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

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# Abstract

# Introduction

## Background

Men who have sex with men (MSM) represent a vulnerable population disproportionately affected by numerous health conditions. First, they represent 70% of new HIV diagnoses [Center for Disease Control and Prevention](#X4cf13d81533c7b267d16e8ce422f52a6b94e857) ([2020](#X4cf13d81533c7b267d16e8ce422f52a6b94e857)) in the United States of America and more than half of new HIV diagnoses in European Union/European Economic area [European Centre for Disease Prevention and Control and WHO Regional Office for Europe](#Xe9d1574ea3592c13d78cb3440bd26eb0dba677a) ([2019](#Xe9d1574ea3592c13d78cb3440bd26eb0dba677a)). They are also more prone to contract other sexually transmitted diseases and *Nesseria Gonorrhea* strains from MSM exhibit higher antimicrobial resistance [Centers for Disease Control and Prevention](#Xac65d4e2802ef6640efb692e7711ad3535446e3) ([2019](#Xac65d4e2802ef6640efb692e7711ad3535446e3)). Furthermore, mental health conditions such as depression, anxiety, suicide attempts or self-harm are more prevalent among MSM ([Liu et al., 2019](#ref-Liu2019); [Luo et al., 2017](#ref-luo2017); [Ross et al., 2018](#ref-ross2018)) and substance use is more common than for their straight counterpart [Medley et al.](#ref-Medley2016) ([2016](#ref-Medley2016)). Moreover, those adverse and oftentimes preventable health outcomes are enmeshed with structural disadvantages such as violence, stigma, discrimination ([Collier et al., 2013](#ref-collier2013); [Lea et al., 2014](#ref-Lea2014); [Lee et al., 2016](#ref-Lee2016)) as well as with poverty, unemployment, unstable housing and poor healthcare access ([Ayhan et al., 2020](#ref-ayhan2020); [Closson et al., 2018](#ref-closson2018))

For more than twenty years, syndemic theory have provided a framework to examine these interrelations between social conditions, mental health and physical health [Singer et al.](#ref-singer2017) ([2017](#ref-singer2017)). Described for the first time in 1996 by Merrill Singer [Singer](#ref-singer1996) ([1996](#ref-singer1996)), a syndemic consists in two more interacting epidemics producing an excess burden in a population because of harmful social conditions [Singer and Clair](#ref-singer2003) ([2003](#ref-singer2003)). To speak of a syndemic, three conditions must be met [Mendenhall and Singer](#ref-mendenhall2020) ([2020](#ref-mendenhall2020)) :

1. Two or more conditions cluster in a given population
2. This clustering is due to an adverse social context such as poverty or stigmatization
3. There is some form of biological, social and/or behavioral interaction between the conditions, significantly worsening the health of the affected population

Syndemic is thus an holistic framework, describing interactions both between diseases themselves and between diseases and the social environment contributing to their emergence, clustering and spread [Singer et al.](#ref-singer2017) ([2017](#ref-singer2017)). As such its value for studying the health of marginalized population such as MSM is undeniable.

## Rationale

However, this theory is not without its flaws. A systematic review conducted in 2015 showed the inadequacy of most of the literature in supporting one of its core tenet [Tsai and Burns](#ref-tsai2015) ([2015](#ref-tsai2015)). Indeed, this paper by Tsai and colleagues demonstrated that, although synergistic interaction between diseases lies in the core of the theory, most papers failed to use relevant statistics to demonstrate the existence of a synergy. More recently, a scoping review published in 2020 confirmed this finding as most recently-published citations failed to describe the interactions between diseases needed to account for a true syndemic [Singer et al.](#ref-Singer2020) ([2020](#ref-Singer2020)). Scholars in the field have been calling for a greater clarity in the use of the concept and urged for researchers to describe more precisely the interactions they observe between health conditions ([Singer et al., 2021](#ref-singer2021) ; [Mendenhall and Singer, 2020](#ref-mendenhall2020)).

However, to our knowledge none of the existing reviews or recommendations were focused on syndemic literature applied specifically on MSM. We thus sought to fill this gap by publishing the first scoping review dedicated to this important topic. Doing so, our goals were to map :

1. the study design used ;
2. the subpopulations of MSM studied ;
3. the psychosocial conditions considered as forming a syndemic and how they were measured;
4. the outcomes studied;
5. the statistics used to evaluate the concept of interaction;
6. the hypothesis for biological and sociobiological interactions proposed by the authors, when available;
7. relevant frameworks that may compliment syndemic theory to better understand the health of MSM and
8. the key findings of these studies

With these data, we wanted to better comprehend the state of the art in the current literature, identify knowledge gaps and suggest recommendations to guide future research in the field.

# Methodology

The complete protocol of this scoping review was already published elsewhere [Anonymous 2020].

Briefly, we applied the framework suggested by Arskey and O’Malley [Arksey and O’Malley](#ref-arksey2005) ([2005](#ref-arksey2005)), with enhancements from Levac et al. [Levac et al.](#ref-levac2010) ([2010](#ref-levac2010)). We also took into account the recommendations formulated by Colqhoun et al. [Colquhoun et al.](#ref-colquhoun2014) ([2014](#ref-colquhoun2014)) and the updated guidance by Peters and colleagues [Peters et al.](#ref-peters2020) ([2020](#ref-peters2020)). We also followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses etension for Scoping Reviews (PRISMA-ScR) [Tricco et al.](#ref-Tricco2018) ([2018](#ref-Tricco2018)). The completed checklist can be found in [Table 1](#PRISMA-ScR) of the supplementary materials.

Screening and data charting was completed using DistillerSR (Evidence Partners, Ottawa, Canada). Scripts, statistics, charts, tables and the present paper was generated using R [R Core Team](#ref-rcoreteam2020) ([2020](#ref-rcoreteam2020)), RStudio [RStudio Team](#ref-rstudioteam2020) ([2020](#ref-rstudioteam2020)) and appropriate packages. To ensure the complete transparency and reproducibility of this article, our data manager uploaded every data used to generate this article on Open Science Framework (DOI : [masked for the anonymity of the review])

Our main research question, *“What is known about Syndemic Theory applied to MSM”* was subdivided into three sub-questions :

1. *“How are studies concerning Syndemic Theory applied to MSM conducted ?”*;
2. *“How is the concept of interaction explored in syndemic research applied to MSM ?”* and
3. *“What were the key findings of these studies ?”*.

To answer those questions, we conducted a systematic search strategy in the following databases : Medline, PsycInfo, Scopus, Cochrane Central Register of Controlled Trials and ProQuest Sociological Abstracts using complex search equations to include every synonym for “men who have sex with men.” The complete search strategy for every database can be found in the Supplementary Material of our protocol. No date limit was applied given the relative novelty of the syndemic literature. A first search using this strategy was conducted the 11th of June 2020 and was subsequently updated on the 09th of February 2021 and finally on the 09th of November 2021.

Search results were downloaded into .RIS files and imported into DistillerSR. After duplicate removal, we screened the title and abstracts for eligibility, using forms generated with DistillerSR by the authors. Articles that met the inclusion criteria or for which eligibility was unclear passed through a second wave in which the full texts were assessed for eligibility. As per protocol, 10% of the titles and abstracts were screened by two reviewers. A Kappa inter-rater reliability score was computed using DistillerSR and was equal to 0.86. As it exceeded our cutoff of 0.8, the rest of the screening process was conducted by the main investigator only. Research were included if they met the following criteria :

* MSM were either the only population studied in the paper or, if studied alongside other populations, such as transgender women, disaggregated data must have been available for MSM
* Syndemic framework was the main focus of the study
* Studies were cohort, case-control, cross-sectional, controlled trials, mixed studies, qualitative studies, systematic reviews or meta-analyses. We excluded letters, commentaries, conference abstracts, editorials or narrative reviews
* Language was English
* The article was published in a peer-reviewed journal

After inclusion of relevant studies, we hand-searched the reference lists to manually add pertinent studies. The same selection process was then applied and these papers are marked as “Additional records identified through other sources” in the study selection flow diagram.

Data charting was also performed using forms generated in DistillerSR by the authors. The complete list of all variables for which data were sought can be found in our protocol. Furthermore, the README file of our *Data* subdirectory contains an exhaustive definition of every variable included. Two departures were made from our initial protocol :

1. We included a variable to chart any additional framework the authors might have used
2. We included variables to chart data for systematic reviews and meta-analyses. These two kind of studies were omitted from our initial protocol as we were not aware of the existence of systematic reviews on syndemic theory applied to MSM by the time we published the protocol. The variables included were general characteristics (authors, year, location, design, total sample size), purpose of the review, number of studies included, hypothesis for biological or bio-social interaction, key findings and additional framework.

Data was then collated, summarised and reported using R, RStudio and relevant packages. Charts were generated to better visualize year of publication, location, population and syndemic conditions studied. Tables were generated to summarise the main variables of every article as well as the measurement methods of the most studied syndemic conditions. These tables can be found respectively in part B and C of the supplementary materials of this paper. Unfortunately, due do time constraints, we did not create any evidence map. However, we generated a SQL database alongside our data. This database contains every study included and provide scholars in the field the opportunity to search relevant studies using complex queries (e.g. to find every study using the CESD to measure depression on Black MSM between 2014 and 2021).

# Results

This section summarizes the findings relevant to our aforementioned research questions. [Table 2](#RefTabQuant), [Table 3](#RefTabQual) and [Table 4](#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)

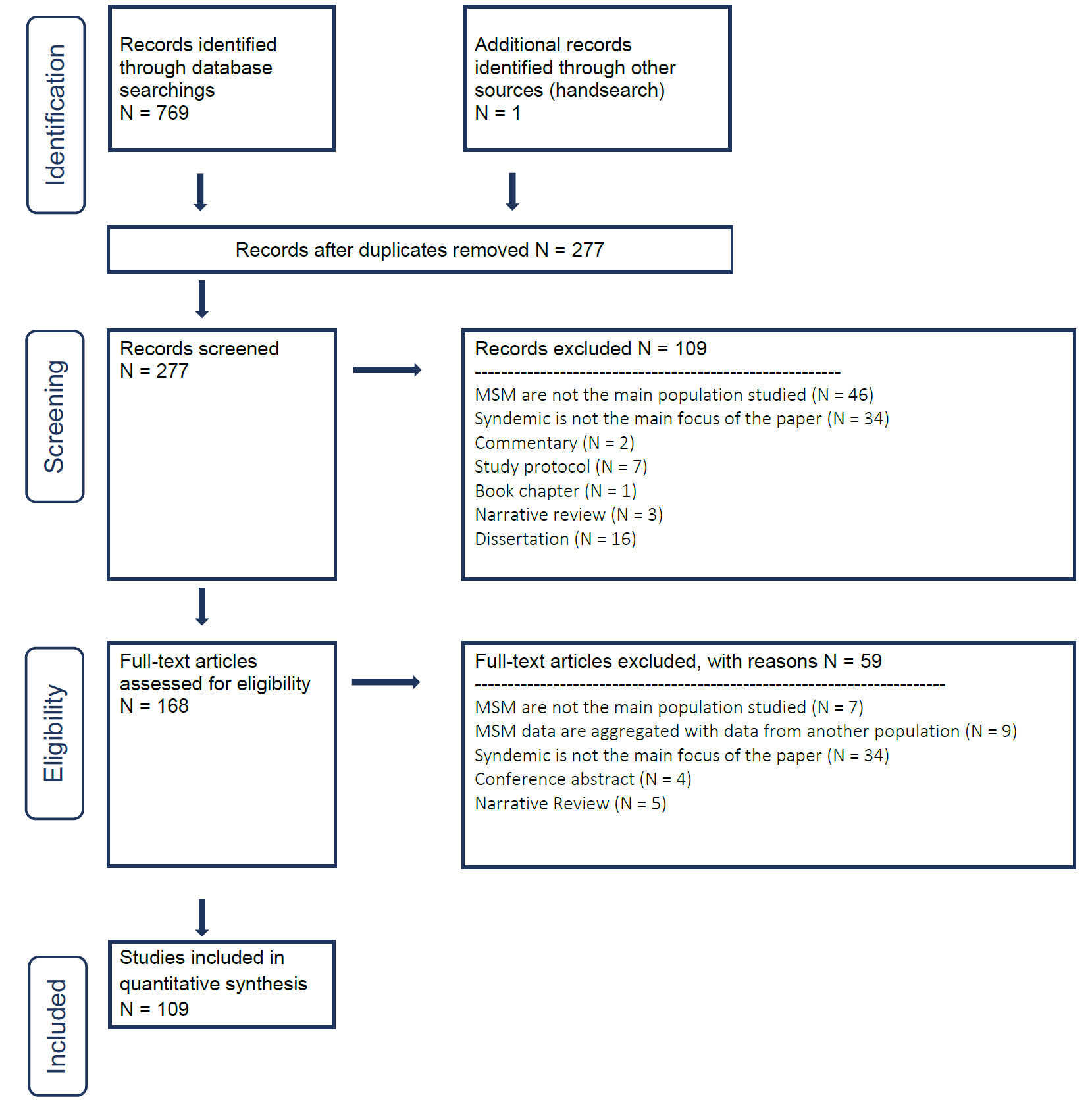


Figure 1: PRISMA flowchart of the search strategy

## 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.

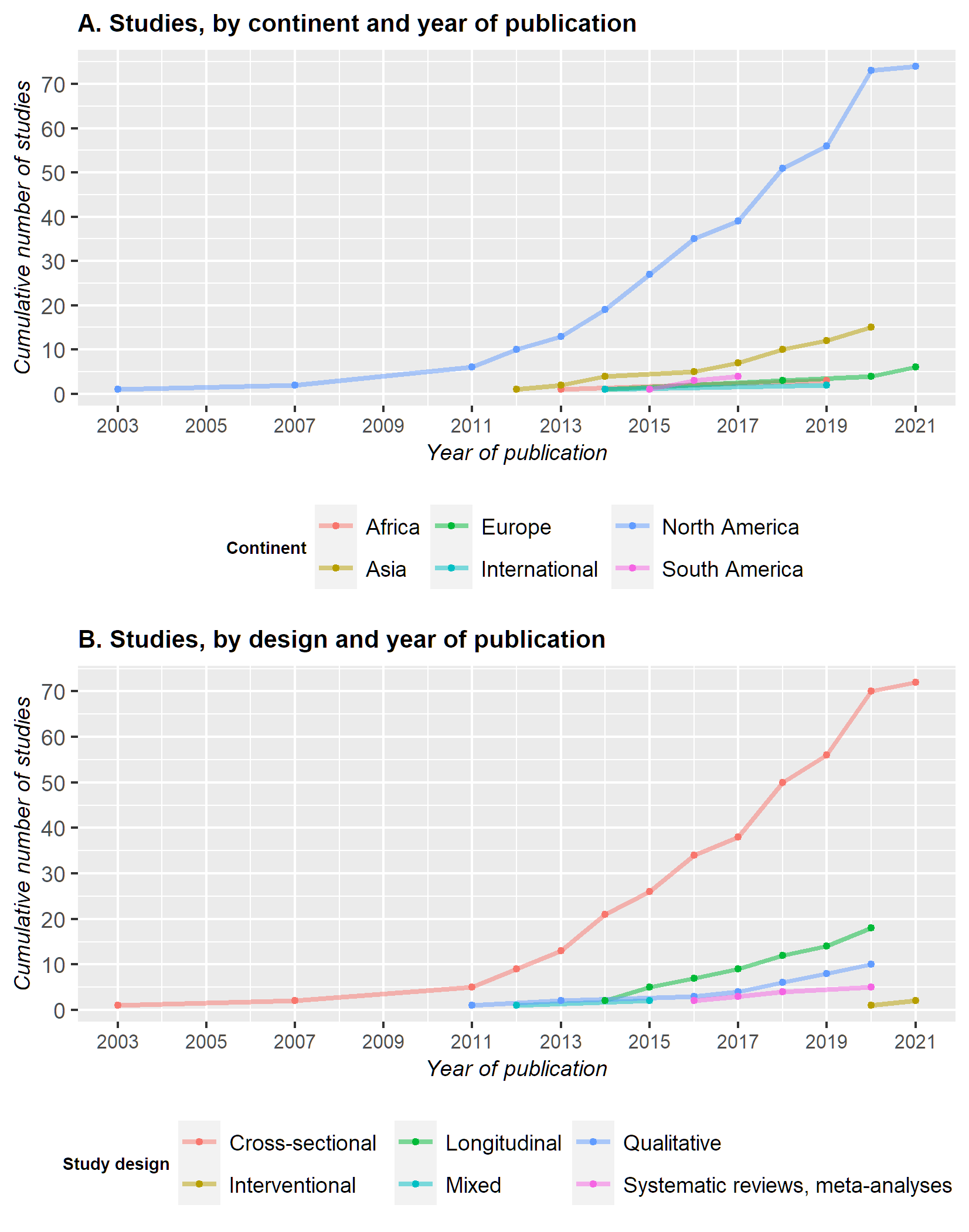


Figure 2: Plot of the cumulative number of studies published yearly

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)).

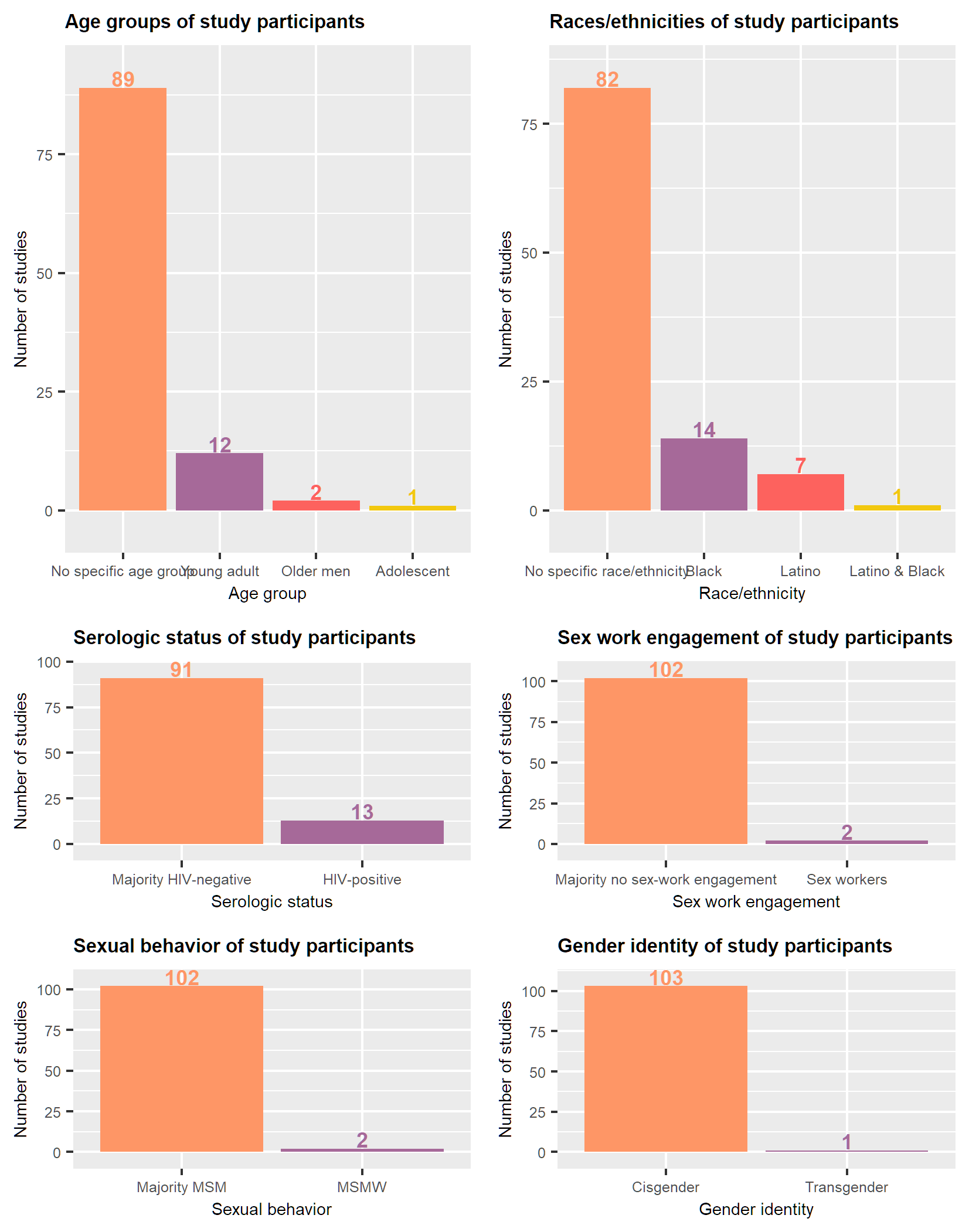


Figure 3: Number of studies focusing on a MSM subpopulation

### 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.

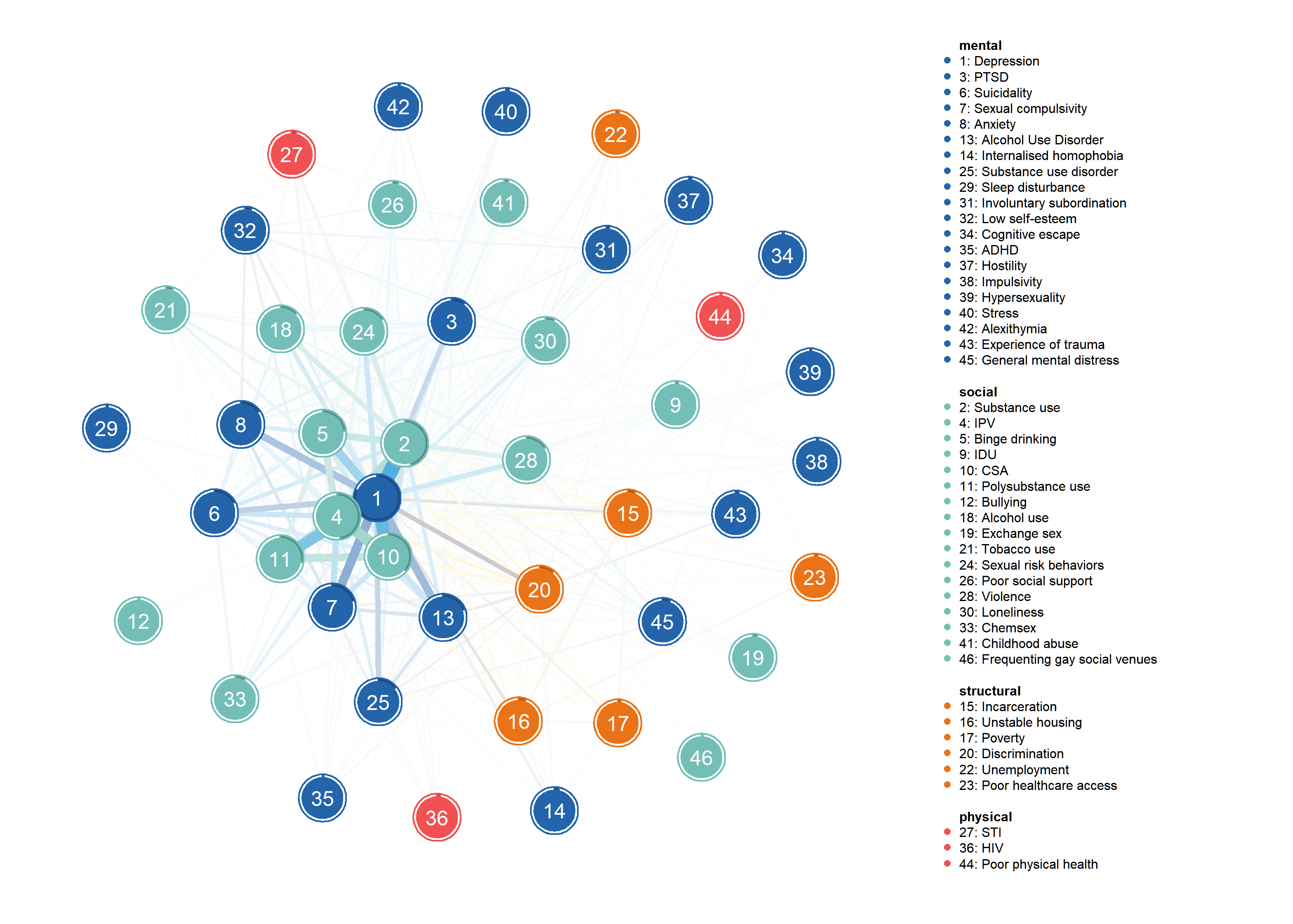


Figure 4: Network of the syndemic conditions studied in quantitative research. As a force-directed network, the most studied and interconnected conditions are the most central. Moreover, each node is circled by a pie chart of their frequency in the review. The thickness of the edges linking two nodes 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 C ( [Table 5](#DepressionTab) to [Table 12](#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

This review is the first Scoping Review to map the current knowledge in Syndemic Theory applied to MSM. We charted and presented detailed data regarding the way research has been done. As such, we offer a precious insight and actionable recommendations for the future of the field. Our search strategy of electronic databases was comprehensive and developed with the help of the director of health sciences library of our institution. We combined this database search with a secondary hand-search of references lists of the included studies. Moreover, we conducted a fully transparent and reproducible review. Other researchers may freely reuse our data and scripts to conduct their own work or use our database to identify papers pertinent for their research projects.

However, even though we took several steps to ensure the comprehensiveness of our search strategy, we may still have missed some relevant literature. Furthermore, one of our inclusion criteria was the centrality of syndemic theory to the screened paper. Even if two reviewers screened a part of the studies independently, this criteria may be somewhat arbitrary and other researchers may have chosen to include papers we rejected or the contrary. Finally, usual limitations of a scoping review apply such as the lack of risk of bias and strength of evidence assessment.

# Conclusion and recommendations

Our review of syndemic research applied to MSM revealed some important limitations that must be addressed in future work. The field of syndemic research would gain to study more MSM subpopulations, in more diverse geographical settings, especially in the Global South. Furthermore, promising methods such as spatial epidemiology or network analysis may help to advance the field while methods such as summary count should be abandoned. Besides, more qualitative and mixed data may enhance our understanding of the complex interactions of a syndemic on the living experiences of marginalized people suffering from it. Moreover, outcomes should be less focused on sexual health and start to explore other potential impact of a syndemic on health. Finally, conditions that constitute a syndemic should be more precisely defined and the measurement of said conditions should be more standardized while taking into account the difficulties of transposing some measures in different sociocultural contexts.

Though we took a critical stance on the current literature, we still consider syndemic to be an useful framework to study the global health of marginalized populations and the current research still offered valuable insights on the health of MSM. It is up to scholars in the field to continue to push research forward in order to improve the health of marginalized populations worldwide.

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