Understanding psychosis complexity through a syndemic framework: A systematic review

Uzma Zahid [a,b,e,*], Erin Grace Lawrence [c,e], Daniela Fonseca de Freitas [a,d,e], Lois A. Parri [b,e], Wesley Quadros [a,e], Phuong Hua [a,c,e], Eli Harriss [e,f], Dominic Oliver [a,e,g,h], Georgina M. Hosang [c,e], Kamaldeep Bhui [a,e,f,g,i,j,**]

[a] Department of Psychiatry, University of Oxford, Oxford, UK
[b] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK
[c] Centre for Psychiatry and Mental Health, Wolfson Institute of Population Health, Queen Mary University of London, UK
[d] Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK
[e] Bodleian Health Care Libraries, University of Oxford, Oxford, UK
[f] Nuffield Department of Primary Care Health Sciences, Wadham College, University of Oxford, Oxford, UK
[g] NIHR Oxford Health Biomedical Research Centre, Oxford OX3 7JX, UK
[h] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK
[i] Queen Mary University London Global Policy Institute, London, UK
[j] Collaborating Centre of World Psychiatric Association, Oxford, UK

ABSTRACT

Psychotic conditions pose significant challenges due to their complex aetiology and impact on individuals and communities. Syndemic theory offers a promising framework to understand the interconnectedness of various health and social problems in the context of psychosis. This systematic review aims to examine existing literature on testing whether psychosis is better understood as a component of a syndemic. We conducted a systematic search of 7 databases, resulting in the inclusion of five original articles. Findings from these studies indicate a syndemic characterized by the coexistence of various health and social conditions, are associated with a greater risk of psychosis, adverse health outcomes, and disparities, especially among ethnic minorities and deprived populations. This review underscores the compelling need for a new paradigm and datasets that can investigate how psychosis emerges in the context of a syndemic, ultimately guiding more effective preventive and care interventions as well as policies to improve the health of marginalised communities living in precarity.

1. Introduction

Psychotic conditions such as schizophrenia exhibit various symptoms including hallucinations, delusions (Dudley et al., 2023), negative symptoms (Sauvé et al., 2019), and cognitive disorganization (Sheffield et al., 2018). In addition to the high rates of comorbidity with other psychiatric and medical conditions, individuals with psychotic illnesses generally have poor social relationships and a reduced quality of life compared to the general population (Dong et al., 2019).

Schizophrenia and psychosis generally emerge from a complex interplay of genetic, biological, social, and environmental factors, with higher rates particularly among immigrant ethnic groups facing low-ethnic-density neighbourhoods (Veling et al., 2008). Despite this, progress in understanding these causes has been hindered by limited research on the intricate social dynamics among minoritised ethnic groups in epidemiological research (Jongsma et al., 2021a). For instance, studies may report higher rates of psychosis among immigrant ethnic groups but may not thoroughly investigate the socio-cultural factors contributing to this disparity. The inadequate consideration of factors such as acculturation stress, discrimination, and social isolation within these populations limits the depth of insight gained from epidemiological research. The predominant focus on genetic and biological

determinants has often overshadowed the nuanced social intricacies that significantly contribute to the aetiology of psychosis.

The prevailing social and genetic epidemiological research tends to emphasize isolated risk factors, missing the comprehensive interplay that contributes to the causative landscape. This limitation hampers the development of targeted interventions that can address the complex and intersecting social determinants of psychosis. To advance the field, there is a critical need for epidemiological studies to adopt a more holistic approach, encompassing a comprehensive examination of social, cultural, and environmental factors. By delving into the complex social dynamics, researchers can not only uncover more accurate risk profiles but also inform the development of more effective and culturally sensitive interventions. Additionally, fostering collaborations between genetic, biological, and social epidemiologists can bridge existing gaps and contribute to a more integrated and nuanced understanding of the factors influencing psychosis, ultimately enhancing the relevance and impact of epidemiological research in mental health.

1.1. The advantage of employing a syndemic approach to the study of psychosis

Emerging research on 'syndemics' offers a helpful theoretical framework to link these diverse influences (Zahid et al., 2023). The concept of a syndemic was initially introduced by Singer to describe the clustering of social and health problems at a population level (Singer, 2000). Singer highlighted the interconnectedness of substance abuse, violence, and HIV/AIDS in an inner-city Hispanic community in the USA, referring to them as the "SAVA" epidemics. These epidemics were intertwined and mutually reinforced within the local context. Singer emphasized the need to address the local epidemics of HIV and substance abuse together, as their transmission pathways were inseparable and influenced by the socio-economic context and structural violence. Recognizing the interlinkages between various health and social conditions becomes crucial when considering interventions.

Similarly, there is a complex relationship between the development and progression of psychosis, ethnic inequalities and other aetiological factors (Morgan et al., 2019; Jongsma et al., 2021b) which may be better understood through a syndemic approach. Psychosis often occurs within a context of various environmental stressors, socio-economic disparities, and biological vulnerabilities. The syndemic framework may be beneficial in accommodating this intricate interplay of multiple factors that operate over the life course of individuals. By acknowledging the role of shared aetiologies applicable to both psychiatric and medical disorders, the syndemic perspective provides a lens through which to understand the heightened risk of premature mortality among individuals with psychosis and severe mental illness, predominantly due to natural causes (Zahid et al., 2023; Oakley et al., 2018).

Syndemic theory also acknowledges and accounts for the importance of place as confirmed by recent evidence (Logeswaran et al., 2023).This is particularly pertinent in urban areas where a concentration of risk factors often leads to a higher prevalence of multimorbidity. The lifestyles shaped by these environments increase the risk of diabetes, characterized by abundant fast-food facilities, limited access to quality foods, insufficient healthcare resources, and the promotion of social isolation (Zahid et al., 2023). Understanding the syndemic nature of health conditions in urban settings is crucial, as it provides insights into the interconnectedness of mental and physical health, emphasizing the need for holistic and integrated healthcare approaches.

Importantly, the syndemic perspective not only helps in understanding the complexity of psychosis but also opens avenues for prevention and intervention strategies. By recognizing the synergistic effects of multiple risk factors, interventions can be designed to address not only the symptoms of psychosis but also the broader array of health challenges individuals may encounter. Moreover, the syndemic framework offers opportunities for targeted prevention efforts, for example in high-risk urban areas, by addressing the root causes and interconnected nature of health issues.

1.2. Aims of the current study

To date, there has been no comprehensive synthesis of studies investigating psychosis within the syndemic framework. Therefore, this review aims to examine and consolidate existing literature on this topic. By doing so, we aim to gain a comprehensive understanding of whether syndemic effects explain the aetiology and trajectory of psychosis, particularly in marginalised groups.

2. Methods

2.1. Search strategy and study selection

The systematic review protocol was registered with PROSPERO (Reference CRD42022355956) and conducted in accordance with PRISMA guidelines (Moher et al., 2009). An information specialist (EH) searched the following databases on 13/11/2023 with no limits for language, study design, or publication dates for this systematic review: Ovid Embase; Ovid Medline; Ovid PsycINFO; Scopus; CINAHL via EBSCOhost; the Cochrane Database of Systematic Reviews; and the Cochrane Central Register of Controlled Trials. The search strategies used text words and exploded index terms to retrieve relevant literature about syndemics and participants with a diagnosis of schizophrenia, schizoaffective and related disorders, or psychosis. The full strategies are available in the appendix. All references were exported to Endnote 20 (Thomson Reuters, New York, NY), and duplicates were removed manually. Studies were eligible for inclusion if they met the following criteria:

1. Included participants that had received a formal diagnosis of a psychotic disorder based on established diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). Additionally, studies were included if they utilized psychometric instruments specifically designed to assess and quantify symptoms indicative of high risk for psychosis or electronic health records.
2. Explicitly tested syndemic theory

2.2. Data extraction

Three authors independently extracted the data into a structured template (UZ, WQ, EGL). Any discrepancies were discussed between the three authors, and unresolved issues were reconciled with a senior researcher (GH). To describe the study characteristics, the following data were extracted: sample size, mean age in years, ethnicity, sex, patient diagnosis, measure of psychosis, location, and source of data.

2.3. Study quality

The methodological quality of studies was assessed with the Joanna Briggs Institute Critical Appraisal tools for cross-sectional and cohort studies (Moola et al., 2015) by two authors (PH and WQ). In case of disagreement, issues were resolved with a senior researcher (UZ). Evaluating the methodology and risk of bias, the tools scored '1' if a criterion was met and '0' if it was omitted. The scores were summed to create a final quality rating of 'low', 'moderate' or 'high' quality. The following scoring parameters were implemented: Checklist for Analytical Cross-Sectional Studies (score out of 8; Low 0–2, Moderate 3–5, High 6–8); Checklist for Cohort Studies (score out of 9; Low 0–3, Moderate 4–6, High 7–9).

3. Results

The search identified 132 articles, 57 were excluded after

deduplication, and 70 were excluded during the full text screening. This resulted in the final inclusion of 5 original articles (Fig. 1).

These five articles examined a syndemic in a total of 534 individuals with psychosis, 156 at risk for psychosis (see Table 1 for summary of studies). Altogether, one study included participants with psychosis (Bhui et al., 2021; Coid et al., 2020, 2021), two studies included participants at risk for psychosis (Coid et al., 2020, 2021) and the remaining two studies included patients with bipolar disorder and schizophrenia (McDonald et al., 2020; Jain et al., 2016). In terms of study design, one study was cohort (McDonald et al., 2020), and the remaining four studies were cross-sectional (Bhui et al., 2021; Coid et al., 2020, 2021; Jain et al., 2016). Table 2 summarises the syndemics investigated in cases relative to controls.

3.1. Key findings from included studies

Table 2 provides the key findings of included studies (n = 5). Bhui et al. (2021) employed a structural equations model to elucidate the factors contributing to psychosis diagnosis, revealing a significant impact of past and current adversities, along with a high biomarker load. Coid et al. (2020) interaction analyses demonstrated a significant increase in psychotic experiences and anxiety when assessing the combined associations of substance misuse with sexual health and sexual health with violence/criminality. McDonald et al. (2020) study uncovered a positive association between a greater number of psychosocial risk factors (mental illness, substance misuse, and trauma) and adverse perinatal outcomes, with higher magnitude effects observed in Black women. Jain et al. (2016) found a significant association between psychotic disorder and increased odds of engaging in unprotected receptive anal intercourse. Lastly, Coid et al. (2021) utilized a second order syndemic factor with four-component latent variables, explaining poor physical health/chronic health conditions and revealing significant multiplicative effects on these outcomes in interaction analyses between risk factors.

Table 3 provides a detailed summary of original research (n = 5) and breaks this down by the three syndemic criteria. *Criterion one* offers a comprehensive examination of the health outcomes and conditions investigated in the included studies. For instance, Bhui et al. (2021) explored psychotic disorders in the UK Biobank adult population, while Coid et al. (2020) focused on psychotic symptoms in a representative sample of men in a deprived area of London. McDonald et al.'s study (McDonald et al., 2020) centred on adverse perinatal outcomes in pregnant women, Jain et al (Jain et al., 2016). examined unprotected receptive anal intercourse and substance use in patients seeking post-exposure prophylaxis, and Coid et al. (2021) explored predictors of poor physical health in a national survey of young men. *Criterion two* highlights the consideration of wider environmental, socio-economic, and political factors in exacerbating negative outcomes. Factors analysed varied across studies, including past and current adversities, socio-economic status, and psychosocial risk factors. *Criterion three* delves into how diseases or health conditions interacted to worsen outcomes, detailing statistical analyses and results. Bhui et al. (2021) employed subgroup analyses and structural equation modelling, while Coid et al. (2020) used confirmatory factor analysis to create syndemic scores. McDonald et al. (2020) utilized multiple logistic regression and stratified analyses, Jain et al. (2016) applied generalized estimating equations and logistic regression, and Coid et al. (2021) employed logistic regression and multiplicative interactions to estimate a syndemic load score.

3.2. Health outcome or health condition

Two studies treated psychosis as a health outcome and primarily sought to explore its relationship with other variables (Bhui et al., 2021; Coid et al., 2020). Bhui et al. (2021) aimed to predict psychotic disorder and identified significant associations between inflammatory biomarkers and psychosis in a general UK population sample (n = 134,456) aged between 40 and 69 years. In another study by Coid et al. (2020) the
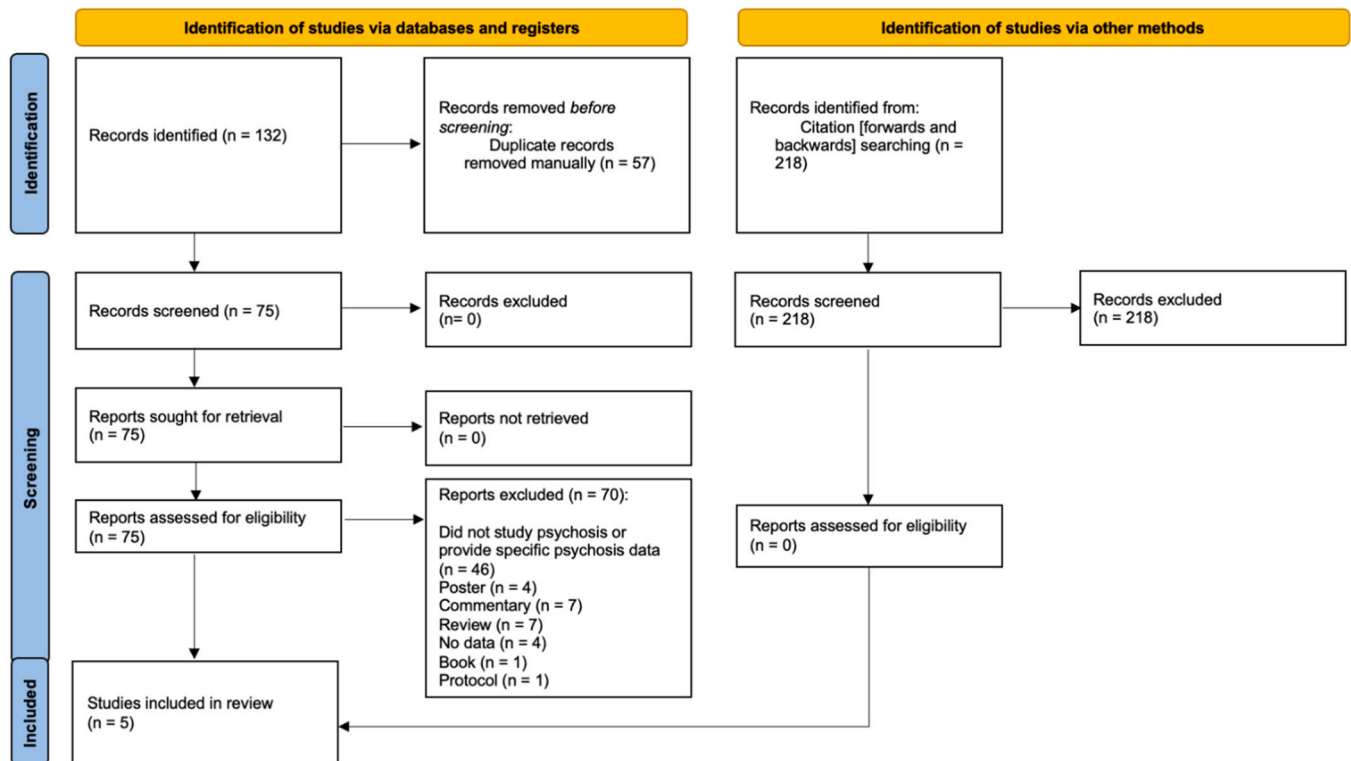

Fig. 1. PRISMA flow diagram showing the identification, screening and inclusion of studies examining syndemics and participants with a diagnosis of schizophrenia, schizoaffective and related disorders, or psychosis.

Table 1
Sample characteristics of examined studies.

Study	Study design	Sample size (n)	Mean age in years (SD)	Age range (years)	Ethnicity (n, %)	Gender (n, %)	Patient diagnosis (n)	Measure of psychosis	Location	Data source	Study period
(Bhui et al., 2021).	Cross-sectional	134 456	55.72 (7.7)	40–69	White British (122 135, 90.84%) White other (8298, 6.17%) Black (900, 0.67%) Asian (840, 0.62%) Other (1968, 1.46%)	M = 60 997, 45.37% F = 73 459, 54.63%	Psychosis (480)	ICD-10	UK	UK Biobank Data	2006–2010
(Coid et al., 2020).	Cross-sectional	3750	NR	18–34	White (2446, 91.23%) BME (235, 8.77%)	All M	At Risk for Psychosis (92)	Psychosis Screening Questionnaire (PSQ)	England, Scotland, Wales, UK Hackney, London, UK	Second Men's Modern Lifestyles Survey – Main Survey	2011
(McDonald et al., 2020).	Cohort	1656	27.5 (6.2)	NR	White (2065, 55.07%) Black (751, 20.03%) Asian (934, 24.91%)	All F	SCZ (1) Bipolar disorder (26)	Clinical Medical Records	Baltimore, USA	Electronic medical records	2012
(Jain et al., 2016).	Cross-sectional	821	32.5 (IQR = 28.8–40.4)	NR	White (497, 30.01%) Black (1003, 60.57%) Hispanic (26, 1.57%) Asian and Other (130, 7.85%)	M = 786, 95.74% F = 24, 2.92% TG/GQ = 11, 1.34%	Bipolar disorder (25) SCZ (2)	Clinical Medical Records	Boston, USA	Electronic medical records	1997–2013
(Coid et al., 2021).	Cross-sectional	2681	NR	18–34	White (591, 71.99%) Black (56, 6.82%) Asian (41, 4.99%) Latino (90, 10.96%) Other (43, 5.24%)	All M	At Risk for Psychosis (64)	Psychosis Screening Questionnaire (PSQ)	England, Scotland, Wales, UK Glasgow, Scotland	Second Men's Modern Lifestyles Survey – National Survey; Glasgow East Survey	2011

Abbreviations: Interquartile Range = IQR; International Classification of Diseases = ICD; Not reported = NR; Psychosis Screening Questionnaire = PSQ; Schizophrenia = SCZ; Schizophrenia affective disorder = SAD; Schizophrenia spectrum disorder = SSD; Transgender/Genderqueer = TG/GQ; Male = M; Female = F.

Table 2
Key findings of included studies.

Author	Key Findings	Study statistics
(Bhui et al., 2021).	In a structural equations model, psychosis diagnosis was explained by past adversity[1] (being hated in childhood, sexual violence), current adversity[2] (low household/ individual income and poor appetite or overeating) and high biomarker load[3] (waist and hip circumference, leukocyte count, and medications).	*s.c. 0.028, p < 0.001[1]* *s.c. 0.038, p < 0.001[2]* *s.c. 0.019, p = 0.048[3]*
(Coid et al., 2020).	Interaction analyses between the combined associations of substance misuse with sexual health[1], and sexual health with violence/criminality[2], revealed that psychotic experiences and anxiety were significantly increased.	Substance Misuse & Sexual Health, OR (CI): 1.17 (1.00–1.36)[1] Sexual Health & Violence/ Criminality, OR (CI): 1.17 (1.01–1.36)[2]
(McDonald et al., 2020).	Having a greater number of psychosocial risk factors (mental illness, substance misuse and trauma) was significantly and positively associated with adverse perinatal outcomes including schizophrenia. These effects were of higher magnitude in Black women, than in non-Black women.	Any number of psychosocial factors, aOR (CI): 1.34 (1.04–1.73) 1 of 3 psychosocial factors, aOR (CI): 1.26 (0.95–1.68) 2 of 3 psychosocial factors, aOR (CI): 1.38 (0.89–2.14) 3 of 3 psychosocial factors, aOR (CI): 2.04 (1.09–3.81)
(Jain et al., 2016).	Having a psychotic disorder was significantly associated with increased odds of engaging in unprotected receptive anal intercourse at the time of exposure, compared to all other exposure modalities.	aOR (CI): 4.86 (1.76–13.5)
(Coid et al., 2021).	A second order syndemic factor with four-component latent variables (violence, substance dependence, psychiatric morbidity, and a diathesis of biological/behavioural risk) was used to estimate synergy between components and explained poor physical health/ chronic health conditions. Higher score in syndemic factors were related to having no education qualifications, NEET, and low social class.	Syndemic Load Model Goodness of Fit indices: RMSEA = 0.034 [95% CI: 0.030–0.038], CFI = 0.953, TLI = 0.941)
	Interaction analyses between risk factors revealed significant multiplicative effects on poor physical health/longstanding conditions.	Physical Health Risk & Mental Health, OR (CI): – 1.56 (1.11–2.17) Mental Health & Substance Misuse, OR (CI): – 1.12 (1.05–1.20)

Abbreviations. Standardised Coefficient = s.c.; Probability = p; Odds Ratio = OR; Adjusted Odds Ratio = aOR; Root Mean Squared Error of Approximation = RMSEA; Confidence Interval = CI; Comparative Fit Index = CFI; Tucker Lewis Index = TLI.

focus was on predicting psychotic symptoms as the main health outcome. The study utilised a nationally representative sample of young men (18–34 years) from England, Scotland, and Wales and two booster samples of men from the London borough of Hackney and Black Minority Ethnic men (n = 3750). The study investigated synergies between psychotic symptoms and indicators of sexual risks, substance misuse, psychiatric morbidity/mental health, and violence and criminality.

Two studies treated psychosis as a health condition and aimed to understand the nature and implications of psychosis itself within the broader health landscape. McDonald et al. (2020) conducted a study on pregnant women (n = 1656) in Maryland, USA. The study aimed to

investigate the relationship between adverse perinatal outcomes (preterm delivery, low birth weight, neonatal intensive care unit admission, or stillbirth) and psychosocial risk factors, including a lifetime history of mental illness, lifetime illicit or licit substance use disorders, and interpersonal trauma. Jain et al. (2016) focused on predicting unprotected receptive anal intercourse (URAI) and any substance use at the time of potential HIV exposure. The study included patients seeking post-exposure prophylaxis (nPEP) in a health center in Boston, USA (n = 821). The outcomes of interest were predicted based on mental disorders such as depression, anxiety, attention deficit disorder (ADD), substance use disorder (SUD), and bipolar disorder and/or schizophrenia.

Coid et al. (2021) considered the interaction between 4 risk factors: 1) psychosis (as part of the mental health construct), 2) violence and criminality indicators, 3) physical health risks, and 4) substance use in predicting poor or long-standing physical health problems (outcome of interest). The concept of syndemic load, derived from confirmatory factor analysis of the four factors was used to assess its association with certain demographic and socio-economic factors. Higher syndemic loads were observed among those with no educational qualifications, unemployment, and NEET. Albeit psychosis is not the primary focus or outcome of interest in this study, the significant observed associations suggest that psychosis can be a manifestation of syndemic effects potentiated by social deprivation.

4. Discussion

4.1. Theorising syndemics

To our knowledge this is the first systematic review of studies exploring syndemics which account for psychosis (as an outcome or predictor/correlate). We set out to identify if syndemic studies exist which include psychosis and how there conducted. Some studies examined psychosis as a health outcome primarily aiming to understand the impact of various psychosocial risk factors on the development or occurrence of psychosis (Bhui et al., 2021; Coid et al., 2020). The goal of such studies was to comprehensively understand the influence of multiple risk factors and interactions on the occurrence and severity of psychosis. On the other hand, studies that approached psychosis as a health condition focused on the characteristics, correlates, and consequences of psychosis (McDonald et al., 2020; Jain et al., 2016). They explored the relationship of psychosis with other health conditions or risk factors, to produce poorer health. This latter approach better aligns with syndemic theory which seeks to understand multiple morbidities in particular places and social contexts amongst disadvantaged and marginalised groups. Both approaches can inform the development of preventive and care interventions.

The key findings from the included studies are:
1) Psychosis and a higher syndemic risk (multiple contextual factors) occur in deprived areas (Coid et al., 2020, 2021);
2) Vulnerable populations, especially ethnic minorities, experience greater adverse health and inequalities because of syndemic processes (McDonald et al., 2020; Jain et al., 2016; Coid et al., 2020, 2021).

4.2. Operationalising the syndemic criteria

Given the limited number of studies examining syndemics with a focus on psychosis, and the absence of established reporting frameworks or testing methods for syndemic processes (Zahid et al., 2023), it is worth pausing to consider how some studies were different from others. For example, Jain et al. (2016) may not fully meet the criteria of testing a syndemic, despite seeking to. One key component of syndemics is the consideration of the wider environmental, socioeconomic, and political factors that interact over time to mutually exacerbate negative outcomes. Jain et al. (2016) primarily focus on the coexistence of health conditions (conforming to the notion of co-occurring epidemics-one component of a syndemic) without investigating the interplay between

Table 3
Summary of findings categorized into three syndemic criteria.

Study	Criterion 1: Two or more diseases or health conditions clustering within a particular population		Criterion 2: Consideration of how the wider environmental context and other socio-economic and political factors contribute over time to mutually exacerbate negative outcomes – factors analysed	Criterion 3: Diseases or health conditions interact to result in adverse disease interaction, which worsens health outcome – statistical analyses and results
	Health conditions considered	**Population**		
(Bhui et al., 2021).	Outcome: Psychotic disorder Significantly associated inflammatory biomarkers (SWR): • Waist circumference • Hip circumference • Leukocyte count • Number of treatments and medications	UKBB adults (40–69 years) (n = 134,456) Tested if associations varied by ethnicity and gender.	• Past adversity: sexual assault & being hated in childhood • Current adversity: low household income and risky health behaviours - poor appetite or overeating	• Subgroup analyses (SUES): low household income was more strongly associated with psychotic disorder in the ethnic minorities and men, as compared to White British and women, respectively. • SEM: past adversity was associated with psychotic disorders, potentially mediated by biomarkers and current adversity. • The association of current adversity and biomarkers was stronger in women. • The association of current adversity and psychosis was stronger in men.
(Coid et al., 2020).	Outcome: Psychotic symptoms Synergies by observable indicators of: • Sexual risks • Substance misuse • Psychiatric morbidity/mental health • Violence and criminality	National SMML in England, Scotland, and Wales representative sample of young men (18–34 years), and two boost samples of men from the London borough of Hackney and Black Minority Ethnic men (n = 3750)	• Place: Deprived area of London (Hackney) • Ethnicity: Black, South Asian • Social class • Local area deprivation – Index of Multiple Deprivation	• LR: All ethnic groups living in Hackney were more likely to be unemployed and in higher deprivation areas. Black men in Hackney showed more psychotic symptoms (all types) and psychiatric hospital admission, higher incidence of all indicators related to sexual risks, mental health, substance misuse, and violence and criminality. South Asian men in Hackney had higher incidence of some indicators of all these four domains and psychiatric admissions, but only more of two types of psychotic symptoms. White men living in Hackney had higher frequency of some substance misuse behaviours, poorer mental and sexual health. • LR and IA: CFA: created individual scores for (i) sexual risk, (ii) mental health, (iii) substance misuse, and (iv) violence. In LR predicting psychotic experiences and anxiety, IA showed multiple effects of substance misuse and sexual risk, and between sexual risk with violence. • A second order, syndemic load factor, on the sexual risks, substance misuse, mental and violence and criminality was estimated. RA showed significant effect of place (with moderation analyses), with the syndemic loads of Black and South Asian living in Hackney people being higher than their national counterparts.
(McDonald et al., 2020).	Outcome: Adverse perinatal outcomes (preterm delivery, low birth weight, neonatal intensive care unit admission or stillbirth) Synergies by: • Lifetime history of mental illness • Lifetime illicit or licit substance use disorders • Interpersonal trauma Sum score of psychosocial risk factors (0−3) created.	Pregnant women in one care centre in Maryland, USA (n = 1656)	• Socio-economic status – measured by type of insurance as proxy) • Educational level • Ethnicity	• MLR: in the sample with all women, any risk factor was associated with greater odd of adverse perinatal outcomes. Women with three risk factors were twice as likely than women with only one. In stratified analyses by ethnicity, the association was only observed for Black women; among non-Black women no significant association with any level of risk was observed (potentially due to lack of statistical power).
(Jain et al., 2016).	Outcomes: Unprotected receptive anal intercourse (URAI) and any substance use at time of exposure to potential HIV. Synergies by:	Patients seeking post-exposure prophylaxis (nPEP) Boston, USA, health centre (n = 821)	None	• GEE-LR: URAI predicted by psychotic disorders, substance use disorder and the syndemic score. Substance use at time of exposure predicted by depression, anxiety, ADD, SUD and the syndemic score.

(continued on next page)

Table 3 (*continued*)

	Syndemic criteria			
Study	**Criterion 1: Two or more diseases or health conditions clustering within a particular population**		**Criterion 2: Consideration of how the wider environmental context and other socio-economic and political factors contribute over time to mutually exacerbate negative outcomes – factors analysed**	**Criterion 3: Diseases or health conditions interact to result in adverse disease interaction, which worsens health outcome – statistical analyses and results**
	Health conditions considered	**Population**		
	• Depression			
	• Anxiety • Attention deficit disorder (ADD) • Substance use disorder (SUD) • Post-traumatic stress disorder (PTSD) • Bipolar disorder and/or schizophrenia Syndemic score of co-occurring mental disorders created (sum score, 0–5).			
(Coid et al., 2021).	Outcome: Poor physical health or long-standing physical health. Predicted by indicators of: • Violence and criminality indicators • Physical health risks • Mental health Substance use	National SMML survey in England, Scotland, and Wales representative sample of young men (18–34 years), and boost sample of East Glaswegian men (n = 2681)	• Place: deprived area of East Glasgow • Local area deprivation – Index of Multiple Deprivation • Educational qualifications • Social class • Social environment – peer encouraging drug use and violence Economic inactivity – not in employment, education or training (NEET)	• LR and MNR: East Glaswegian more likely to be single, UK born, White background, have no educational qualifications, being unemployed or from lower social class, NEET and living in higher area deprivation. • Regression analyses: Higher odds for East Glaswegian men for substance and gaming addictions, several violent activities, and poorer health and health habits. • IA in LR: multiplicative interactions between violence and substance use, physical health risks and mental health, and mental health and substance use. • A syndemic load score (SOF), derived from confirmatory FA from (i) violence and criminality indicators (ii) physical health risks (iii) mental health, and (iv) substance use (FOF). The syndemic load was associated with being single, having no educational qualifications, low social class, NEET, peers encouraging drugs and crime, and amongst individuals who were single and older age (25–34). The magnitude of these associations was higher among East Glaswegian men.

UK Biobank sample = UKBB; Second Men's Modern Lifestyles = SMMS; Stepwise Regression = SWR; Structural Equation Model = SEM; Seemingly Unrelated Estimation = SUES; Logistic Regression = LR; Multiple Logistical Regression = MLR; Multinomial Regression = MNR; Factor Analysis = FA; Second-Order Factors = SOF; First-Order Factors = FOF; Confirmatory Factor Analysis = CFA; Interaction analyses = IA; Generalised Estimating Equation for Logistic Regression = GEE-LR.

these health conditions and broader societal and environmental factors. Therefore, while these studies shed light on the concurrent presence of health issues, they may not fully capture the broader contextual factors contributing to mutually exacerbating negative health outcomes. Indeed, when it comes to marginalised groups, ethnicity, migration status, trauma, adverse childhood experiences, histories of persecution in the heritage group, can all contribute and interact with contemporary social adversity. Indeed the intergenerational transmission of trauma and the effects of stress in mothers on their babies are also relevant. No studies tackle all these components. Nevertheless, the heterogeneity of methodologies, outcomes, and factors across the studies presents a promising starting point, reflecting the expansive perspectives within psychosis and syndemics and laying the groundwork for potential replication and validation studies.

4.3. Novel data sets and methods

To better understand the aetiology and risk for psychosis and disparities, there is a compelling and urgent need for the development of a new dataset that comprehensively examines all elements of a syndemic. While the studies included in our review provide valuable insights into the co-occurrence of psychosis and other health conditions within specific populations, they underscore the limitations of current data sets, statistical methods, reporting frameworks, and paradigms for psychosis research. These limitations stem from the studies primarily focusing on the concurrent presence of health issues without extensively investigating the intricate interplay between historical and contemporary conditions, meaning making, and the broader societal, environmental, and political factors that exacerbate negative outcomes. New data science methods (machine learning and artificial intelligence [AI]) might offer novel opportunities to pool data and evaluate patterns of risk factors and health conditions (Thesmar et al., 2019; Oliver, 2022). For

instance, there are three ways these methods can be applied: 1. machine learning algorithms could integrate diverse datasets encompassing electronic health records, socio-economic data, and environmental variables to create a more nuanced and comprehensive understanding of a syndemic. These algorithms can identify complex patterns and interactions among various risk factors, predict the likelihood of psychosis based on historical, environmental, and individual-level factors. 2. They can employ natural language processing to analyse narratives, and leverage advanced generative AI, such as large language models like OpenAI's ChatGPT, to uncover nuanced insights into meaning-making processes related to psychosis (Rezaii et al., 2019; Blease and Torous, 2023). 3. Social network analysis and dynamic modelling using AI could explore the influence of social connections and the evolving impact of environmental and political factors on psychosis prevalence, potentially aiding resource allocation at a service-level (Skinner et al., 2022).

4.4. Implications for policy and practice: bridging research to real-world interventions

Understanding the syndemic nature of health challenges in psychosis has profound implications for policy and practice in healthcare. Firstly, interventions must adopt a holistic approach that recognizes and addresses the interconnectedness of mental and physical health. Policies should prioritize integrated healthcare models that bridge traditionally separated domains of mental and physical health services. Additionally, there is a crucial need for policies that address the social determinants contributing to psychosis, such as poverty, systemic inequalities, and inadequate access to education and healthcare (Anglin et al., 2021). Multi-level interventions that encompass community engagement, health education, and targeted support for vulnerable populations are paramount (Schensul and Trickett, 2009). Furthermore, the findings underscore the importance of early intervention and prevention strategies that consider the complex interplay of risk factors and health conditions. In the future, mental health services could identify individuals at risk, employing predictive modelling based on machine learning algorithms, and offering tailored interventions. Collaborative efforts between mental health professionals, policymakers, and community stakeholders are essential to create a comprehensive and effective response to the syndemic challenges. By prioritizing such interventions, policymakers and practitioners can work towards mitigating the negative impact of psychosis, promoting health equity, and enhancing the overall well-being of communities.

4.5. Limitations

There are several limitations to this review. The relatively small number of studies and heterogeneities between them (in terms of sample size, population, study design) preclude a meta-analysis and some direct comparisons. Indeed, even synthesis is difficult for study designs that are quite unique. Studies are undertaken in different places, and even two urban spaces can differ in so many ways, for example, there are contrasts in the ethnic composition of people living in Glasgow and London both in the UK. The cross-sectional nature of most of the studies (four out of five) does not enable us to draw causal inferences between psychosis and studied conditions of social adversity or other long-term illness. On the positive side, given this is a new paradigm to explain psychosis, it was heartening to see such varied studies, with significant sample sizes, and all undertaken to a reasonably good standard as evidenced in the quality scores.

4.6. Future research

Moving forward, future research in the field should aim to address these six critical gaps and build upon existing knowledge to advance our understanding of syndemics associated with psychosis. **1.** There is a need for longitudinal studies that track the dynamic interplay of risk factors and health conditions over time, considering the cumulative impact on mental health outcomes. Long-term investigations can provide valuable insights into the trajectories of syndemics and facilitate the identification of critical intervention points for prevention and early intervention strategies. **2.** future research should explore the intersectionality of various risk factors, such as migration status, discrimination, trauma, and adverse childhood experiences. Investigating how these factors interact and contribute to syndemic processes can inform more comprehensive and tailored interventions that account for the unique challenges faced by diverse populations. **3.** From a methodological perspective, there is an opportunity to develop standardized reporting frameworks and testing methods for syndemic processes in the context of psychosis. This can enhance the comparability of studies, facilitate meta-analyses, and contribute to the establishment of evidence-based practices in the field. **4.** The development of more nuanced and culturally sensitive interventions. Understanding the specific socio-cultural contexts that contribute to syndemic processes, especially in marginalized populations, can inform the design of targeted and effective interventions. **5.** Finally, a key area of further research is replication; the SAVA syndemic, being well-known and extensively researched, serves as an example. At the moment, we need researchers to explore specific syndemics, such as diabetes, psychosis, ethnicity, and the stress pathway through cortisol, aiming to establish a similarly well-researched foundation for psychosis syndemics.

5. Conclusion

In conclusion, the current systematic review represents a critical step in understanding the complex interplay between syndemics and psychosis. It sheds light on the distinct approaches to studying psychosis as both an outcome and a health condition. The findings reveal a higher risk of syndemic effects among individuals living with psychosis, leading to adverse impacts on quality of life and heightened rates of psychotic symptoms, particularly affecting vulnerable populations. The implications for policy and practice highlight the importance of holistic interventions, integrated healthcare models, and targeted strategies addressing social determinants. Understanding psychosis complexity through a syndemic framework is pivotal for unravelling the complicated interplay of factors and advancing mental health research.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105614.

References

Anglin, D.M., Ereshefsky, S., Klaunig, M.J., et al., 2021. From womb to neighborhood: A racial analysis of social determinants of psychosis in the united states. Am. J. Psychiatry 178 (7), 599–610.

Bhui, K., Halvorsrud, K., Mooney, R., Hosang, G.M., 2021. Is psychosis a syndemic manifestation of historical and contemporary adversity? findings from UK biobank. Br. J. Psychiatry 219 (6), 686–694.

Blease, C., Torous, J., 2023. ChatGPT and mental healthcare: Balancing benefits with risks of harms. BMJ Ment. Health 26 (1).

Coid, J., Rodriguez, R.G., Kallis, C., et al., 2020. Ethnic disparities in psychotic experiences explained by area-level syndemic effects. Br. J. Psychiatry 217 (4), 555–561.

Coid, J., Zhang, Y., Bebbington, P., et al., 2021. A syndemic of psychiatric morbidity, substance misuse, violence, and poor physical health among young scottish men with reduced life expectancy. SSM-Popul. Health 15, 100858.

Dong, M., Lu, L., Zhang, L., et al., 2019. Quality of life in schizophrenia: A meta-analysis of comparative studies. Psychiatr. Q 90, 519–532.

Dudley, R., Watson, F., O'Grady, L., et al., 2023. Prevalence and nature of multi-sensory and multi-modal hallucinations in people with first episode psychosis. Psychiatry Res 319, 114988.

Jain, S., Oldenburg, C.E., Mimiaga, M.J., Mayer, K.H., 2016. High levels of concomitant behavioral health disorders among patients presenting for HIV non-occupational post-exposure prophylaxis at a boston community health center between 1997 and 2013. AIDS Behav. 20, 1556–1563.

Jongsma, H.E., Karlsen, S., Kirkbride, J.B., Jones, P.B., 2021b. Understanding the excess psychosis risk in ethnic minorities: The impact of structure and identity. Soc. Psychiatry Psychiatr. Epidemiol. 56 (11), 1913–1921.

Jongsma, H.E., Karlsen, S., Kirkbride, J.B., Jones, P.B., 2021a. Understanding the excess psychosis risk in ethnic minorities: The impact of structure and identity. Soc. Psychiatry Psychiatr. Epidemiol. 56 (11), 1913–1921.

Logeswaran, Y., Dykxhoorn, J., Dalman, C., Kirkbride, J.B., 2023. Social deprivation and population density trajectories before and after psychotic disorder diagnosis. JAMA Psychiatry.

McDonald, L.R., Antoine, D.G., Liao, C., Lee, A., Wahab, M., Coleman, J.S., 2020. Syndemic of lifetime mental illness, substance use disorders, and trauma and their association with adverse perinatal outcomes. J. Inter. Violence 35 (1-2), 476–495.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann. Intern Med 151 (4), 264–269.

Moola, S., Munn, Z., Sears, K., et al., 2015. Conducting systematic reviews of association (etiology): The joanna briggs institute's approach. JBI Evid. Implement. 13 (3), 163–169.

Morgan, C., Knowles, G., Hutchinson, G., 2019. Migration, ethnicity and psychoses: Evidence, models and future directions. World Psychiatry 18 (3), 247–258.

Oakley, P., Kisely, S., Baxter, A., et al., 2018. Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis. J. Psychiatr. Res 102, 245–253.

Oliver, D., 2022. The importance of external validation to advance precision psychiatry. Lancet Reg. Health–Eur. 22.

Rezaii, N., Walker, E., Wolff, P., 2019. A machine learning approach to predicting psychosis using semantic density and latent content analysis. NPJ Schizophr. 5 (1), 9.

Sauvé, G., Brodeur, M.B., Shah, J.L., Lepage, M., 2019. The prevalence of negative symptoms across the stages of the psychosis continuum. Harv. Rev. Psychiatry 27 (1), 15–32.

Schensul, J.J., Trickett, E., 2009. Introduction to multi-level community based culturally situated interventions. Am. J. Community Psychol. 43, 232–240.

Sheffield, J.M., Karcher, N.R., Barch, D.M., 2018. Cognitive deficits in psychotic disorders: A lifespan perspective. Neuropsychol. Rev. 28, 509–533.

Singer, M., 2000. A dose of drugs, a touch of violence, a case of AIDS: Conceptualizing the SAVA syndemic. Free Inquiry Creat. Sociol. 28 (1), 13–24.

Skinner, A., Occhipinti, J., Song, Y.J.C., Hickie, I.B., 2022. Population mental health improves with increasing access to treatment: Evidence from a dynamic modelling analysis. BMC Psychiatry 22 (1), 1–11.

Thesmar, D., Sraer, D., Pinheiro, L., Dadson, N., Veliche, R., Greenberg, P., 2019. Combining the power of artificial intelligence with the richness of healthcare claims data: Opportunities and challenges. Pharmacoeconomics 37, 745–752.

Veling, W., Susser, E., Van Os, J., Mackenbach, J.P., Selten, J., Hoek, H.W., 2008. Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. Am. J. Psychiatry 165 (1), 66–73.

Zahid, U., Hosang, G.M., de Freitas, D.F., Mooney, R., Bhui, K., 2023. Ethnic inequality, multimorbidity and psychosis: Can a syndemic framework resolve disputed evidence? Schizophrenia 9 (1), 37.