2018a)) would be hard to measure and model using quantitative data. As Alexander Tsai previously pointed out, the inevitable simplification needed to estimate statistical models may lead to over-simplification of diseases dynamics [Tsai](#ref-Tsai2018a) ([2018](#ref-Tsai2018a)) . As such, we concur that mixed method are direly needed to complement robust statistical estimation with insights on sociocultural mechanisms and on the lived experiences of people facing this clustering of adverse conditions. Unfortunately, our review only identified 2 studies employing such mixed methodology. Future research would gain to take advantage of qualitative data to support and deepen their quantitative findings.

Finally, we identified 2 interventional studies with mixed results. While co-targeting interconnected syndemic conditions is supported by a meta-analysis [Pantalone et al.](#ref-Pantalone2020) ([2020](#ref-Pantalone2020)), a better understanding of how syndemic operate may be needed before offering efficient syndemic-based interventions.

## Subpopulations

Studying the health of MSM pose a challenge regarding the diversity of this population. While nearly half of the studies included in our sample studied a subpopulation of MSM, the number of MSM subpopulation is such that most MSM subpopulation remain undeserved. For example, Young Black MSM are specifically studied in 2 studies while representing 52% of the new HIV diagnosis among MSM aged 13-24 years in 2018 [Center for Disease Control and Prevention](#X4cf13d81533c7b267d16e8ce422f52a6b94e857) ([2020](#X4cf13d81533c7b267d16e8ce422f52a6b94e857)).

This discrepancy between the number of studies focusing on a subpopulation and the very high prevalence of some syndemic condition such as HIV infection is even more concerning when considering that dual-minority identity may expose to different stressors and outcomes. For example, some study found that Black MSM had a higher rate of HIV seroconversion than White MSM while being exposed to less syndemic conditions [Mustanski et al.](#ref-Mustanski2017) ([2017](#ref-Mustanski2017)) . These findings are supported by qualitative data suggesting that intersectional theory offers the context needed to understand syndemics among Black MSM which differ from syndemics among White MSM [Quinn](#ref-Quinn) ([2019](#ref-Quinn)) .

MSMW are another example of undeserved population with conflicting results. In a cross-sectional study using syndemic sum count, Latino MSMW with two or more syndemic conditions had a 7.09 Odds Ratio to engage in receptive condomless anal sex but no statistically significant difference were found for insertive condomless anal sex or condomless vaginal sex [Muñoz-Laboy et al.](#ref-Munoz-Laboy2018) ([2018](#ref-Munoz-Laboy2018)). On the other hand, in another study the number of syndemic conditions was associated with HIV diagnosis for MSM but not for MSW or MSMW [Bränström and Pachankis](#ref-Branstrom2018) ([2018](#ref-Branstrom2018)). Among young MSM and MSMW, one study found more syndemic conditions and a greater association between them for MSMW compared to MSM [Mustanski et al.](#ref-Mustanski2014) ([2014](#ref-Mustanski2014)). On the contrary, Ferlatte et al. found that MSM were more likely than MSMW to suffer from two or more syndemic conditions [Ferlatte et al.](#ref-ferlatte2018) ([2018b](#ref-ferlatte2018)). These conflicting findings may be partly due to the difficulty to define and operate bisexuality in research [Swan](#ref-swan2018) ([2018](#ref-swan2018)), difference between age groups or differences in syndemic mechanism for MSMW compared to MSM. Outside the field of syndemic literature, studies suggest that bisexual men suffer from a similar or higher burden in mental health condition compared to gay men ([Chaudhry and Reisner, 2019](#ref-Chaudhry2019); [Ross et al., 2018](#ref-ross2018); [Salway et al., 2019](#ref-salway2019)) and literature specific to bisexual men remains scarce. Syndemic theory should thus seek to study forward the specificity of this population. First, there’s a need to better conceptualize and define bisexuality in the field - should we still use solely behavior-based definition (as in MSMW) or should we incorporate self-definition of one’s sexual orientation ? Then, researchers should see to disaggregate data concerning MSMW/bisexual men from data concerning MSM/gay men whenever possible. Lastly, more research focused on MSMW/bisexual men is needed.

Finally transgender MSM were included in only one study of our sample. As stated in our result, this is concerning, especially when every other study exclude transgender men by design. As such, this population of MSM is the one we know the less about. The study from Reisner and colleagues suggested that transgender MSM who had socially affirmed their gender were exposed to similar risk patterns as cisgender MSM [Reisner et al.](#ref-Reisner2016a) ([2016](#ref-Reisner2016a)). The health of transgender men remains greatly understudied and the few available studies suggest high rates of adverse conditions such as violence, notably sexual violence [Testa et al.](#ref-Testa2012) ([2012](#ref-Testa2012)), suicide attempts [Haas et al.](#ref-Haas2014) ([2014](#ref-Haas2014)), chlamydial and gonoccocal infections [Pitasi et al.](#ref-Pitasi2019) ([2019](#ref-Pitasi2019)) and HIV infection [Becasen et al.](#ref-Becasen2019) ([2019](#ref-Becasen2019)). Researcher should therefore include transgender men in their studies and conduct research focused on transgender MSM. Indeed, syndemic theory represents a promising framework for transgender men as its premises of social adversities producing and concentrating diseases in a population allows to explore the health of transgender men without pathologizing them.

## Syndemic conditions

A clear lack of consensus exists in the choice of syndemic conditions and the way they should be measured. We identified 46 different conditions in our quantitative sample and 9 of them were only studied once. Some of these conditions are past event (e.g. history of trauma or childhood sexual abuse) while most were current conditions. Given the cross-sectional nature of 77% of the quantitative paper, we can’t disentangle how past experiences may influence the emergence of a syndemic.

Furthermore, studies diverge on what represents a syndemic condition and what may lead to the emergence of a syndemic. For example, childhood sexual abuse is mostly seen as a syndemic condition per se but may very well be a risk factor to the emergence of a syndemic, as hypothesized by some authors [Herrick et al.](#ref-Herrick2013) ([2013](#ref-Herrick2013)). The same question may be asked for discrimination, trauma, impulsivity, bullying, poor social support, loneliness, childhood abuse, poor healthcare access, etc. Qualitative and longitudinal studies are needed to distinguish between syndemic conditions and pathways to the emergence of a syndemic. Conflating the two in cross-sectional studies does very little to advance our understanding of syndemic theory or to implement public health interventions.

Furthermore, even when the same condition was studied in multiple papers, the differences in measurement methods impedes greatly the reproducibility of the results. For example, let us imagine a participant with a CESD score of 16, who uses marijuana on a regular basis and cocaine once in a while and who is victim of sexual intimate partner violence. This man would have been classified as depressed in 46% of studies using the CESD, a polysubstance user in 27% of studies considering polysubstance use and as a victim of intimate partner violence in 47% of studies taking IPV into account. In other words, the same person could have been classified as having 0, 1, 2 or even 3 syndemic conditions, depending on the study. Considering that most studies use a summation score of the number of syndemic conditions to conduct regression analysis, it seems evident that the results would greatly vary according to the way the syndemic conditions are measured.

It is beyond the scope of this paper to discuss in details which syndemic conditions should be retained for future research and how to best measure them, but without a greater homogeneity in the field, the confidence and reproducibility of the results will remain an issue.

## Outcomes

Taken together, 97% of the quantitative studies in our sample had an HIV-related outcome, whether in the form of sexual risk behaviors, HIV diagnosis, HIV screening, adherence to antiretroviral therapy, PrEP use, viral load or engagement in HIV care.

This omnipresence of HIV in syndemic literature applied to MSM is doubly understandable. The first description of a syndemic, the SAVA syndemic, incorporated AIDS as part of a syndemic [Singer](#ref-singer1996) ([1996](#ref-singer1996)). Then, a few years later, the first paper on syndemic in the MSM population had HIV-related outcomes, in the form of HIV serostatus and CAS [Stall et al.](#ref-Stall2003) ([2003](#ref-Stall2003)). Furthermore MSM were the first and most severely affected population when the AIDS epidemic started [De Cock et al.](#ref-decock2012) ([2012](#ref-decock2012)). Nowadays, male-to-male sexual contact still represents nearly 70% of the new HIV cases in the USA [Center for Disease Control and Prevention](#X4cf13d81533c7b267d16e8ce422f52a6b94e857) ([2020](#X4cf13d81533c7b267d16e8ce422f52a6b94e857)). While we can’t deny the importance of the HIV pandemic, notably for MSM, we would argue that HIV is not the only issue in need of attention.

Indeed, MSM are also disproportionately affected by suicide, anxiety, depression and substance use to name a few ([Luo et al., 2017](#ref-luo2017); [Medley et al., 2016](#ref-Medley2016); [Ross et al., 2018](#ref-ross2018)). Moreover, with the advances in antiretroviral therapy and the subsequent decline in HIV-related mortality, gay men were more likely to die from suicide than from HIV in Canada in 2011 [Hottes et al.](#ref-hottes2015) ([2015](#ref-hottes2015)). Even if the estimates in this paper overestimated suicide’s mortality among MSM, suicide would still be a leading cause of death in this population while being studied as an outcome in only 3 papers in our sample.

Furthermore, when studying HIV as an outcome, we would argue that condomless anal sex should be replaced by better proxies. First, without refinement, this outcome fails to capture the changes in HIV prevention strategies such as PrEP or Treatment as Prevention (TasP). Only 2 studies in our sample took PrEP use and an undetectable viral load into account when considering condomless anal sex as a risk factor for HIV acquisition. When the first paper on syndemic theory applied to MSM were published, engaging condomless anal sex would have led to a high risk of acquiring HIV. Nowadays, people could be on PrEP, forego the use of a condom and still be at a very low risk of acquiring HIV [Calabrese et al.](#ref-calabrese2017) ([2017](#ref-calabrese2017)) and our methodologies should reflect this change. In addition, qualitative research gives insight in risk practices and offers a more nuanced view on this topic than a binary variable of consistent condom use for anal intercourses. One such paper published in 2017 showed that risk practice fell into different subjectivities such as active and consistent pursuit of condomless sex, lack of assertiveness to a partner’s initiative of condomless anal sex and combination of episodic risk practices and reduction strategies [Adam et al.](#ref-Adam2017) ([2017](#ref-Adam2017)). Besides, some studies showed that participants with a greater number of syndemic conditions would engage more frequently in condomless anal sex while not being more likely to test positive for HIV ([Mustanski et al., 2017](#ref-Mustanski2017); [Pitpitan et al., 2016](#ref-Pitpitan2016)). On the other hand, a paper from 2018 found that having a greater number of syndemic conditions was associated to HIV self-report but not to condomless anal sex [Chuang et al.](#ref-chuang2018) ([2018](#ref-chuang2018)). Taken together, we thus postulate that condomless anal sex should at least be replaced by “condomless anal sex without consistent PrEP use or with a detectable viral load” when an investigator seek to use sexual risk behaviors as an outcome.

In summary, we recommend that future research should focus on other aspects of MSM’s health than HIV infection and, when studying HIV as an outcome to prefer laboratory-based outcomes or more refined sexual risk variables than condomless anal sex.

## Statistics and interaction

One of the tenets of syndemic theory is that there exists some form of biological, social and/or psychological interaction between the diseases [Mendenhall and Singer](#ref-mendenhall2020) ([2020](#ref-mendenhall2020)). As others have already pointed before us, the extent to which syndemic literature had proved this core principle remains very limited [Tsai and Burns](#ref-tsai2015) ([2015](#ref-tsai2015)). Indeed, 45% of our quantitative sample of studies used solely a summation score of the syndemic conditions to conduct regression analysis. Two issues arise from this statistical approach. First, summation score are additive by essence, thus unsuitable to demonstrate an interaction [Tsai and Burns](#ref-tsai2015) ([2015](#ref-tsai2015)). Secondly, two psychometric assumptions are made by such a model : (1) the unidimensionality of the construct and (2) equal factor weighting [Halkitis et al.](#ref-Halkitis2013a) ([2013](#ref-Halkitis2013a)). Put simply, using a summation score would imply that (1) every condition form a single construct and that (2) every condition contributes equally to said construct (which would mean for example that feeling depressed during the past 14 days and having an history of childhood sexual abuse would contribute equally to a syndemic). The unidimensionality aspect of the construct has received some empirical support by Mustanski et al. as well as by Starks et al. using respectively Structural Equation Modeling and Latent Class Analysis ([Mustanski et al., 2014](#ref-Mustanski2014); [Starks et al., 2014](#ref-Starks2014)). However constraining factor loadings to be equal resulted in worse fit in both studies.

In short, the result of our review suggests that as much as 45% of the quantitative literature on syndemic theory applied to MSM doesn’t empirically support the presence of a syndemic and employs questionable statistical assumptions. Those studies are more an exploration of psychosocial risk factors associated to HIV acquisition or progression than the holistic framework syndemic is supposed to be.

As mentioned in the results, two statistically distinct models may be envisioned apart from synergistically interacting epidemics : mutually causal epidemics and serially causal epidemics ([Tsai, 2018](#ref-Tsai2018a)). As such, mediation analysis, path analysis or structural equation modeling may prove useful to assess an interaction.

More recently, a new statistical approach inspired from research in psychopathology has been used to model syndemics : network analysis ([Jasper S. Lee et al., 2020](#ref-Lee); [J. S. Lee et al., 2020](#ref-lee2020)). The core principle of this approach is that mental disorders arise from causal interactions between symptoms in a network [Borsboom](#ref-borsboom2017) ([2017](#ref-borsboom2017)). Applied to syndemic theory, a syndemic would then be the network and the various conditions would then be the nodes of the network. Furthermore, one of the benefits of this approach reside in the theoretical possibility to identify influential nodes in a network : nodes that play a significant part in the activation of the network and that could be the prime target of an intervention in order to deactivate the network [Robinaugh et al.](#ref-robinaugh2016) ([2016](#ref-robinaugh2016)). In short, in addition to be statistically sound and coherent with the model of mutually causal epidemics, network analysis could offer actionable data to improve the health of MSM by identifying which conditions should be prioritized for interventions.

We recommend that future work should let go of the summation score approach and attempt to clarify which model of interaction receives the most empirical support in order to implement effective public health interventions. Indeed as reminded by Chakrapani et al. the three models have different programmatic implications [Chakrapani et al.](#ref-Chakrapani2019) ([2019b](#ref-Chakrapani2019)). In the case of synergistically interacting epidemics, a single intervention may yield greater health improvement than if no interaction was present. For mutually causal epidemics, multicomponent interventions addressing the various epidemics should be implemented in order to produce an improvement. Finally, for serially causal epidemics, intervening at the root cause of a syndemic may prevent the development of a syndemic cascade.

## Additional framework

Resilience theory was the most frequently used framework to compliment syndemic theory.

Social support was shown to moderate the effect of syndemic conditions on viral load, providing a significant protective effect ([Friedman et al., 2016](#ref-friedman2016)). Moreover, a paper using Latent Transition Analysis to evaluate the impact of syndemic conditions on substance use showed that Black MSM with more social support were more likely to stay in the low-risk class or transitioning from the high risk class to the low-risk class ([Turpin et al., 2020](#ref-turpin2020)). However, Chakrapani et al. found no moderation of social support on the relationship between syndemic conditions and risk taking ([Chakrapani et al., 2017](#ref-Chakrapani2017)).

On the topic of resilience resources, Zhang et al didn’t find evidence of a moderating effect of resilience on the relationship between syndemic conditions and physical activity ([Zhang et al., 2019](#ref-Zhang2019)). O’Leary et al. didn’t find a buffering effect of resilience factors on the relationship between syndemic conditions and sexual risk behaviors, though optimism and education buffered the relationship between syndemic conditions and self-reported HIV status ([O’Leary et al., 2014](#ref-OLeary2014a)). On the other hand, Kurtz et al found that, among MSM living with HIV, serosorting was positively associated with higher levels of two resilience factors : coping self-efficacy and positive coping skills ([Kurtz et al., 2012](#ref-Kurtz2012)). Similarly, Hart et al. found that psychosocial strengths were associated with lesser odds of engaging in condomless anal sex, despite the presence of syndemic conditions ([Hart et al., 2017](#ref-Hart2017)).

In qualitative studies, resilience was also found to exert a protective effect against syndemic conditions ([Adam et al., 2018](#ref-adam2018); [Chakrapani et al., 2019a](#ref-Chakrapani2019a); [Reed and Miller, 2016](#ref-Reed2016)). Besides, the review by Woodwards et al. found a protective effect of most resilience resources identified against HIV [Woodward et al.](#ref-woodward2017) ([2017](#ref-woodward2017)).

Minority stress represents another interesting framework as it allows to explain how social stigma can get into the skin of minorized populations [Meyer](#ref-Meyer2003) ([2003](#ref-Meyer2003)). Finally, as aforementioned, intersectionality may offer an useful framework to explore how syndemics operate among different subpopulations of MSM, especially MSM living with a dual-minority identity such as Black MSM.

We recommend that future work continue to explore the impact of resilience in partially counteracting syndemic to develop public health intervention that aim at fostering resilience resources among MSM. Furthermore, an intersectional lens should be used more often to elucidate the mechanisms of syndemic among MSM with a dual-minority identity.

# Strengths and limitations

# Conclusion and recommendations

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# Supplementary Materials

### A. Reference tables

Table 1: Reference table of the included quantitative studies

| **References** | **Location** | **Design** | **Subpopulation** | **Syndemic conditions studied** | **Outcomes** | **Statistics used to model interaction** | **Key findings** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Achterbergh et al. 2021** | Netherlands | Randomized controlled trials (during 12 months intervention group (N=76) received tailored feedback and help-seeking advice on mental health screening to increase help-seeking behaviors (primary endpoint) as well as reducing sexual risk behaviors and STI incidence (secondary endpoint) ; control group (N=79) consisted of participants that didn't received results of their mental health screening nor tailored feedback or help-seeking advice) |  | depression, IPV, sexual compulsivity, anxiety, AUD, discrimination, substance use disorder, ADHD, alexithymia | engaging in sexual risk behaviors, HIV diagnosis, STI diagnosis, help-seeking behaviors | regression analysis using a summation score | This syndemic-based intervention to enhance help-seeking among high-risk MSM failed to improve help-seeking behaviours, STI incidence and sexual risk. Nonetheless, the extremely high incidence of STI incidence and mental health-related problems call for other type of interventions. |
| **Batchelder et al. 2019** | USA | Cross-sectional | MSM with a history of childhood sexual abuse | depression, PTSD, anxiety, substance use disorder | engaging in sexual risk behaviors, healthcare use, STI diagnosis | regression analysis using a summation score, significant product term in regression | There is an additive relationship between the number of psychiatric diagnoses and ER visits as well as condomless anal sex. No relationship was found between psychiatric diagnoses and STD. No interaction was found. |
| **Beymer et al. 2016** | USA | Longitudinal (66 months) | Latino MSM | substance use, IPV, sexual risk behaviors, STI | HIV diagnosis | Cox proportional hazards models | In this sample of Latino MSM, predictors of HIV seroconversion included history of STI, condomless anal sex, Methamphetamine Use, Central American birthplace, experience of IPV and same ethnicity of last sexual partner. |
| **Biello et al. 2014** | Vietnam | Cross-sectional | MSM engaged in sex work | depression, substance use, CSA, AUD, violence | engaging in sexual risk behaviors | regression analysis using a summation score | Experiencing a higher number of syndemic condition was associated with greater odds of engaging in condomless anal sex in this sample of Vietnamese male sex workers who have sex with men. This relationship was mainly driven by childhood sexual abuse and alcohol use disorder |
| **Biello et al. 2016** | Latin America | Cross-sectional | MSM living with HIV | depression, IPV, suicidality, sexual compulsivity, CSA, AUD, chemsex | adherence to antiviral medication, healthcare use, linkage to HIV care | regression analysis using a summation score | Experimenting syndemic conditions was associated with less engagement in HIV-related care, uptake of ART and adherence to ART among this sample of HIV positive MSM living in Latin America |
| **Blashill et al. 2020** | USA | Cross-sectional | Latino MSM | depression, substance use, IPV, binge drinking, CSA, polysubstance use, incarceration, unstable housing, poverty | PrEP-related outcomes | regression analysis using a summation score | Structural barriers such as unstable housing represent greater obstacles to being aware of the existence of PrEP than psychosocial conditions. However, once PrEP has been initiated, psychosocial conditions like intimate partner violence account for a greater variance in PrEP adherence. |
| **Blondeel et al. 2021** | Portugal | Cross-sectional |  | sexual risk behaviors, chemsex, frequenting gay social venues | HIV diagnosis, STI diagnosis | cluster analysis | 6 clusters with diverse patterns of sexual risk taking and STI/HIV vulnerability were identified. Among these clusters, the one with the highest HIV prevalence was the oldest one, reported the most condomless anal sex and had sex the most frequently with transgender partners, women and sex workers. |
| **Brandstrom and Pachankis 2018** | Sweden | Population-based cohort study | disagregated data for Men who have Sex with Men and Women | depression, binge drinking, suicidality, violence | HIV diagnosis | regression analysis using a summation score, observed/expected ratio | Sexual minority men are more likely to be diagnosed with HIV and to suffer from psychosocial conditions. However, the clustering of syndemic conditions and HIV was only found for gay men, not bisexual men |
| **Buttram et al. 2015** | USA | Mixed Quantitative cross-sectionnal and qualitative analysis with grounded theory | Black MSM | substance use disorder, violence, general mental distress |  | no interaction studied | Compared to White MSM, Black MSM experienced a wide range of disparities such as substance use, substance use disorder, exchange sex, unstable housing, unemployment, low educational attainment, arrest history, low social support and low satisfaction with one's living situation |
| **Byg et al. 2016** | USA | Cross-sectional | MSM living with HIV | depression, IPV, substance use disorder | glycemic control | multivariate linear regression | Poorer glycemic control was associated with a detectable viral load, high triglycerides and substance use |
| **Card et al. 2018** | Canada | Cross-sectional |  | depression, polysubstance use | engaging in sexual risk behaviors | moderation analysis, mediation analysis | AUDIT scores were not associated with risky sexual behaviors. The association between polysubstance use and depression was associated with greater odds of serodiscordant condomless anal sex. 18,2% of the effect of depression on serodiscordant CAS was mediated by polysubstance use. |
| **Carrico et al. 2018** | USA | Intact group design |  | depression, CSA, substance use disorder, sleep disturbance, childhood abuse | dysregulation of the hypoathalamic-pituitary-adrenal axis | moderation analysis | In meth-using MSM living with HIV, there is a disaggregation of the functional relationship between ACTH and cortisol, compared to HIV-negative, non-meth-using men |
| **Chakrapani et al. 2017** | India | Cross-sectional |  | depression, alcohol use, violence | engaging in sexual risk behaviors | regression analysis using a summation score | In this sample of Indian MSM, there was a positive relationship between the number of syndemic conditions and sexual risk taking. This relationship was moderated by resilient coping but not by social support. |
| **Chakrapani et al. 2019b** | India | Cross-sectional |  | substance use, alcohol use, violence | engaging in sexual risk behaviors | Relative Excess Risk due to Interaction (RERI), significant product term in regression, mediation analysis, path analysis | In this population-based study of Indian MSM, the authors found empiric support to three models of interacting epidemics : synergistically interacting epidemics, serially causal epidemics and mutually causal epidemics, with the strongest support for the model of synergistically interacting epidemics |
| **Chakrapani et al. 2020** | India | Pretest-posttest nonequivalent groups (during 12 months intervention group (N=229) received a Motivational Interview-based HIV prevention intervention to reduce condomless anal intercourse by improving condom self-efficacy and by addressing co-occurring psychosocial conditions ; control group (N=230) consisted of MSM receiving standard of care in another NGO) |  | depression, AUD, internalised homophobia | engaging in sexual risk behaviors | Relative Excess Risk due to Interaction (RERI), significant product term in regression, mediation analysis | This motivational interview-based intervention guided by syndemic theory was effective in improving consistent condom use and in reducing the three psychosocial conditions investigated (depression, alcohol use and internalised homophobia). Synergy was present for depression and alcool use and for depression and internalised homophobia on inconsistent condom use. Mediation analysis revealed that the intervention led to a reduction in alcool use and internalised homophobia which improved condom self-efficacy which ultimately led to an improvement in consistent condom use |
| **Chandler et al. 2020a** | USA | Cross-sectional | Black MSM | depression, IPV, binge drinking, polysubstance use | PrEP-related outcomes | regression analysis using a summation score, Relative Excess Risk due to Interaction (RERI) | BMSM on PrEP were most likely to suffer from IPV, engage in problematic binge drinking and polysubstance use. Synergy was found between all the syndemic conditions |
| **Chandler et al. 2020b** | USA | Cross-sectional | Black MSM | depression, IPV, binge drinking, polysubstance use, sexual risk behaviors | HIV\_screening | regression analysis using a summation score, Relative Excess Risk due to Interaction (RERI) | The men most at risk were more likely to test, such as the syndemic variables did not adequately explain discrepancy in HIV screening among BMSM. Synergy in preventing HIV screening was present between poly drug use, depression and binge drinking as well as between binge drinking, depression and sexual risk behaviors. |
| **Chandler et al. 2020c** | USA | Cross-sectional | Black MSM engaged in sex work | depression, IPV, polysubstance use, violence | STI diagnosis | mediation analysis, Structural Equation Modeling | In this sample of BMSM engaged in sex work, there were a direct relationship between syndemic conditions and engagement in sex work as well as between engagement in sex work and past-year STI diagnosis. Furthermore, syndemic conditions were found to partially mediate the relationship between engagement in sex work and past-year STI, accounting for 64,2% of this relationship. |
| **Chuang et al. 2018** | Taiwan | Cross-sectional |  | IPV, discrimination, substance use disorder | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | Experiencing a greater number of syndemic conditions was associated with higher odds of self-reported postive HIV status but not with condomless anal sex nor number of partners |
| **Dyer et al. 2012** | USA | Cross-sectional | Black MSM | depression, substance use, IPV, binge drinking, sexual compulsivity, stress | engaging in sexual risk behaviors, syndemic conditions as the outcomes | regression analysis using a summation score | Gay-related and non-gay-related victimization in school, perception of failures in masculinity, social connectedness, internalized homophobia, discrimination and life satisfaction were associated with having 2 or more syndemic conditions. Furthermore, having 3 or more syndemic conditions was associated with condomless anal sex |
| **Dyer et al. 2020** | USA | Longitudinal (12 months) | Black MSM, disagregated data for Black Men who have Sex with Men and Women | depression, substance use, IPV, binge drinking, incarceration, discrimination, experience of trauma | STI diagnosis | Latent Class Analysis/Latent Profile Analysis, mediation analysis | Different syndemic profiles were found for BMSMO and BMSMW. Furthermore BMSMO had higher STI incidence compared to BMSMW and this difference in incidence was partly mediated by high risk sexual behaviors. |
| **Eaton et al. 2013** | South Africa | Cross-sectional | Men who have Sex with Men and Women | substance use, IPV, CSA, alcohol use, sexual risk behaviors, violence | having sex with both men and women | no interaction studied | In multivariate analysis, self-reported positive HIV status and childhood sexual abuse were associated with higher odds of reporting sex with both men and women. Furthermore recent interpartner violence, recent sexual violence and childhood sexual abuse were significantly inter-associated but were not associated with sexual risk or substance/alcohol use |
| **Ferlatte et al. 2014** | Canada | Cross-sectional |  | depression, substance use disorder, loneliness | engaging in sexual risk behaviors | regression analysis using a summation score | Experiencing multiple anti-gay experiences was associated with syndemic conditions : a greater number of syndemic conditions was then subsequently associated with greater odds of engaging in serodiscordant condomless anal sex |
| **Ferlatte et al. 2015** | Canada | Cross-sectional |  | depression, substance use, anxiety, tobacco use, sexual risk behaviors, STI, HIV | suicidality | regression analysis using a summation score | Syndemic theory is appropriate for studying suicide ideation and attempts among MSM. Notably, those reporting 3 syndemic conditions had 6.9 times the odds of suicide ideation and 16,29 times the odds of suicide attempts, mainly driven by anxiety and depression. |
| **Ferlatte et al. 2018a** | Canada | Cross-sectional |  | substance use, IPV, binge drinking, suicidality, general mental distress | STI diagnosis | regression analysis using a summation score, Relative Excess Risk due to Interaction (RERI) | Healthcare discrimination, a cumulative count of syndemic and a cumulative count of antigay stigma were associated with syphilis diagnosis in the past 12 months. The RERI for cumulative count of syndemic conditions was not significant. IPV and substance use were associated with syphilis, after adjusting for other syndemic conditions. |
| **Ferlatte et al. 2018b** | Canada | Cross-sectional | disagregated data for Men who have Sex with Men and Women | depression, substance use, binge drinking, suicidality, anxiety | engaging in sexual risk behaviors, syndemic conditions as the outcomes | regression analysis using a summation score | Gay men were more likely to experiment two or more syndemic conditions compared to bisexual men and female-partnered MSM. This difference was mainly driven by higher odds of consuming party drugs and being treated for anxiety/depression. Furthermore, being single, younger than 45 years old, of Indigenous ancestry, earning less than $60,000 per year and living in an urban environment were also associated with higher odds of experimenting two or more syndemic conditions |
| **Friedman et al. 2014** | USA | Cross-sectional | disagregated data for Men who have Sex with Men and Women | depression, sexual compulsivity, unstable housing, violence | engaging in exchange sex, engaging in sexual risk behaviors, engaging in chemsex | regression analysis using a summation score, hierarchical negative binomial regression | Among MSMW, syndemic conditions explained 31,1% of the variance in exchange sex but only 3.6% of the variance in chemsex. Exchange sex, in turn was associated with serodiscordant condomless anal sex while chemsex alone was not. Furthermore no direct association between syndemic conditions and serodiscodant condomless anal was found |
| **Friedman et al. 2015** | USA | Longitudinal (78 months) | MSM living with HIV | depression, polysubstance use, sexual risk behaviors | adherence to antiviral medication, viral load | regression analysis using a summation score, mediation analysis, Structural Equation Modeling | In this longitudinal study, the sum of syndemic conditions was associated with lower ART adherence and higher viral load among MSM living with HIV. Furthermore, the effect of syndemic conditions on viral load was partially mediated by ART adherence. |
| **Friedman et al. 2016** | USA | Longitudinal (72 months) | MSM living with HIV | depression, polysubstance use, sexual risk behaviors | adherence to antiviral medication, viral load | regression analysis using a summation score, moderation analysis | Among MSM living with HIV, functional social support moderates the effect of syndemic conditions on viral load suppression, providing a significant protective effect |
| **Guadamuz et al. 2014** | Thailand | Longitudinal (3.8 year) |  | substance use, suicidality, alcohol use, exchange sex, poor social support, violence | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | A higher number of syndemic conditions was significantly associated with greater odds of condomless anal sex, a higher HIV prevalence and a higher HIV incidence |
| **Halkitis et al. 2012** | USA | Mixed (cross-sectional quantitative method and discovery interview) | Older MSM living with HIV | depression, substance use, PTSD, alcohol use | engaging in sexual risk behaviors | regression analysis using a summation score | High prevalence of psychiatric conditions (PTSD and depression) as well as substance use among older MSM living with HIV. These psychosocial burdens are associated with unprotected anal intercourse. |
| **Halkitis et al. 2013** | USA | Cross-sectional | Young MSM | depression, substance use, PTSD, suicidality, alcohol use, sexual risk behaviors, loneliness |  | Structural Equation Modeling | A second-order model consisting of drug use and mental health burden was associated with a first-order model for unprotected sex, both indicated by numerous variables |
| **Halkitis et al. 2015** | USA | Longitudinal (36 months) | Young MSM | depression, substance use, PTSD, suicidality, alcohol use, sexual risk behaviors, loneliness |  | Confirmatory Factor Analysis | There was an increased use of substance and sexual risk behaviors with increasing age of this cohort of YMSM. Furthermore, the relative contribution of the syndemic indicator variables on the latent constructs varied accros time while still loading onto one latent construct across the four time points |
| **Harkness et al. 2018** | USA | Longitudinal (12 months) | MSM living with HIV | depression, substance use, PTSD, binge drinking, anxiety, CSA, polysubstance use | adherence to antiviral medication | regression analysis using a summation score | Participants' average syndemic score over the 12 months period predicted their non-adherence scores but not the time-specific changes in their average level. Furthermore, the effects of syndemic conditions on viral load may be mediated by non-adherence. |
| **Harkness et al. 2019** | USA | Longitudinal (12 months) | MSM living with HIV | depression, substance use, PTSD, binge drinking, anxiety, CSA, polysubstance use | engaging in sexual risk behaviors | regression analysis using a summation score | Syndemic score significantly predicted serodiscordant CAS and this effect was attributable to variation in score within person during the study as well as variation of mean score between participants |
| **Hart et al. 2017** | Canada | Longitudinal (6 months) |  | depression, CSA, polysubstance use, discrimination | engaging in sexual risk behaviors | regression analysis using a summation score | Psychosocial strengths were associated with a lesser odds of engagement in condomless anal sex, despite the presence of syndemic conditions. Psychosocial strenghts may operate in the same way as syndemic conditions but in an opposite direction. |
| **Herrick et al. 2013** | USA | Cross-sectional | MSM living with HIV | depression, substance use, IPV, sexual compulsivity, stress | syndemic conditions as the outcomes | hierarchical negative binomial regression | In this life-course approach of syndemic production among MSM, current forms of adversity (i.e. event discrimination, current marginalization and general life satisfaction) accounted for the largest contribution to the model while early life events also contributed significantly with childhood victimization and self-perception of failing masculinity attainment remaining significantly associated to the syndemic outcome variable after controlling for all other factors |
| **Herrick et al. 2014** | USA | Longitudinal (24 months) | Young MSM | depression, substance use, binge drinking | engaging in sexual risk behaviors | regression analysis using a summation score, mediation analysis | A greater number of syndemic conditions was associated with increased odds of sexual risk behaviors. Furthermore, experiences of adversity play an important role in syndemic formation and syndemic conditions mediate the pathway from adversity to sexual risk behaviors |
| **Hirshfield et al. 2015** | USA | Cross-sectional |  | depression, polysubstance use, incarceration, alcohol use | engaging in sexual risk behaviors | regression analysis using a summation score | MSM with encounters with 4 or more partners constitute a particularly high risk subgroup of MSM, with more condomless anal sex, polysubstance use, STI diagnosis and HIV prevalence. Furthermore, a higher count of syndemic conditions was associated with odds of participating in encounters with 4 or more partners. |
| **Hugh Klein 2011** | USA | Cross-sectional |  | depression, substance use, low self-esteem | engaging in sexual risk behaviors | Structural Equation Modeling | Emotional neglect in childhood and demographic factors influenced self-esteem which, in turn, along with substance use and several demographic and psychological functioning variables, influenced attitudes toward condom. This last variable predicted engagement in condomless anal and oral sex |
| **Jiang et al. 2020** | China | Cross-sectional |  | depression, IPV, CSA, chemsex | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score, Relative Excess Risk due to Interaction (RERI), moderation analysis | Depression and use of rush popper before sexual intercourse interacted to increase the number of sexual partners. CSA and use of rush popper before sexual intercourse interacted to increase the risk of HIV infection. Neither education nor income moderated the effects of syndemic factors on sexual risks taking or HIV infection |
| **Jie et al. 2012** | China | Cross-sectional |  | depression, IPV, binge drinking, CSA, polysubstance use | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score, mediation analysis | Experiencing a greater number of syndemic conditions was associated with sexual risk behaviors and HIV infection and the relationship between syndemic conditions and HIV infection seems to be partially mediated by sexual risk behaviors |
| **Kurtz et al. 2012** | USA | Cross-sectional | disagregated data for MSM living with HIV | substance use disorder, violence, cognitive escape, general mental distress | engaging in sexual risk behaviors | multivariate logistic regression | Serosorting among MSM living with HIV was positively associated with lower levels of cognitive escape and higher levels of two resilience factors : coping self-efficacy and positive coping skills. Among HIV-negative men, serosorting was positively associated with lower levels of cognitive escape, violence victimization and severe mental distress as well as with higher levels of coping self-efficacy and social engagements and with lower levels of negative coping skills |
| **Lee et al. 2020a** | USA | Cross-sectional |  | depression, substance use, IPV, binge drinking, suicidality, sexual compulsivity, anxiety, IDU, CSA |  | Exploratory Factor Analysis, Network Analysis | Network analysis is a valuable methodology to examine patterns of synergistic relationships among psychosocial conditions that form a syndemic and may be preferable to EFA. Suicidal ideation, IDU, substance use and depression were the four most central nodes, suggesting that they may be important psychosocial syndemic indicators to investigate as well as targets of intervention |
| **Lee et al. 2020b** | USA | Cross-sectional | Latino MSM | depression, substance use, IPV, IDU, CSA, incarceration, unstable housing, poverty, alcohol use | engaging in sexual risk behaviors | Network Analysis | Network analysis is feasible for studying syndemics. CAS and alcohol use were significantly associated as well as CSA and alcohol use, non-injection substance use and IPV. The four most central nodes were unstable housing, incarceration, CSA and CAS |
| **Li et al. 2016** | China | Cross-sectional |  | depression, substance use, sexual compulsivity, anxiety, sexual risk behaviors, poor social support, loneliness, involuntary subordination, low self-esteem, impulsivity | suicidality | regression analysis using a summation score | A higher number of syndemic conditions was associated with greater suicidal ideation among MSM, especially when the number of syndemic conditions reaches five. Among these conditions, only involuntary subordination and sexual risk taking remained significant in multivariate analysis |
| **Martinez et al. 2016** | USA | Cross-sectional | Latino MSM | depression, binge drinking, CSA, discrimination | engaging in sexual risk behaviors | regression analysis using a summation score | 90% of this sample of Latino MSM reported at least one syndemic condition and having a greater number of syndemic conditions was associated with higher odds of CAS and multiple sexual partners |
| **Martinez et al. 2020** | USA | Cross-sectional | Latino MSM | binge drinking, exchange sex, discrimination | engaging in sexual risk behaviors | regression analysis using a summation score | Having 2 or more syndemic conditions increased the number of male partners and CAS with casual partners in this sample of Latinx MSM in Philadelphia |
| **McDaid et al. 2019** | International | Cross-sectional |  | depression, IPV, suicidality, anxiety, STI, poor physical health | syndemic conditions as the outcomes | observed/expected ratio | Syndemic indicators of poor physical, mental and sexual health cluster and are partly influenced by a pathogenic social context and salutogenic community assets |
| **Mimiaga et al. 2015a** | Latin America | Cross-sectional |  | depression, IPV, suicidality, sexual compulsivity, CSA, AUD, chemsex | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | he number of syndemic conditions was associated with higher odds of engaging in CAS and self-report of HIV diagnosis |
| **Mimiaga et al. 2015b** | USA | Longitudinal (48 months) |  | depression, substance use, binge drinking, CSA, polysubstance use | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score, mediation analysis | In this longitudinal study, experiencing a greater number of syndemic conditions was associated with higher odds of HIV seroconversion over the 4-years follow-up and this effect was partially mediated by sexual risk behaviors |
| **Moeller et al. 2011** | USA | Cross-sectional |  | depression, substance use, anxiety, hostility | engaging in sexual risk behaviors | regression analysis using a summation score | A greater number of syndemic conditions was associated with condomless anal sex with both HIV-positive and HIV-negative partners but not with HIV status |
| **Morrison et al. 2018** | Canada | Cross-sectional |  | depression, sexual compulsivity, AUD, substance use disorder | engaging in sexual risk behaviors | regression analysis using a summation score, significant product term in regression | MSM seeking PEP in this sample were affected by a high burden of syndemic conditions. Furthermore, the number of syndemic conditions in an individual was associated with an increased HIV risk |
| **Muñoz-Laboy et al. 2018** | USA | Cross-sectional | Latino Men who have Sex with Men and Women | depression, CSA, polysubstance use | engaging in sexual risk behaviors, STI diagnosis | regression analysis using a summation score | Among this sample of LMSMW, having at least 2 syndemic conditions predicted lifetime STI and condomless receptive anal sex but not condomless insertive anal sex nor condomless vaginal sex |
| **Mustanski 2014** | USA | Cross-sectional | Young MSM, disagregated data for Men who have Sex with Men and Women | depression, substance use, IPV, binge drinking, sexual risk behaviors | suicidality | Structural Equation Modeling, Confirmatory Factor Analysis | Experiences of victimization and bullying increased the syndemic burden of all youths and subsequently syndemic burden increased suicide attempts. These findings held true for young men who have sex with women (YMSW), young men who have sex with men (YMSM) and young men who have sex with men and women (YMSMW). However, these relationships were much stronger among sexual minority youths and syndemic conditions clustered with particular strength among YMSMW |
| **Mustanski et al. 2007** | USA | Cross-sectional | Young MSM | substance use, IPV, binge drinking, violence, general mental distress | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | Experiencing a greater number of syndemic conditions was associated with higher odds of condomless anal sex, multiple sex partners and reported positive HIV status |
| **Mustanski et al. 2017** | USA | Longitudinal (12 months) | Young MSM, disagregated data for Black & Latino MSM | depression, IPV, binge drinking, suicidality, CSA, polysubstance use, AUD, discrimination | engaging in sexual risk behaviors, HIV diagnosis, STI diagnosis | Structural Equation Modeling | The study found evidence of a predictive ability of syndemic factors on sexual risk behaviors but there were no association with HIV/STI incidence. Furthermore, Black YMSM had both the highest seroconversion rate in the sample and a lesser burden in syndemic conditons compared to White and Latino YMSM, questioning the usefulness of syndemic theory on Black MSM or the need to take into account other syndemic conditions to explain the high rates of HIV acquisition among Black MSM |
| **Ng et al. 2020** | Malaysia | Cross-sectional | disagregated data for MSM living with HIV | depression, IPV, suicidality, CSA, chemsex | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | In this sample of Malaysian MSM, condomless anal sex was associated with depression and chemsex while self-reported HIV status was associated with depression, suicidal risk, chemsex and a history of CSA. Furthermore, self-reported HIV status was associated with the number of syndemic conditions |
| **Nostlinger et al. 2020** | Belgium | Longitudinal (18 months) |  | depression, substance use | engaging in sexual risk behaviors | regression analysis using a summation score, significant product term in regression | There was an interaction effet of recreational effect and drug use, potentiating sexual risk behaviors at baseline but not at 9 months or 18 months follow-up |
| **O'Leary et al. 2014** | USA | Cross-sectional | Black MSM | depression, IPV, CSA, AUD, substance use disorder | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | Experiencing a higher number of syndemic conditions was associated with greater odds of engaging in condomless anal sex and a higher prevalence of self-reported positive HIV status. Optimism and education buffered the relationship between syndemic conditions and self-reported HIV status but other resilience factors (connection to gay community, religiosity, Black pride and income) did not. Furthermore, none of the resilience factors buffered the relationship between syndemic conditions and sexual risk behaviors |
| **OCleirigh et al. 2018** | USA | Cross-sectional |  | substance use, IPV, suicidality, CSA | HIV diagnosis, healthcare use | regression analysis using a summation score | Experiencing syndemic conditions was associated with an increase in medical visits, medical costs and odds of self-reporting a positive HIV status |
| **Oginni et al. 2019** | Nigeria | Cross-sectional |  | depression, substance use, IPV, suicidality, alcohol use, tobacco use, childhood abuse | engaging in sexual risk behaviors | regression analysis using a summation score | Compared to straight men, MSM had greater odds of having experienced childhood adversity, IPV, depressive symptoms and suicidal thoughts. Furthermore experiencing a greater number of syndemic condition was associated with higher odds of engaging in sexual risk behaviors |
| **Ogunbajo et al. 2019** | Nigeria | Cross-sectional |  | depression, substance use, PTSD, AUD, tobacco use | engaging in sexual risk behaviors | regression analysis using a summation score | Association between PTSD and alcohol dependence as well as between alcohol dependence and hard drug use. The number of syndemic conditions was associated with a greater number of male partners but not with inconsistent condom use |
| **Pantalone et al. 2018** | USA | Cross-sectional | MSM living with HIV | IPV, suicidality, CSA, polysubstance use | adherence to antiviral medication, engaging in sexual risk behaviors, healthcare use | regression analysis using a summation score | In this sample of MSM living with HIV, the number of syndemic conditions was associated with ART adherence, having one syndemic condition was associated with inpatient medical admissions in the past year. Serodiscordant condomless anal sex was not associated with the syndemic count variable |
| **Parsons et al. 2012** | USA | Cross-sectional |  | depression, IPV, sexual compulsivity, CSA, polysubstance use | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | Sexual compulsivity was significantly associated with depression and IPV in multivariate analysis, as well as with self-reported positive HIV status and serodiscordant condomless anal sex. Furthermore, experiencing a greater number of syndemic conditions was associated with higher odds of engaging in sexual risk behaviors and reporting a positive HIV status |
| **Parsons et al. 2015** | USA | Cross-sectional |  | depression, IPV, sexual compulsivity, CSA, polysubstance use, hypersexuality | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score, mediation analysis | In this sample of highly sexually active MSM, sexual compulsivity and hypersexuality seemed to act as a syndemic condition associated with an increase in HIV risk rather than as a mediator of syndemic conditions on HIV risk. Furthermore, these findings provide support for a three group conceptualization of hypersexuality and sexual compulsivity (one, both or none) |
| **Parsons et al. 2017** | USA | Cross-sectional |  | depression, IPV, sexual compulsivity, CSA, polysubstance use | engaging in sexual risk behaviors | regression analysis using a summation score | Among a U.S. national sample of MSM, the sum of syndemic conditions was associated with greater likelihood of reporting sexual risk behaviours. Furthermore, MSM living in non-urban areas were more likely to experience sexual compulsivity. |
| **Perry et al. 2019** | USA | Cross-sectional | Adolescent MSM | substance use, CSA, AUD, general mental distress | engaging in sexual risk behaviors | regression analysis using a summation score | Syndemic conditions emerge early in the lifespan and are associated with early sexual experiences. Internalizing symptoms, problematic alcohol use, CSA and marijuana use were highly prevalent and interrelated. |
| **Pitpitan et al. 2016** | Mexico | Cross-sectional |  | depression, substance use, sexual compulsivity, internalised homophobia, violence | engaging in sexual risk behaviors | regression analysis using a summation score, moderation analysis | The number of syndemic conditions was associated with higher odds of engaging in condomless anal sex with a stranger. This effect was more pronounced in MSM who are out to less than 50% of their acquaintances |
| **Quinn et al. 2020** | USA | Longitudinal (18 months) | Latino MSM | incarceration, unstable housing, unemployment, poor healthcare access | engaging in sexual risk behaviors, viral load | regression analysis using a summation score | Experiencing structural syndemic conditions was associated with more sexual risk behaviors, both from HIV-positive and HIV-negative participants as well as with a detectable viral load among HIV-positive participants |
| **Reisner et al. 2016** | USA | Cross-sectional | Transgender MSM | depression, IPV, binge drinking, anxiety, CSA, polysubstance use, childhood abuse | engaging in sexual risk behaviors, STI diagnosis | regression analysis using a summation score, moderation analysis | In this sample of transgender MSM, syndemic conditions were associated with higher odds of engaging in condomless vaginal and/or anal sex and this association was fully moderated by social gender affirmation, suggesting similar sexual risk patterns for TMSM who have socially afirmed their gender identity as for cisgender MSM |
| **Safren et al. 2018** | USA | Longitudinal (6 months) |  | depression, IPV, sexual compulsivity, anxiety, CSA, AUD, substance use disorder | engaging in sexual risk behaviors | regression analysis using a summation score, mediation analysis | Cross-sectional analysis showed an indirect effect of syndemic conditions on condomless sex through lowered condom self-efficacy. However, a full longitudinal model was not supported by the data as changes in condom self-efficacy was not associated with changes in condomless sex |
| **Santos et al. 2014** | International | Cross-sectional |  | depression, substance use, unstable housing, discrimination, poor healthcare access, violence | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | Experiencing a higher number of syndemic conditions was associated with higher odds of engaging in condomless anal sex and self-reported positive HIV status |
| **Scheer et al. 2021** | USA | Cross-sectional |  | suicidality, polysubstance use, AUD, HIV | engaging in sexual risk behaviors | Latent Class Analysis/Latent Profile Analysis | Four classes of syndemic conditions were identified and class membership was associated with HIV risk behaviors. Notably, the MSM concurrently engaging in polysubstance use and living with HIV engaged in more HIV risk behaviors while MSM presenting higher levels of alcohol misuses demonstrated reduced HIV risk behaviors. |
| **Semple et al. 2017** | Mexico | Cross-sectional |  | depression, substance use, PTSD, sexual compulsivity, CSA, AUD, discrimination, sexual risk behaviors, hostility | having experienced sexual violence | multivariate linear regression | There is a high reported frequency of sexual violence among MSM in Tijuana. Furthermore, the authors suggest a model of co-occurring psychosocial factors such as CSA, adult homophobia, depressive symptoms and hostility that increase the odds of sexual violence experiences among MSM |
| **Shuper et al. 2020** | Canada | Cross-sectional |  | depression, substance use, AUD | PrEP-related outcomes | regression analysis using a summation score, significant product term in regression | Problematic alcohol use and cocaine use were found to be additively associated with PrEP nonadherence but no synergy were found between these two conditions. Furthermore, depression was not shown to be associated with PrEP nonadherence in this sample |
| **Stall et al. 2003** | USA | Cross-sectional |  | depression, IPV, CSA, polysubstance use | engaging in sexual risk behaviors, HIV diagnosis | regression analysis using a summation score | A greater number of syndemic conditions was associated with positive HIV status and sexual risk behaviors |
| **Starks 2014** | USA | Cross-sectional |  | depression, IPV, sexual compulsivity, CSA, polysubstance use |  | Latent Class Analysis/Latent Profile Analysis, Confirmatory Factor Analysis | In this study, constraining factor loadings to be equal, as it is done with summary score of syndemic conditions, significantly reduced model fit. In the other hand, a latent class analysis produced two ordinal categories of low syndemic burden and high syndemic burden, which is consistent with an underlying unidimensional syndemic stress factor |
| **Starks et al. 2016** | USA | Cross-sectional |  | depression, IPV, sexual compulsivity, CSA, polysubstance use | engaging in sexual risk behaviors | regression analysis using a summation score | The sum of syndemic conditions experienced by the partners in a couple was associated with condomless sex during first sexual intercourse and with non-disclosure of HIV status prior to first condomless anal sex |
| **Storholm et al. 2011** | USA | Cross-sectional | Young MSM | substance use, alcohol use, tobacco use, sexual risk behaviors, chemsex |  | point-biserial correlation | YMSM who reported smoking cigarettes were more likely to use marijuana, cocaine, inhalant nitrates, ecstasy, methamphetamine, hallucinogens, Adderall/Ritalin without prescription and to use alcohol until intoxication. Furthermore, they were also more likely to ingage in sexual risk behaviors such as use of substance before or during sex |
| **Sullivan and Eaton 2020** | USA | Cross-sectional | Black MSM | depression, substance use, AUD, exchange sex | PrEP-related outcomes | regression analysis using a summation score | MSM with a lower socio-economical status were less likely to be aware of PrEP and experiencing multiple syndemic conditions was associated with reduced odds of using PrEP although, taken independently, these conditions were not associated with PrEP use |
| **Tan et al. 2016** | Canada | Case series |  | depression, AUD, substance use disorder |  | no interaction studied | A high burden of mental health problem was found in this sample of MSM PrEP Users. Using self-administered questionnaire was a feasible and useful strategy for screening those conditions |
| **Tomori et al. 2018** | India | Cross-sectional |  | depression, substance use, IPV, CSA, AUD | engaging in sexual risk behaviors, STI diagnosis | regression analysis using a summation score, Relative Excess Risk due to Interaction (RERI) | There is an additive relationship between the count of syndemic conditions and condomless sex but not with syphilis. As for interaction, RERI were significant only for IPV and depression for condomless anal sex and for alcohol dependence and substance use for syphilis |
| **Tulloch et al. 2015** | Canada | Cross-sectional |  | depression, IPV, polysubstance use | engaging in sexual risk behaviors | regression analysis using a summation score, mediation analysis | The number of syndemic conditions mediated the relationship between childhood physical abuse and sexual risk as well as between verbal victimization and sexual risk |
| **Turpin et al. 2020a** | USA | Cross-sectional | Young MSM | depression, substance use, IPV, bullying, violence | engaging in sexual risk behaviors | Latent Class Analysis/Latent Profile Analysis | A syndemic of victimization, sexual violence, IPV, substance use and depression was identified in a latent profile comprising 1/8th of the sample. This profile was strongly associated with substance use at last sexual intercourse and number of partners but not with condom use. |
| **Turpin et al. 2020b** | USA | Longitudinal (12 months) | Black MSM | depression, substance use, IPV, internalised homophobia, discrimination, poor social support, experience of trauma | substance use | Latent Transition Analysis | Using latent transition analysis, three profiles of high-risk syndemic status with different proportions of syndemic factors and a low risk profile were identified. Moreover, social support strongly moderated the association between these profiles and substance use at 12 months in that BMSM with better social support had more chance to stay in the low risk profile or to transition from high risk to low risk. |
| **Vanden Berghe et al. 2014** | Belgium | Cross-sectional |  | depression, sexual risk behaviors, chemsex | engaging in sexual risk behaviors | moderation analysis | Depressive symptoms and sexual sensation seeking were more present in MSM who engaged in condomless anal sex in the past 6 months while use of alcohol or substance or alcohol just before or during sex was not. However, this study found no evidence that depressive symptoms moderated the effect of risk perception of condomless anal sex on engaging in condomless anal sex. |
| **Walters et al. 2020** | USA | Cross-sectional | MSM living with HIV | depression, IPV, polysubstance use | engaging in exchange sex | regression analysis using a summation score | Exchange sex was associated with being a Black MSM, < 30 years, annual incomes < 20.000$, recent depressive symptoms, polydrug use, stimulant use and having experienced past and present IPV |
| **Wang et al. 2017** | China | Cross-sectional |  | depression, sexual compulsivity, anxiety, loneliness, low self-esteem | engaging in sexual risk behaviors | regression analysis using a summation score | In this sample of MSM living in China, a significant proportion of respondent had at least two syndemic conditions which was associated with higher odds of engaging in condomless anal sex |
| **Wang et al. 2018** | China | Cross-sectional |  | depression, sexual compulsivity, anxiety, poor social support, loneliness, involuntary subordination, low self-esteem | engaging in sexual risk behaviors | regression analysis using a summation score | Syndemic conditions are additively associated with multiple sex partners |
| **Wu Elwin 2018** | USA | Cross-sectional | Black MSM | substance use, IPV, binge drinking, CSA, sexual risk behaviors |  | regression analysis using a summation score | CSA is an important antecedent in the formation of a syndemic in black MSM in the USA |
| **Yu et al. 2013** | China | Cross-sectional |  | depression, substance use, IPV, alcohol use, tobacco use | engaging in sexual risk behaviors | multivariate linear regression | High prevalence of smoking was found in this sample of Chinese MSM and the level of smoking was associated with alcohol use, substance use and depressive symptoms. Furthermore, sexual risk taking was positively associated with smoking, alcohol use, substance use and IPV |
| **Zepf et al. 2020** | USA | Cross-sectional | Older MSM living with HIV | depression, substance use, PTSD, IPV, binge drinking, violence | adherence to antiviral medication | regression analysis using a summation score | Experiencing syndemic conditions is associated with decreased medication adherence ; PTSD and stiulant use had the strongest influence on medication adherence in the final model. |
| **Zhang et al. 2019** | USA | Longitudinal (12 months) | Black MSM | depression, IPV, CSA, AUD, unemployment, substance use disorder | physical activity | regression analysis using a summation score, moderation analysis | Number of syndemic conditions at baseline predicted lower levels of physical activity. No synergistic interaction was found. No evidence of a moderating effect of resilience on the relationship between syndemic conditions and physical activity |

Table 2: Reference table of the included qualitative studies

| **References** | **Location** | **Analysis method** | **Subpopulation** | **Bio-social interaction** | **Key findings** |
| --- | --- | --- | --- | --- | --- |
| **Adam et al. 2017** | Canada | thematic analysis |  |  | Life story interviews of MSM affected by at least two syndemic conditions revealed one major pathway of syndemic production (childhood adversity leading to depression, substance abuse and risk taking) and two minor modes characterised by migration stress or transition stress from home to college or work. Furthermore, risk practice fell into different subjectivities (active and consistent pursuit of condomless sex, lack of assertiveness to a partner's initiative of CAS and combination of risk reduction strategies) |
| **Adam et al. 2018** | Canada | comparative |  |  | Some of the men interviewed in this study found safety from family in school but a more sizeable part encoutered bullying which compounded their distress at home. Furthermore, some found refuges from hostile home and school environment through books, pop culture and internet chat. Finally, during adolescence a subset of men experienced sexual relationships with older men who brought emotional stability and personal growth |
| **Bruce et al. 2011** | USA | thematic analysis, cross case analysis | Young MSM living with HIV |  | The results of this study suggests links between experiences of marginalization in childhood/aolescence and subsequent search for gay peers and migration to larger city and/or gay neighboorhood. This migration exposes YMSM to a range of risk factors such as experimentation with substance and sex. Compared to straight youth, this risk may be heightened due to lack of support. On the other hand, access to gay spaces also offers resilience resources such as a sense of community and peer support. |
| **Cassels et al. 2020** | USA | thematic analysis | Latino & Black MSM |  | Geographic mobility represents a syndemic condition in itself as it was found to magnify many HIV risk factors such as racism, lack of social cohesion or place attachement, barriers to HIV care and high-risk sexual encounters. When, geographic mobility was tied with housing instability, its direct contribution to the syndemic was found to be above and beyond its role in housing insecurity |
| **Chakrapani et al. 2019** | India | framework analysis |  | Multiple forms of intersecting stigma (i.e. same-sex sexuality, gender non-conformity, sex work and socio-economic stigmas) contribute to the production of syndemic conditions (i.e. depression, suicidality, internalized homonegativity, violence and problematic alcohol use as a coping strategy) which in turn increase HIV risk. Family support and communities of MSM may serve as a resilience resource and counteract the negative effects of stigma and syndemic conditions. | Intersecting stigma related to same-sex attraction, gender non-conformity and sex work contribute to the production of syndemic conditions which may in turn increase sexual risk behaviors. Family and community of MSM may serve as resilience and counteract the effects of stigma and syndemic conditions |
| **Lyons et al. 2013** | USA | grounded theory | Young MSM living with HIV | The marginalization of YMSM within their school, communities of origin and families result in a lack of gay-specific HIV prevention education, role model and productive goal-related activities, all of them being linked to HIV infection. | Alcohol use, substance use, marginalization, family rejection, lack of social support and lack of gay-specific HIV prevention as well as role models contributed to the HIV infection in YMSM. |
| **Maionara et al. 2020** | USA | thematic analysis | Young Black MSM | Economic dependency and fear of violence may maintain YBMSM in dysfunctional relationships plagued by intimate partner violence and substance abuse which increase their odds of incarceration and HIV infection. Their criminal records may then prevent YBMSM from achieving formal employment. Methamphetamine is a way of coping with this structural violence and eventual HIV diagnosis but represents a potential factor in transmitting HIV to others, notably during sex parties. | Methamphetamine use, intimate partner violence and incarceration may form a syndemic in the lives of young black men who have sex with men, increasing their vulnerability of acquiring or transmitting HIV |
| **Pollard et al. 2018** | England | framework analysis |  | Maladaptive coping strategies to minority stress and the performative resistant space of the gay scene contribute to chemsex use and HIV risks | The experience of chemsex and HIV-risk is entangled in complex narratives in which drug use is related to marginalisation, loneliness and a gay scene that acted both as a space of personal affirmation and resistance and as a barrier to fulfilling psychosocial needs such as meaningful emotional conections. |
| **Quinn 2019** | USA | thematic content analysis | Black MSM | Intersectional structural violence (e.g. racial neighborhood segregation, poverty, unemployment, violence, unstable housing, incarceration and poor healthcare access) leads to expectations surrounding masculinity which conflicts with the sexual orientation of BMSM and results in internalized homophobia. Internalized homophobia, in turn, produce poor mental health, suicidal ideation as well as substance abuse and sexual risk taking as a coping mechanism. Furthermore, the use of PrEP, perceived as a “gay pill” is less often considered. This all leads to an increase in HIV infection. | Intersectionality provides the context needed to understand syndemics among BMSM, which differs from syndemics among white MSM due to intersecting stigma and harmful social conditions unique to BMSM. These structural inequities, notably racial neighborhood segregation, shape the expectations surrounding masculinity, which result in societal and internalized homophobia, producing distress, depression, suicidal ideation, substance use and HIV risk behavior. |
| **Reed et al. 2016** | USA | analytic induction | Young Black MSM |  | Young Black MSM experimenting syndemic conditions have more conflicted identities, notably between their racial and sexual identities, and are disconnected both from their family and the gay community. Sense of community may thus be an important mediator between adversity and syndemics |

Table 3: Reference table of the included reviews

| **References** | **Design** | **Purpose of the review** | **Number of included studies** | **Key findings** |
| --- | --- | --- | --- | --- |
| **Lassiter et al. 2016** | Systematic review | Examining the effects of spirituality and religion on MSM's health and proposing a framework for integrating these factors into HIV research with MSM | 9 | Religion and spirituality have mixed effect on syndemic conditions of MSM but may be more beneficial for the health of MSM of color than for white MSM. All in all, religion and spirituality was completey absent from syndemic quantitative research and very sparse in syndemic conditions research focused on MSM |
| **Lewis and Wilson 2017** | Systematic review | Examine the HIV prevalence and associated risk behaviours among migrant and ethnic minority MSM in North America and Europe | 24 | Ethnic minority MSM are faced with high rates of HIV prevalence and associated risk factors such as substance use and condomless anal sex. Furthermore, the high prevalence of these factors in samples comprised mostly or entirely of immigrant MSM gives credit to the hypothesis that transational migration is part of a syndemic. |
| **Pantalone et al. 2020** | Systematic review and meta-analysis | To have a better understanding of the state of interventions co-targeting interrelated syndemic conditions and HIV-related health behaviors of sexual minority men | 43 | The meta-analysis showed a small significant positive effect of combined behavioral interventions to improve syndemic conditions (mental health, drug and alcohol use ; d=0.20) and sexual risk behaviors (d=0.16) with significant heterogeneity. More sessions (9 or more) and individual rather than group interventions showed grater efficacy. |
| **Rooney et al. 2018** | Meta-analysis | (1) Determine which syndemic conditions are significantly associated with sexual compulsivity among MSM ; (2) calculate the mean effect size of these conditions with sexual compulsivity; (3) determine if this effect varies as a function of the type of syndemic condition | 36 | Sexual compulsivity was significantly associated with 7 syndemic indicators (anxiety, depression, childhood sexual abuse, alcohol use, substance use, interpartner violence and sexual risk. The two strongest associations were with depression and anxiety |
| **Woodward et al. 2016** | Systematic review | Identify a set of resilience ressources among MSM burdened with minority stress and psychosocial conditions which may improve HIV prevention | 20 | 31 resilience ressources were identified, with the most frequently cited being social support and incomes. Most of these resources were associated with a lower HIV risk. |

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### B. Measurement tables

Table 4: Summary of the studies including depression or depressive symptoms as a syndemic condition and the criteria used to screen this condition

| **Use of a scale or a criteria** | **Number of studies** | **Scale or criteria used** | **Number of studies** | **Cutoff used** | **References** |
| --- | --- | --- | --- | --- | --- |
| Scale | 66 | CESD | 24 | 16 | **Zhang et al. 2019** |
| **Morrison et al. 2018** |
| **Wang et al. 2017** |
| **Friedman et al. 2016** |
| **Tulloch et al. 2015** |
| **Friedman et al. 2015** |
| **Herrick et al. 2014** |
| **Herrick et al. 2013** |
| **Dyer et al. 2012** |
| **Tan et al. 2016** |
| **Ng et al. 2020** |
| 22 | **Vanden Berghe et al. 2014** |
| 23 | **Wang et al. 2018** |
| **Parsons et al. 2017** |
| **Hart et al. 2017** |
| **Li et al. 2016** |
| **Starks 2014** |
| **Jie et al. 2012** |
| **Parsons et al. 2012** |
| **Stall et al. 2003** |
| 27 | **Carrico et al. 2018** |
| Continuous | **Hugh Klein 2011** |
| **Turpin et al. 2020b** |
| **Dyer et al. 2020** |
| CESD-10 | 10 | 10 | **Chandler et al. 2020a** |
| **Ogunbajo et al. 2019** |
| **Chandler et al. 2020b** |
| **Martinez et al. 2016** |
| **Biello et al. 2016** |
| **Mimiaga et al. 2015a** |
| **Biello et al. 2014** |
| **Shuper et al. 2020** |
| **Chandler et al. 2020c** |
| **Sullivan and Eaton 2020** |
| PHQ-9 | 8 | 10 | **Zepf et al. 2020** |
| **Nostlinger et al. 2020** |
| **Harkness et al. 2019** |
| **Tomori et al. 2018** |
| 15 | **McDaid et al. 2019** |
| 5 | **Chakrapani et al. 2020** |
| **Safren et al. 2018** |
| Having at least 5 positive items in addition to the depressed mood and/or loss of interest items | **Harkness et al. 2018** |
| BDI-II | 5 | 16 | **Halkitis et al. 2012** |
| 17 | **Pitpitan et al. 2016** |
| Continuous | **Semple et al. 2017** |
| **Halkitis et al. 2015** |
| **Halkitis et al. 2013** |
| Depression subscale of the Brief Symptom Inventory | 4 | 0.5 (raw-score) | **Parsons et al. 2015** |
| 0.8 (raw score) | **Muñoz-Laboy et al. 2018** |
| 65 (T-score) | **Starks et al. 2016** |
| Not specified | **Moeller et al. 2011** |
| PHQ-2 | 3 | 3 | **Walters et al. 2020** |
| **Hirshfield et al. 2015** |
| **Santos et al. 2014** |
| PHQ-8 | 3 | 10 | **Blashill et al. 2020** |
| Continuous | **Lee et al. 2020a** |
| **Lee et al. 2020b** |
| HADS | 2 | 10 | **Card et al. 2018** |
| 8 | **Achterbergh et al. 2021** |
| Zung Self Rating Depression Scale | 2 | 0.5 | **Jiang et al. 2020** |
| 40 | **Oginni et al. 2019** |
| BDI-FS | 1 | 7 | **Chakrapani et al. 2017** |
| CESD-12 | 1 | 10 | **Yu et al. 2013** |
| CESD-5 | 1 | 1 | **O'Leary et al. 2014** |
| CESD-SF | 1 | 13 | **Mimiaga et al. 2015b** |
| The Depression Symptom Scale (DSS-9) | | | **Friedman et al. 2014** |
| Criteria | 10 | Being on medication for depression in the last 12 months | | | **Ferlatte et al. 2015** |
| **Brandstrom and Pachankis 2018** |
| **Ferlatte et al. 2018b** |
| Clinical diagnosis based on the DSM-IV | | | **Batchelder et al. 2019** |
| **Mustanski et al. 2017** |
| During the past 12 months having felt so sad or hopeless almost every day for 2 weeks in a row that the respondent stopped doing some usual activities | | | **Turpin et al. 2020a** |
| **Mustanski 2014** |
| Feeling snap and unable to snap out of it for most of the time or being in treatment for depression | | | **Ferlatte et al. 2014** |
| Medical diagnosis of depression in the EMR | | | **Byg et al. 2016** |
| Self-report of a medical diagnosis | | | **Reisner et al. 2016** |

Table 5: Summary of the studies including intimate partner violence as a syndemic condition and the criteria used to screen this condition

| **Use of a scale or a criteria** | **Number of studies** | **Type(s) of violence screened or scale used** | **Number of studies** | **Reference period or cutoff used** | **References** |
| --- | --- | --- | --- | --- | --- |
| Criteria | 38 | physical IPV, sexual IPV, psychological IPV | 12 | Past year | **Oginni et al. 2019** |
| Past 6 months | **Turpin et al. 2020b** |
| Past 5 years | **Biello et al. 2016** |
| **Starks et al. 2016** |
| **Mimiaga et al. 2015a** |
| **Parsons et al. 2015** |
| **Stall et al. 2003** |
| **Achterbergh et al. 2021** |
| Lifetime | **Lee et al. 2020a** |
| **Safren et al. 2018** |
| **Mustanski et al. 2007** |
| **Dyer et al. 2020** |
| physical IPV, psychological IPV | 8 | Past 5 years | **Starks 2014** |
| **Herrick et al. 2013** |
| **Dyer et al. 2012** |
| **Parsons et al. 2012** |
| Past 12 months | **McDaid et al. 2019** |
| **Ferlatte et al. 2018a** |
| Not specified | **Jie et al. 2012** |
| Lifetime | **Walters et al. 2020** |
| physical IPV | 7 | Past month | **Mustanski 2014** |
| Past 4 months | **Eaton et al. 2013** |
| Past 12 months | **Chandler et al. 2020a** |
| **Chandler et al. 2020b** |
| **Chandler et al. 2020c** |
| Lifetime | **Tomori et al. 2018** |
| **Tulloch et al. 2015** |
| physical IPV, sexual IPV | 6 | Past 6 months | **Mustanski et al. 2017** |
| Lifetime | **Turpin et al. 2020a** |
| **OCleirigh et al. 2018** |
| **O'Leary et al. 2014** |
| **Ng et al. 2020** |
| **Reisner et al. 2016** |
| physical IPV, sexual IPV, psychological IPV, gay-related IPV | 2 | Past 5 years | **Jiang et al. 2020** |
| Lifetime | **Chuang et al. 2018** |
| Not specified | 2 | Not specified | **Byg et al. 2016** |
| Lifetime | **Beymer et al. 2016** |
| physical IPV, sexual IPV, psychological IPV, gay-related IPV, HIV-related IPV | 1 | Past month | **Wu Elwin 2018** |
| Scale | 7 | HITS | 3 | Continuous | **Lee et al. 2020b** |
| 11 | **Zepf et al. 2020** |
| **Blashill et al. 2020** |
| CTS2 | 3 | Responding yes to at least one item | **Parsons et al. 2017** |
| Not specified | **Zhang et al. 2019** |
| Continuous | **Pantalone et al. 2018** |
| Authors' scale (physical and psychological) | 1 | continuous | **Yu et al. 2013** |
| Physical intimate partner violence: 36 studies ; 80% of studies with IPV as a syndemic condition | | | | | |
| Psychological intimate partner violence: 23 studies ; 51% of studies with IPV as a syndemic condition | | | | | |
| Sexual intimate partner violence: 21 studies ; 47% of studies with IPV as a syndemic condition | | | | | |
| Gay-related intimate partner violence: 3 studies ; 7% of studies with IPV as a syndemic condition | | | | | |
| HIV-related intimate partner violence: 1 studies ; 2% of studies with IPV as a syndemic condition | | | | | |

Table 6: Summary of the studies including substance use as a syndemic condition and the substances specifically screened in the studies

| **Type of substances screened** | **Number of studies** | **Reference period** | **References** |
| --- | --- | --- | --- |
| stimulants | 6 | Past month | **Zepf et al. 2020** |
| Past 6 months | **Mimiaga et al. 2015b** |
| **Herrick et al. 2013** |
| **Dyer et al. 2020** |
| Past 3 months | **Harkness et al. 2019** |
| **Harkness et al. 2018** |
| stimulants, ecstasy, hallucinogens, depressants | 4 | Past 4 months | **Moeller et al. 2011** |
| Past 12 months | **Ferlatte et al. 2015** |
| **Ferlatte et al. 2018a** |
| **Ferlatte et al. 2018b** |
| stimulants, marijuana, opioids | 3 | Past month | **Semple et al. 2017** |
| Past 3 months | **Wu Elwin 2018** |
| Lifetime | **Oginni et al. 2019** |
| stimulants, ecstasy, hallucinogens, marijuana, depressants, opioids, inhalants | 3 | Past month | **Halkitis et al. 2015** |
| **Halkitis et al. 2013** |
| Past 3 months | **Storholm et al. 2011** |
| stimulants, opioids | 2 | Past 6 months | **OCleirigh et al. 2018** |
| **Tomori et al. 2018** |
| not\_specified | 2 | Past month | **Biello et al. 2014** |
| Past 12 months | **Santos et al. 2014** |
| marijuana | 2 | Past month | **Blashill et al. 2020** |
| Lifetime | **Perry et al. 2019** |
| stimulants, marijuana, inhalants | 1 | Past 4 months | **Eaton et al. 2013** |
| stimulants, marijuana | 1 | Past month | **Mustanski 2014** |
| stimulants, inhalants | 1 | Past 3 months | **Sullivan and Eaton 2020** |
| stimulants, hallucinogens, marijuana, depressants, inhalants | 1 | Lifetime | **Shuper et al. 2020** |
| stimulants, hallucinogens, depressants, opioids, inhalants | 1 | Past 3 months | **Lee et al. 2020a** |
| stimulants, hallucinogens, depressants, opioids | 1 | Past month | **Lee et al. 2020b** |
| stimulants, hallucinogens, depressants, NPS, opioids | 1 | Lifetime | **Ogunbajo et al. 2019** |
| stimulants, hallucinogens, depressants, NPS | 1 | Past 3 months | **Nostlinger et al. 2020** |
| stimulants, ecstasy, opioids, inhalants | 1 | Past 6 months | **Dyer et al. 2012** |
| stimulants, ecstasy, NPS, opioids | 1 | Lifetime | **Turpin et al. 2020a** |
| stimulants, ecstasy, marijuana, depressants, opioids | 1 | **Yu et al. 2013** |
| stimulants, ecstasy, marijuana | 1 | **Li et al. 2016** |
| stimulants, ecstasy, inhalants | 1 | Past 12 months | **Beymer et al. 2016** |
| stimulants, ecstasy, hallucinogens, marijuana, depressants, opioids | 1 | Past month | **Hugh Klein 2011** |
| stimulants, ecstasy, hallucinogens, marijuana, depressants | 1 | Past 12 months | **Mustanski et al. 2007** |
| stimulants, ecstasy, hallucinogens, depressants, opioids, inhalants | 1 | Lifetime | **Pitpitan et al. 2016** |
| stimulants, ecstasy, hallucinogens, depressants, opioids | 1 | Past 3 months | **Herrick et al. 2014** |
| stimulants, ecstasy, hallucinogens, depressants, inhalants | 1 | Past 4 months | **Guadamuz et al. 2014** |
| stimulants, depressants, opioids, inhalants | 1 | Past 6 months | **Turpin et al. 2020b** |
| marijuana, opioids | 1 | Past 12 months | **Chakrapani et al. 2019b** |
| marijuana, inhalants | 1 | Past month | **Halkitis et al. 2012** |
| Stimulants : cocaine/crack, amphetamine (37 studies ; 86%) | | | |
| Ecstasy (17 studies ; 40%) | | | |
| Hallucinogens : ketamine, psilocybine, phencyclidine (17 studies ; 40%) | | | |
| Marijuana (17 studies ; 40%) | | | |
| Depressants : GHB/GBL, benzodiazebines (19 studies ; 44%) | | | |
| NPS : New Psychoactive Substances : synthetic cannabinoids, cathinones (3 studies ; 7%) | | | |
| Opioids : opioids misuse, heroin (19 studies ; 44%) | | | |
| Inhalants : nitrous oxyde, Popper : (13 studies ; 30%) | | | |

Table 7: Summary of the studies including childhood sexual abuse as a syndemic condition and the criteria used to screen this condition

| **Use of a scale or a criteria** | **Number of studies** | **Scale or criteria used1** | **Number of studies** | **Cutoff used** | **References** |
| --- | --- | --- | --- | --- | --- |
| Definition | 28 | Finkelhor definition | | | **Lee et al. 2020a** |
| **Blashill et al. 2020** |
| **Lee et al. 2020b** |
| **Harkness et al. 2019** |
| **Safren et al. 2018** |
| **Harkness et al. 2018** |
| **Mimiaga et al. 2015b** |
| Any unwanted sexual experience before 18 years old | | | **Semple et al. 2017** |
| **Biello et al. 2016** |
| **Starks et al. 2016** |
| **Mimiaga et al. 2015a** |
| **Biello et al. 2014** |
| **Ng et al. 2020** |
| Any unwanted sexual experience before 17 years old with someone at least 10 years older | | | **Parsons et al. 2015** |
| **Starks 2014** |
| **Parsons et al. 2012** |
| **Stall et al. 2003** |
| Any unwanted sexual experience before 15 years old | | | **OCleirigh et al. 2018** |
| **Reisner et al. 2016** |
| Having experienced unwanted sexual activity with someone older at 16 years old or younger | | | **Parsons et al. 2017** |
| Having experienced sexual abuse as a child | | | **Eaton et al. 2013** |
| Any unwanted sexual experience before 17 years old | | | **Martinez et al. 2016** |
| Any unwanted sexual experience before 16 years old with someone at least 5 years older | | | **Jie et al. 2012** |
| Any unwanted sexual experience before 16 years old | | | **Tomori et al. 2018** |
| Any unwanted sexual experience before 13 years old | | | **Mustanski et al. 2017** |
| Any sexual experience before 13 years old with someone at least 4 years older | | | **Muñoz-Laboy et al. 2018** |
| Any sexual experience before 12 years old, any unwanted sexual experience between 12 years old and 16 years old or any sexual experience with an adult or someone at least 5 years older before 16 years old | | | **Jiang et al. 2020** |
| Any sexual experience before 11 years old, any unwanted sexual experience between 11 years old and 17 years old or any sexual experience with someone at least 4 years older before 17 years old | | | **Wu Elwin 2018** |
| Scale | 6 | CTQ Sexual Abuse subscale | 3 | 5 | **Perry et al. 2019** |
| **Hart et al. 2017** |
| 13 | **Carrico et al. 2018** |
| WSHQ-CSA | 2 |  | **Zhang et al. 2019** |
| **O'Leary et al. 2014** |
| Sexual abuse subscale of the Childhood Maltreatment Interview Schedule - Short Form (CMIS-SF) | 1 | Endorsement of any one item | **Pantalone et al. 2018** |
| 1Finkelhor definition : any sexual experience before 13 years old with someone at least 5 years older or any sexual experience between 13 and 17 years old with someone at least 10 years older (Finkelhor 1994) | | | | | |

Table 8: Summary of the studies including polysubstance use as a syndemic condition and the criteria used to screen this condition

| **Number of substances to qualify as polysubstance use** | **Number of studies** | **Inclusion of marijuana in the substances count** | **Reference period** | **References** |
| --- | --- | --- | --- | --- |
| At least 3 categories of substance use | 16 | Marijuana not included | Past month | **Blashill et al. 2020** |
| Past 3 months | **Chandler et al. 2020a** |
| **Chandler et al. 2020b** |
| Past 12 months | **Pantalone et al. 2018** |
| Marijuana included | Past 6 weeks | **Parsons et al. 2015** |
| Past 6 months | **Card et al. 2018** |
| **Tulloch et al. 2015** |
| **Stall et al. 2003** |
| Past 4 months | **Muñoz-Laboy et al. 2018** |
| Past 3 months | **Harkness et al. 2019** |
| **Harkness et al. 2018** |
| **Parsons et al. 2017** |
| **Starks 2014** |
| **Parsons et al. 2012** |
| Past 2 months | **Hirshfield et al. 2015** |
| Past 12 months | **Reisner et al. 2016** |
| More than one category of substance use | 9 | Marijuana not included | Past 3 months | **Walters et al. 2020** |
| **Hart et al. 2017** |
| Marijuana included | Past 6 months | **Mustanski et al. 2017** |
| **Friedman et al. 2016** |
| **Friedman et al. 2015** |
| **Jie et al. 2012** |
| Past 3 months | **Starks et al. 2016** |
| **Scheer et al. 2021** |
| **Chandler et al. 2020c** |
| At least 3 categories of substance, excluding stimulants | 1 | Marijuana included | Past 6 months | **Mimiaga et al. 2015b** |

Table 9: Summary of the studies including binge drinking as a syndemic condition and the criteria used to screen this condition

| **Number of episodes to qualify as binge drinking** | **Number of studies** | **Reference period** | **References** |
| --- | --- | --- | --- |
| At least one episode | 12 | Past month | **Blashill et al. 2020** |
| **Martinez et al. 2020** |
| **Martinez et al. 2016** |
| **Herrick et al. 2014** |
| Past 6 months | **Mustanski et al. 2017** |
| **Jie et al. 2012** |
| **Dyer et al. 2012** |
| **Reisner et al. 2016** |
| **Dyer et al. 2020** |
| Past 3 months | **Lee et al. 2020a** |
| **Wu Elwin 2018** |
| Past 12 months | **Zepf et al. 2020** |
| At least one per week, every week | 4 | Past 3 months | **Harkness et al. 2019** |
| **Harkness et al. 2018** |
| Past 12 months | **Mustanski et al. 2007** |
| **Ferlatte et al. 2018b** |
| At least one per month | 2 | Past 12 months | **Chandler et al. 2020a** |
| **Chandler et al. 2020b** |
| More than one per week, every week | 2 | Past 12 months | **Brandstrom and Pachankis 2018** |
| **Ferlatte et al. 2018a** |
| At least 3 episodes | 1 | Past month | **Mustanski 2014** |
| Having at least 4 drinks everyday or at least 6 drinks on a typical drinking day | 1 | Not specified | **Mimiaga et al. 2015b** |

Table 10: Summary of the studies including violence as a syndemic condition and the criteria used to screen this condition

| **Type(s) of violence screened** | **Number of studies** | **violence\_period** | **References** |
| --- | --- | --- | --- |
| sexual | 5 | Past 4 months | **Eaton et al. 2013** |
| Lifetime | **Turpin et al. 2020a** |
| **Guadamuz et al. 2014** |
| **Biello et al. 2014** |
| **Mustanski et al. 2007** |
| physical, sexual, psychological | 4 | Past 12 months | **Friedman et al. 2014** |
| Lifetime | **Pitpitan et al. 2016** |
| **Buttram et al. 2015** |
| **Kurtz et al. 2012** |
| physical, sexual | 2 | Past 12 months | **Chakrapani et al. 2019b** |
| Lifetime | **Zepf et al. 2020** |
| physical | 2 | Past 12 months | **Chandler et al. 2020c** |
| Lifetime | **Brandstrom and Pachankis 2018** |
| physical, sexual harassment by police, physical harassment by police | 1 | Not specified | **Chakrapani et al. 2017** |
| physical, psychological | 1 | Past 12 months | **Santos et al. 2014** |
| Physical violence: 10 studies ; 22% of studies with violence as a syndemic condition | | | |
| Psychological violence: 5 studies ; 11% of studies with violence as a syndemic condition | | | |
| Sexual violence: 11 studies ; 24% of studies with violence as a syndemic condition | | | |
| Physical harassment by the Police: 1 studies ; 2% of studies with violence as a syndemic condition | | | |
| Sexual harassment by the Police: 1 studies ; 2% of studies with violence as a syndemic condition | | | |

Table 11: Summary of the studies including anxiety as a syndemic condition and the criteria used to screen this condition

| **Type of anxiety disorder screened, if specified** | **Number of studies** | **Criteria or scale used** | **Number of studies** | **Reference period or cutoff used** | **References** |
| --- | --- | --- | --- | --- | --- |
| not specified | 5 | Being on medication for anxiety | 2 | Past 12 months | **Ferlatte et al. 2015** |
| **Ferlatte et al. 2018b** |
| BSI | 1 | Not specified | **Moeller et al. 2011** |
| Self-report of having an anxiety disorder | 1 |  | **Reisner et al. 2016** |
| HADS | 1 | 8 | **Achterbergh et al. 2021** |
| generalized anxiety disorder | 4 | GAD-7 | 4 | 10 | **McDaid et al. 2019** |
| **Wang et al. 2018** |
| **Wang et al. 2017** |
| **Li et al. 2016** |
| social phobia, panic disorder, generalized anxiety disorder | 3 | MINI-SPIN, PHQ | 2 |  | **Harkness et al. 2019** |
| **Harkness et al. 2018** |
| Clinical diagnosis based on the DSM-IV | 1 | **Batchelder et al. 2019** |
| social phobia | 2 | SPIN | 2 | 19 | **Lee et al. 2020a** |
| **Safren et al. 2018** |