Mental health outcomes in transgender and non-binary people: an umbrella review

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KEY POINTS (100/100 words)

Question: What available evidence describes mental health and neurodevelopmental outcomes in trans and non-binary people?

Findings: In this umbrella review, data from 24 reviews demonstrated consistent evidence of worse mental health and neurodevelopmental outcomes in trans and non-binary people, compared to cisgender or general population groups.

Meaning: This review suggests stark inequalities in mental health outcomes for trans and non-binary people, but also highlights the gaps and limitations of the existing evidence base. Research acknowledging the diversity amongst people minoritised by their gender identity and investigating the mental health consequences for multiply disadvantaged trans and non-binary people is urgently required.

ABSTRACT (346/350 words)

Importance

Experiences of marginalisation by gender minority people may predispose them to poor mental health outcomes than cisgender peers. Understanding mental health conditions in transgender (trans) and non-binary people is an essential step in addressing potential inequities in outcome for gender minority people.

Objective

We synthesised reviews of mental health and neurodevelopmental conditions in trans and non-binary people to describe epidemiology, key themes and research gaps.

Evidence Review

Three bibliographic databases (Embase, MEDLINE and PsycINFO) were systematically searched from inception to 21 August 2023 to identify reviews addressing mental health and neurodevelopmental outcomes in trans and non-binary people. Articles were screened by two reviewers and prespecified data extracted. Quality of included reviews was appraised against AMSTAR2 criteria. The study protocol was registered with PROSPERO (CRD42023449644).

Findings

Of 7,496 unique records, 41 met inclusion criteria with 24 reviews synthesised after excluding those containing overlapping primary studies. Pooled prevalence estimates from meta-analyses were identified for five outcomes: suicidal ideation (50% [95%CI:42-57%]); suicide attempts (29% [95%CI:25-34%]); non-suicidal self-injury (NSSI) (47% [95%CI:40-54%]); eating disorders (18% [95%CI:16-19%]); and autistic spectrum conditions (11% [95%CI:8-16%]). Meta-analyses comparing trans and cisgender groups reported higher odds of suicidal ideation (OR 3.48 [95%CI:2.41-4.91]), suicide attempts (OR 3.45 [95%CI:2.40-4.64]), NSSI (OR 3.42 [95%CI:1.99-5.89]) and post-traumatic

stress disorder (OR 2.52 [95%CI:2.22-2.87]). Worse outcomes were reported across all narrative syntheses comparing trans and cisgender/general population groups, except for problem gambling where the limited evidence base was conflicting. No reviews assessed incidence or mortality, and there was limited disaggregation of non-binary people or by specific gender subgroups (e.g. trans men and trans women). Review quality was generally poor. Reviews highlighted heterogeneity in definitions of gender identity and outcome ascertainment, and unrepresentative sample populations as limitations of primary studies.

Conclusions and Relevance

A growing body of evidence suggests trans people experience worse mental health outcomes than cisgender people, but there are substantial gaps and methodological weaknesses in existing literature. Research applying an intersectional lens, using longitudinal data and reflecting diversity and the experience of multiple disadvantage in the gender minority population is required to ensure evidence-informed policy and health service development.

Text (3105/3000)

Introduction

Transgender (trans) people are those whose gender identity differs from societal expectations based on their sex assigned at birth.[1] Non-binary is used to describe gender identities that are beyond the girl/women or boy/man binary gender paradigm and some, but not all, non-binary people will identify under the trans umbrella.[2] Increased visibility of trans and non-binary (TNB) identities and opportunities for online connection have seen a growing number of people openly express gender minority identities.[3] Although there is significant diversity within the TNB population, the group is unified by a shared experience of minoritisation.[4]

A large body of research published across disparate disciplines has investigated mental health outcomes in the TNB population. Qualitative evidence and survey data consistently report high risk of adverse mental health outcomes in TNB people,[5-7] yet the epidemiology of mental health and neurodevelopmental conditions, particularly in comparison to cisgender people, remains poorly understood.

By summarising key findings from thematically similar systematic reviews, umbrella reviews can be valuable in providing an overarching understanding of the available evidence base, its quality and key research gaps.[8] Therefore, we aimed to synthesise and appraise evidence describing prevalence, incidence and mortality associated with mental health and neurodevelopmental conditions in TNB people. Additionally, we sought to characterise methodological challenges and identify knowledge gaps in the existing literature.

Methods

PRISMA guidelines were followed in reporting this review (Supplement 1).[9] The protocol was registered with PROSPERO [10] (Supplement 2). On 21 August 2023, Embase, MEDLINE and APA

PsycINFO were searched without restrictions for three concepts: 1) TNB people; 2) mental health and neurodevelopmental conditions; 3) reviews. Search terms identifying TNB people were intentionally broad and endeavoured to capture the complexity in conceptualisations of gender between cultures and over time (Supplement 3). The "Paperfetcher" platform automated handsearching of two specialist journals.[11]

The population of interest was TNB adults aged ≥18 years. Comparison to cisgender people was not essential for inclusion. Outcomes of interest were mental health and neurodevelopmental conditions. Review articles using "systematic" methodology were included (Supplement 4).

Title-abstract and full-text screening were conducted independently by two researchers (KJH and DJC/DC/SVK/RT/NS) and disagreements were resolved by discussion. Overlap of primary studies between reviews was assessed using citation matrices.[12,13] Where more than 20% of primary studies were shared, the "most recent, highest quality, most relevant or most comprehensive" review was retained in the final sample.[14]

Study characteristics were extracted by a single reviewer (KJH) and checked by a second reviewer (DJC) (Supplement 5). Quality of reviews was assessed using the AMSTAR2 tool,[15] with minor amendments to reflect the lack of necessity for a comparator group (Supplement 6). Overall quality was rated from high to critically low depending on presence of critical weaknesses.[15]

For meta-analyses, we present synthesised data descriptively and results are as reported in original reviews. Reviews without meta-analysis have been compiled by narrative synthesis.[16] An effect direction plot summarises evidence comparing outcomes in TNB and cisgender/general populations (Supplement 7).[17]

Results

Our search returned 7,496 unique records after removal of 2,949 duplicates. Title and abstract screening excluded 7,296 articles, with 200 reviews retrieved for full-text review. In total, 84 reviews

met the inclusion criteria, with 41 reviews relevant to mental health (Figure 1).[18-58] In total, 17 reviews were excluded because of overlap (Supplement 8), leaving 24 reviews for synthesis.[19-22,26,28,29,32,34-39,41,43-46,48-51,54,55]

Table 1 summarises characteristics of included reviews (detailed data in Supplement 9). Reviews were published between 2017 and 2023. They included 754 primary studies relevant to the umbrella review question, published between 1983 and 2022. The rate of primary study publication increased over time. More than half (50.5%) of primary research was conducted in North America. 129 primary studies (17.1%) were conducted in low- and middle-income countries (LMIC) and only five studies included participants from a low-income country (all Syrian, n=24). All reviews were published in English. Six reviews considered TNB people within broader reviews looking at groups minoritised by gender modality (describing the relationship between a person's gender identity and gender assigned at birth)[1] or sexual orientation, and six reviews investigated specific subgroups (trans women sex workers, migrants, sexual minority trans women) or geographic regions (LMIC, Middle East, China). No reviews synthesised evidence of incidence or mortality of mental health conditions.

Means of ascertaining gender identity were heterogenous across primary studies and included self-report, documentation of TNB identity in electronic health records (EHR) or use of attendance at gender-affirming health services as a proxy. Similarly, there was heterogeneity in the assessment of outcomes across reviews, including self-report, diagnostic codes in EHR and various screening or diagnostic tools.

Most reviews used narrative synthesis (n=18), but seven reviews included meta-analysis. Five meta-analyses reported pooled prevalence estimates for suicidal ideation, suicide attempts, non-suicidal self-injury (NSSI), eating disorders (ED) and autistic spectrum conditions (ASC) (Table 2).[32,34,37,46] Three meta-analyses compared odds of outcome (suicidal ideation, suicide attempts, NSSI and post-traumatic stress disorder (PTSD)) between TNB and cisgender people. Twelve narrative syntheses drew comparison between TNB and cisgender/general populations for multiple outcomes (Figure 2).

Quality of included reviews was limited by common methodological weaknesses including lack of review protocol (71% of reviews), failure to assess risk of bias (only 46% of reviews used quality appraisal tools) and failure to justify the exclusion of primary studies (96% of reviews) (Supplement 10).

Prevalence of Mental Health Conditions

Suicide and non-suicidal self-injury

A published meta-analysis of international evidence reported high lifetime prevalence of suicidal ideation (50% [95%CI:42-57], I^2:88.4%) and suicide attempts (29% [95%CI:25-34], I^2:99.1%) in TNB people (Figure 2; Supplement 11).[34] In subgroup analysis, there was little difference in lifetime prevalence estimates for trans men and trans women for both suicidal ideation (trans men: 53% [95%CI:44-62], I^2:88.9%; trans women: 43% [95%CI:33-55], I^2:90.9%) or attempts (trans men: 22% [95%CI:13-31], I^2:96.8%; trans women: 26% [95%CI:22-30], I^2:89.6%) (Supplement 12). A further meta-analysis comparing TNB and cisgender people found elevated risk of suicidal ideation and suicide attempts in the TNB group, with odds ratios (OR) of 3.48 (95%CI:2.41-4.93) and 3.45 (95%CI:2.60-4.64) respectively.[38] One narrative review considered the role of ethnicity, education and income on suicide-related outcomes in TNB people in Canada and USA.[19] Prevalence estimates calculated by averaging prevalences reported in primary studies were similar to the estimates from meta-analysis (lifetime average suicide ideation: 46.55% (range 18.18-95.5); lifetime average suicide attempts: 27.19% (range 8.57-52.40)). The authors suggested patterns of suicide-related behaviour may differ by ethnicity and educational attainment, with insufficient data to draw conclusions about any relationship with income. No reviews addressed suicide-related mortality.

Two reviews addressed NSSI. Meta-analysis of 15 studies estimated lifetime prevalence of 46.65% (n=4,724, 95%CI:39.35-54.10, I^2:95.0%) for NSSI in TNB people.[59] Past-year estimates of NSSI were similar (46.61%, n=3,590, 95%CI:34.45-58.12, I^2:97.2%) despite drawing on fewer primary studies and a smaller sample population. Prevalence estimates for the heterosexual/cisgender group were

significantly lower (lifetime: 14.57%; past-year: 10.64%). A smaller meta-analysis of seven studies found a similarly elevated risk of NSSI in TNB individuals compared to cisgender peers (OR 3.42 [95%CI:1.99-5.89]).[38]

Depression and anxiety

No meta-analyses addressing prevalence or incidence of depression or anxiety were identified. The most comprehensive narrative review of depression drew on 71 primary studies.[45] Lifetime prevalence of depression ranged from 13.5% to 85.0%. However, there was significant heterogeneity in primary studies, particularly in context and methods of outcome ascertainment. Although several primary studies reported separate prevalence estimates for trans men and trans women, overall findings were contradictory in describing the trans subgroup with greatest burden of depression. In total, 20 primary studies compared estimates of depression prevalence in TNB people with cisgender or general population estimates, with 15 reporting higher prevalence in TNB groups (Figure 3). The remaining five studies found no difference between TNB and cisgender people, but of these, four studies included fewer than 200 TNB participants and two used cisgender men who have sex with men (MSM) as the comparator group. Three additional reviews reported higher prevalence of depression in TNB people compared to cisgender people, although each included a small number of primary studies.[26,36,51]

A single review narratively synthesised 17 primary studies assessing anxiety disorders and symptoms in TNB people.[43] Prevalence estimates for current anxiety disorders showed considerable variability (5% to 36.1%), and five of six studies comparing TNB and cisgender groups showed higher prevalence amongst TNB people (Figure 3). The scope of anxiety disorders included in these estimates was broad and the authors highlighted limited data describing patterns of specific anxiety disorders. A further review including 12 primary studies found similar variation in prevalence estimates (anxiety symptoms prevalence range: 14.7-66.3%; anxiety diagnosis prevalence range: 6-98%).[45]

Two reviews with meta-analyses addressed risk of PTSD. The first compared PTSD risk in TNB people against cisgender controls and reported higher risk in the TNB group (OR 2.52 [95%CI:2.22-2.87], I^2:79%).[39] The second review found similar findings in a subset of the TNB population – trans, sexual minority women. When compared to cisgender peers, an elevated risk of PTSD was reported (OR 1.75 [95%CI:1.22-2.50]).[49]

Eating disorders

A meta-analysis of five primary studies reported pooled prevalence of ED in TNB people of 17.70% (n=1,953, 95%CI:16.32-19.08, I^2:91.3%), when outcomes were assessed using ED-specific instruments. Meta-analysis by gender subgroup reported higher lifetime prevalence of ED in trans men (19.46% [n=1,327, 95%CI:17.72-21.21, I^2:89.9%]) than trans women (14.72% [n=627, 95%CI:12.45-16.98, I^2:92.7%]).[46] By contrast, a narrative review cited a markedly lower overall prevalence of feeding and eating disorders in TNB people(0.15-1.37%), however this estimate came from a single primary study (n>10,000) using US healthcare records.[29] A further narrative synthesis reported higher prevalence in TNB than cisgender or general populations in 11 of 13 cross-sectional studies (Figure 3).[46]

Neurodevelopmental conditions

A meta-analysis of 25 studies reported a pooled prevalence estimate of 11% (n=8,662, 95%CI:8-16) for ASC in TNB populations, although 13 primary studies included children and young people.[32] A narrative review reported prevalence estimates between 5.5 to 29.6% in clinical studies of ASC in adult TNB populations.[21] Significant changes in ASC diagnostic criteria and awareness across the review timeframe may partially account for this wide range of prevalence estimates.[60] Both reviews acknowledge heterogeneity in primary studies as a limitation, but conclude ASC to be more prevalent in TNB than cisgender people. Additionally, both reviews found estimates differ by method of outcome ascertainment, with primary studies utilising self-report reporting higher prevalence than those employing medical records. A single narrative review including three primary

studies of ADHD in TNB adults reported higher prevalence compared to cisgender adults with estimates of 4.1 to 11% (Figure 3).[28] Again, differences in outcome ascertainment was suggested as a possible explanation of variation in estimates. Besides ASC and ADHD, no reviews related to other neurodevelopmental outcomes were found.

Other psychiatric conditions

A single review compiled evidence of personality disorder (PD) prevalence from 10 primary studies, but heterogeneity across studies was high. Only two small primary studies (n<100) reported prevalence estimates for aggregated PDs and a single primary study comparing TNB and cisgender people reported higher prevalence of PD in the TNB group (Figure 3). One review synthesises the limited data available describing prevalence of enduring mental health conditions. Prevalence estimates for psychotic disorders were reported in two primary studies; both with small sample sizes (n<200) and one examining only individuals with experience of detransition.[45]

A narrative review addressing problem gambling was unable to estimate prevalence in transgender people due to lack of population-based studies, and no effect direction was reported because of inconsistent findings across the small number of primary studies (Figure 3).[35] A further narrative review sought to present an overview of various addictions for trans men, trans women and non-binary people.[48] However, limited primary data meant authors often relied on a single primary study and disaggregation within the TNB population was impossible.

Common themes across reviews

Several critiques of primary studies appeared repeatedly across reviews (Panel 1). Multiple reviews highlight potential measurement bias arising from different outcome definitions and means of ascertainment in primary studies, and uncertain validity of screening and diagnostic tools in TNB populations. Selection bias as a consequence of unrepresentative samples was also highlighted as an issue. This arose from sampling approaches, including convenience sampling and/or snowballing and

recruitment from gender-related healthcare services, that do not reflect the broader trans population of interest. Generalisability of findings is limited by the predominance of white/Caucasian participants and North American setting in primary studies. Limited engagement with TNB communities by researchers was noted in several reviews.

Discussion

This review of 24 reviews found consistent evidence of poor outcomes in TNB adults across a range of mental health and neurodevelopmental conditions. Reviews most commonly presented evidence of suicide-related research. Pooled prevalence estimates suggest half of TNB people experience suicidal ideation and nearly a third (29%) will make at least one suicide attempt. These prevalence estimates are higher than those observed in the general population, suggesting greater risk of suicide-related behaviours in TNB people.[61] No reviews addressing suicide mortality were identified, but primary studies have reported greater suicide mortality amongst TNB people compared to the general population. [62] Although only identified for a small number of outcomes, pooled prevalence estimates were higher than general population estimates across all reported conditions.[59,61,63,64] In direct comparisons with cisgender or general populations, higher prevalence was reported across all available outcomes for TNB people, except for problem gambling where the limited evidence base reported conflicting results. Some caution is warranted in interpreting our findings, as effect directions were often reliant on single or few primary studies because of lack of appropriate comparators in the literature. However, the direction of effects is consistent across reviews and the observed disparities are predicted by the Minority Stress model.

This review serves to highlight significant knowledge gaps in current understanding of mental health in gender minority people. Robust prevalence estimates were lacking for some common mental health conditions, such as depression and anxiety, because of limited population data and challenges in synthesising evidence from heterogenous primary studies. Incidence data were scarce across all outcomes, reflecting the reliance on cross-sectional studies in existing literature. The limited

longitudinal studies to date are typically undertaken in clinical settings, with small participant numbers and a focus on evidencing effects of gender-affirming interventions over relatively short time periods. In recent years, a few primary studies utilising EHR have demonstrated their potential to address the lack of longitudinal data and make causal inference in trans health.[65] Although the absence of variables capturing gender modality presents challenges for identification of gender minoritised people in EHR and other routine datasets, their utilisation has potential to address inequalities in representation of TNB people in administrative data research.

Few reviews presented disaggregated results by specific gender identities, instead approaching TNB people as a homogenous group. Disregarding diversity within the TNB community risks obscuring nuanced disparities in this population, given primary studies have shown differential risks of health outcomes for transmasculine and transfeminine people.[65] Access to and satisfaction with gender-affirming care are important sources of heterogeneity in the experience of TNB people, and represent factors not well captured in reviews. Data describing mental health of non-binary people were largely absent. Some primary studies included non-binary participants, but no reviews provided disaggregated data for this group. Recent census data suggest non-binary people account for nearly half the gender minority population living in Scotland, reflecting previous survey findings both in the UK and internationally.[66-69] There is an urgent need for research capturing outcomes in non-binary people to address their erasure.

There was limited consideration of the effects of intersecting marginalised characteristics in the existing literature. Yet within TNB communities, experience of disadvantage is not universal.[70] An intersectional lens is essential to understand the role of multiple disadvantage on mental health outcomes in TNB people. In particular, limited evidence of the role of ethnicity was highlighted by several reviews. Ethnicity was not widely reported when describing participant demographics of primary studies, and where documented, most study participants were white. Reviews in specific geographic settings demonstrated variation in experiences of TNB people dependent on the cultural,

religious and legal context of their place of residence.[26,50] To better understand the global picture and to reflect culturally specific conceptualisation of gender identity, research with participants living outside North America and Western Europe would be beneficial in addressing their underrepresentation.

The main strength of this review of reviews is its use of a systematic search strategy, without language or date restrictions, to provide to our knowledge the first comprehensive overview of the existing literature synthesising mental health and neurodevelopmental outcomes in TNB people. This review is timely given the current socio-political climate which has seen increasingly anti-TNB hostility globally. Public fervour around gender identities incongruent with birth-assigned sex or beyond the gender binary and experiences of transphobia in the UK might be expected to drive mental health disparities in gender minority people through the mechanisms described in the Minority Stress model.[71] Unmet demand for gender-affirming healthcare has resulted in growth of waiting lists and substantial delays in accessing care. The period around a decision to pursue gender-affirming care has been identified as a time of particular vulnerability in an individual's mental health.[72,73] Thus, this review presents a timely summary of existing evidence describing mental health in TNB people for healthcare providers and policymakers.

Our review has some limitations. First, gender identity was often poorly defined, and it was often unclear if non-binary people were included in study populations. The risk of their omission was mitigated in part by our use of search terms specific to non-binary identities. Given the rapid evolution of terminology in this field, future researchers should ensure clarity when defining gender identity and its operationalisation to provide transparency about the inclusion of non-binary people. Many reviews did not specify comparison groups in their research questions, reflecting limited use of appropriate control groups in the primary literature. Some studies used cisgender-MSM as a comparator, but their shared experience of Minority Stress reduces the generalisability of findings to a general population.[4] Despite utilising broad search terms and avoiding language restrictions to

capture international evidence, all reviews were published in English and many only searched for English language primary studies. Therefore, our findings may have limited applicability in non-English speaking settings. Finally, the methodological weaknesses identified as critiques of primary studies represent sources of bias inherent to our results, particularly the potential for measurement and selection biases. Reliance on potentially biased sampling approaches may have been required to overcome challenges in participant recruitment.

Conclusions

Quantifying the mental health burden facing TNB people is an important step with significant implications for both delivery of care and shaping healthcare policy. This review has identified a consistent body of evidence reporting poor mental health outcomes amongst TNB people and has highlighted critical evidence gaps which should be urgently addressed to ensure their mental health needs can be addressed by evidence-informed policy and practice.

Figures

Figure 1. PRISMA flowchart showing study selection for inclusion in umbrella review on mental health and neurodevelopmental outcomes in trans and non-binary people.

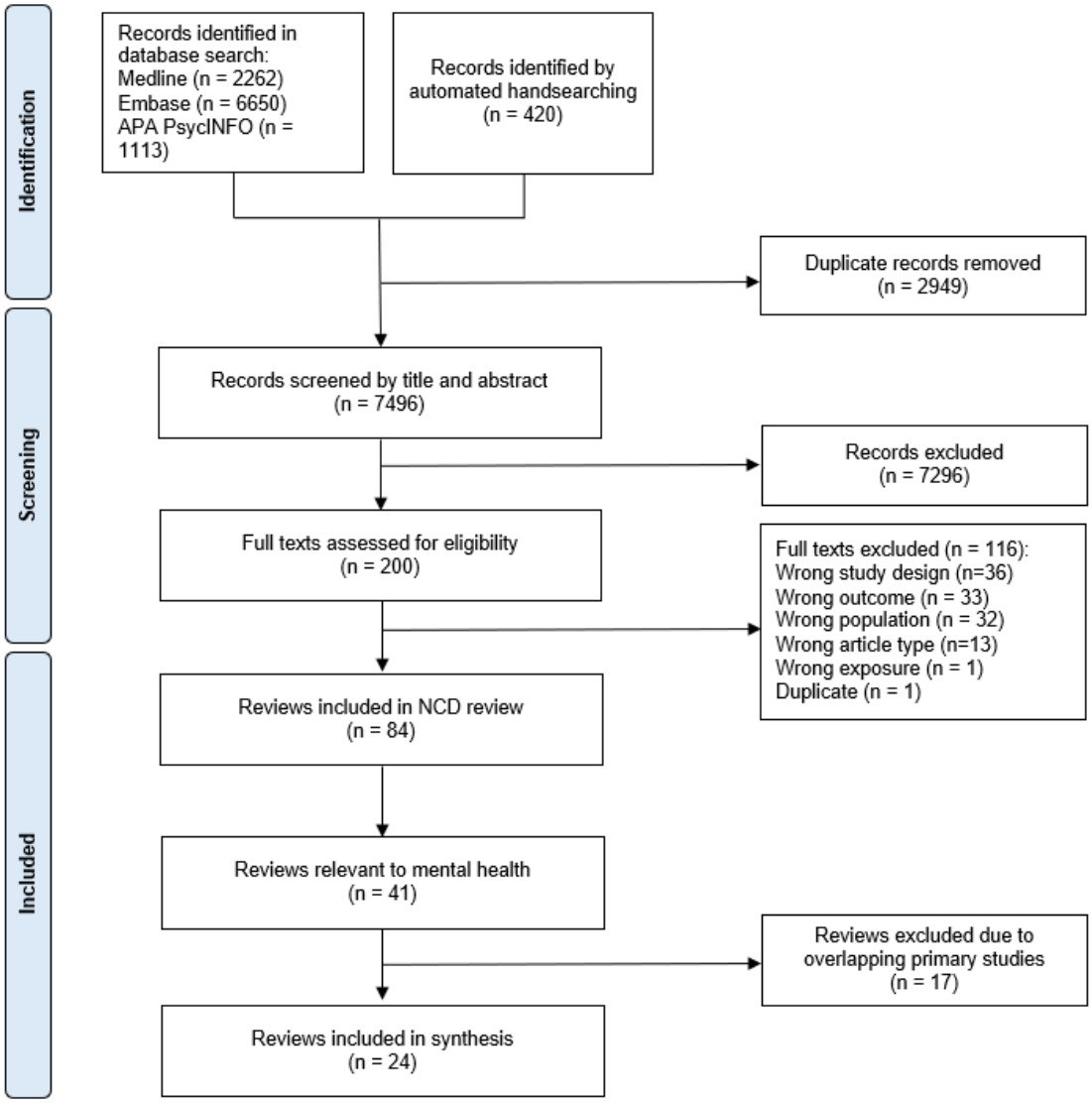
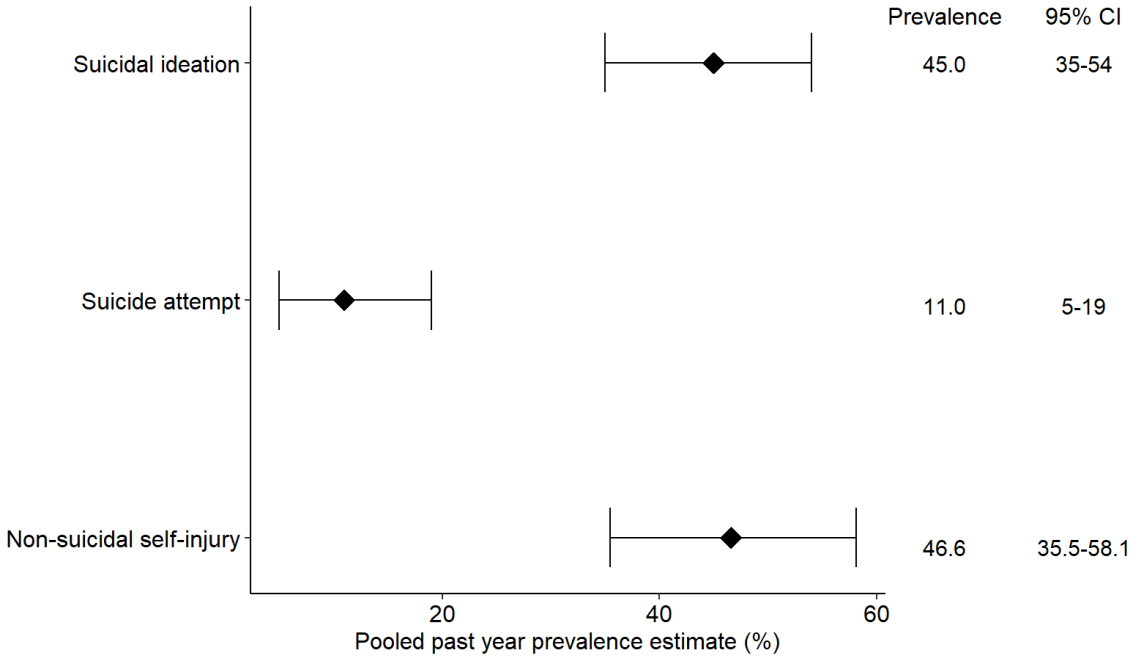


Figure 2. Forest plots of pooled past-year and lifetime prevalence estimates for various mental health outcomes in trans and non-binary populations from five meta-analyses.

Past-year Prevalence



Lifetime Prevalence

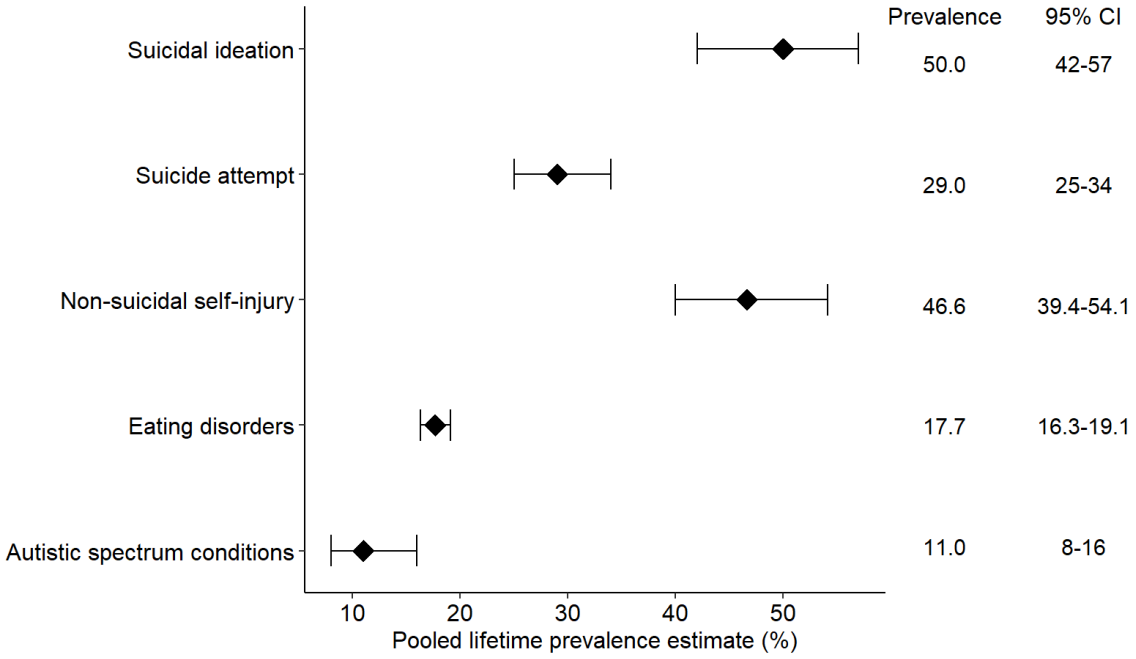
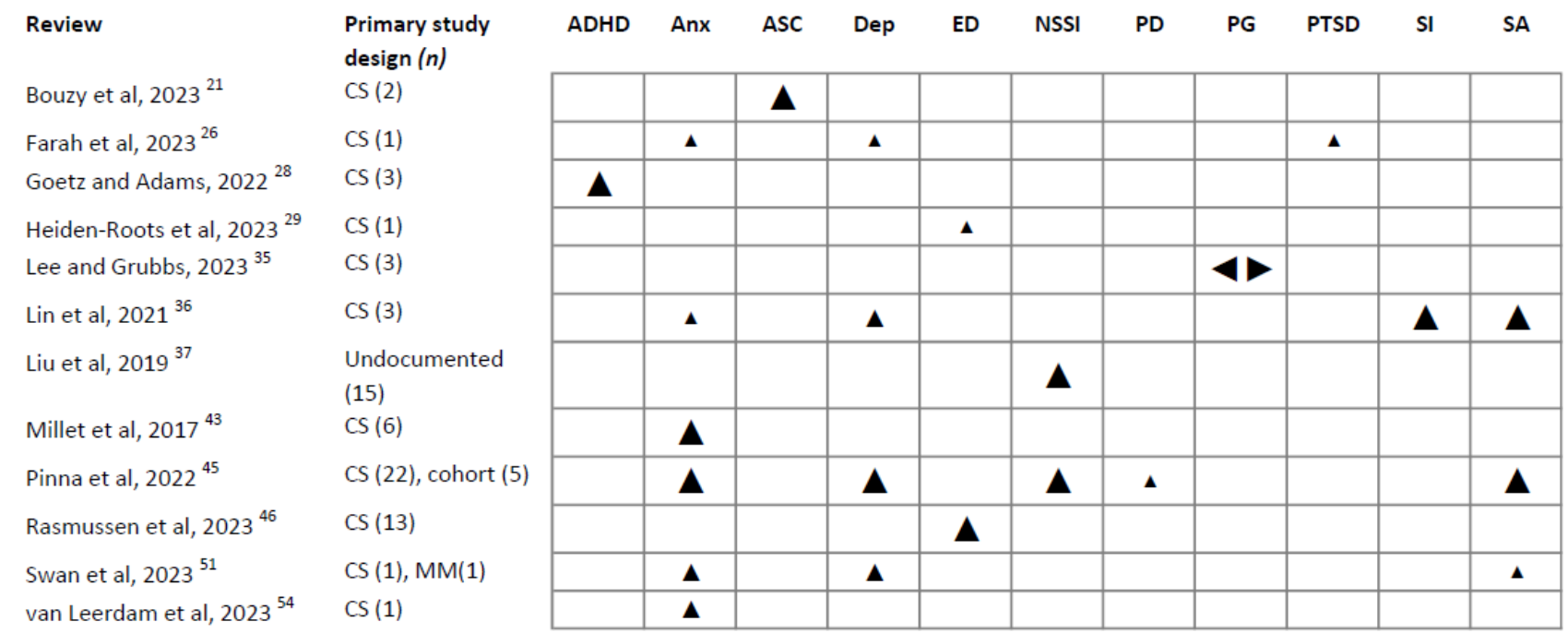


Figure 3. Effect direction plot for mental health and neurodevelopmental outcomes in trans and non-binary populations compared to cisgender/general populations.



LEGEND

ADHD: attention deficit hyperactivity disorder; Anx: anxiety; ASC: Autistic spectrum conditions; CS: cross-sectional; Dep: depression; ED: eating disorder; MM: mixed methods; NSSI: non-suicidal self-injury; PD: personality disorder; PG: problem gambling; PTSD: post-traumatic stress disorder; SI: suicidal ideation; SA: suicide attempt.

Effect direction: ▲= higher risk/prevalence of mental health outcomes, ▼ = lower risk/prevalence of mental health outcomes, ◄► = no change/conflicting findings

Sample size: Final sample size in transgender group. ▲ = sample >300; ▲ = sample 50-300; ▲ = sample <50

Tables

Table 1. Summary descriptives of reviews included in data synthesis for umbrella review of mental health and neurodevelopmental outcomes in trans and non-binary people (n=24).

Author (year)	***Summarised aim***	***Participant demographics & setting***	***Number of primary studies relevant to review$***	***Date range of primary studies relevant to review***	***Mental health outcomes assessed***	***Outcome assessment***	***Tool for assessing quality of primary studies***	***Method of synthesis***	***Review quality #***
Adams and Vincent, 2019 [19]	To assess impact of race/ethnicity, education and income on lifetime suicidal behaviour in trans people.	Canada and USA	64	1997 – 2017	Suicide	Self-report	None	NS	Critically low
Aggarwal et al, 2021 [20]	To review health needs and barriers of TWSW.	TWSW; USA	19	2008 - 2016	General*	Self-report	STROBE	NS	Critically low
Bouzy et al, 2023 [21]	To assess co-occurrence of ASD and GD.	International	35	1992 – 2022	ASC	Screening tools	None	NS	Critically low
Castro et al, 2022 [22]	To review health of trans migrants.	Trans migrants; international	6	2013 – 2018	General*	Self-report; EHR	MMAT	NS	Critically low
Farah et al, 2023 [26]	To review trans health in the Middle East.	Middle East	12	2010 – 2021	General*	Self-report	None	NS	Critically low
Goetz and Adams, 2022 [28]	To summarise literature on ADHD and trans identity.	International	17	2014 -2021	ADHD	Self-report; EHR	None	NS	Critically low
Heiden-Rootes et al, 2023 [29]	To examine evidence of TNB adult experience eating and body-image related issues.	International	59	1988 – 2022	Eating disorders	Self-report; EHR; screening tools	4 questions from STROBE	NS	Critically low
Kallitsounaki and Williams, 2022 [32]	To appraise evidence of co-occurrence of ASD and GD.	International	47	2010 – 2021	ASC	Self-report; EHR; screening tools	None	MA	Critically low
Kohnepoushi et al, 2023 [34]	To determine global prevalence of suicidal thoughts and behaviours in trans people.	International	65	1997 – 2022	Suicide	Self-report	NOS	MA	Critically low
Lee and Grubbs, 2023 [35]	To synthesis research related to gambling in SGM individuals.	SGM people; International	4	2003 – 2022	Addiction	Screening tools	None	NS	Critically low

Lin et al, 2021[36]	To summarise mental health of TGNC individuals in China.	China	30	2015 – 2021	General*	Self-report; screening tools	SQAC	NS	Critically low
Liu et al, 2019[37]	To synthesise evidence of NSSI in SGM individuals.	SGM people; international	18	2014 – 2019	NSSI	Screening tools	None	MA	Critically low
Marchi et al, 2022[38]	To summarise NSSI, suicidal ideation and behaviour in LGBTIQ people.	International	13	2014 – 20210	Suicide; NSSI	Self-report; screening tools	Cochrane ROB	MA	Critically low
Marchi et al, 2023[39]	To summarise PTSD in LGBTQ people.	International	7	2010-2022	PTSD	DSM/ICD criteria; screening tools	Cochrane ROB	MA	Low
Millet et al, 2017[43]	To describe prevalence of anxiety symptoms and disorders in trans people.	International	25	2000 – 2017	Anxiety	EHR; screening tools	None	NS	Critically low
Mongelli et al, 2018 [44]	To synthesis evidence describing mental health and experience of MS in LGBT people.	International	11	2014 – 2018	Depression; suicide	Self-report	None	NS	Critically low
Pinna et al, 2022 [45]	To summarise evidence of mental health in trans people.	International	145	1997 - 2021	General*	Self-report; EHR; screening tools	None	NS	Critically low
Rasmussen et al, 2023 [46]	To synthesis evidence of eating disorders in trans people.	International	24	2005 – 2021	Eating disorders	Screening tools	JBI Critical Appraisal Checklist	MA	Critically low
Ruppert et al, 2021 [48]	To describe addictions in TGD subgroups.	International	15	1992 – 2020	Addiction	Self-report; screening tools	None	NS	Critically low
Scheer et al, 2023 [49]	To assess PTSD in sexual minority women.	Trans sexual minority women; international.	14	2016 - 2022	PTSD	Self-report; screening tools	NIHQAT	MA	Critically low
Scheim et al, 2020 [50]	To review trans men's health outcomes in LMIC.	Trans men, LMIC.	17	2000 - 2020	General*	Self-reporting; EHR	None	NS	Critically low
Swan et al, 2022 [51]	To assess mental health outcomes in trans people undergoing GAS.	Trans people with GAS; international.	20	2006 – 2021	General*	Self-report; screening tools	CASP, MMAT, NIQHAT	NS	Critically low
van Leerdam et al, 2023 [54]	To assess the evidence of GAHT on GD, psychological wellbeing and QOL.	International	15	1983 – 2018	Anxiety; depression	Screening tools	None	NS	Critically low
Vigny-Pau et al, 2021 [55]	To assess risk and protective factors for suicide and NSSI in trans people.	International	52	2006 – 2020	Suicide; NSSI	Self-report	NOS	NS	Critically low

ASC: autistic spectrum conditions; CASP: Critical appraisal skills programme checklist; Cochrane ROB: Cochrane risk of bias tool; EHR: electronic health records; GAS: gender-affirming surgery; GAHT: gender-affirming hormone treatment; GD: gender dysphoria; JBI: Joanna Briggs Institute; LGBT: lesbian, gay bisexual and transgender; LGBTIQ: lesbian, gay, bisexual, transgender, intersex and queer; LGBTQ: lesbian, gay, bisexual, trans and queer; MA: meta-analysis; MS: minority stress; MMAT: Mixed methods appraisal tool; NIH: National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies; NOS: Newcastle Ottawa score; NS: narrative synthesis; NSSI: non-suicidal self-injury; PTSD: post-traumatic stress disorder; QOL: quality of life; SGM: Sexual and gender minority; SQAC: Standard quality assessment criteria for evaluating primary research papers from a variety of fields; STROBE: Strengthening the reporting of observational studies in epidemiology; TGNC: transgender and gender non-conforming; TNB: transgender and non-binary; TWSW: Transgender women sex workers.

[$] Number of primary studies relevant to the review represents the total number of primary studies relevant to mental health and neurodevelopmental outcomes specifically in trans and non-binary people, and does not include primary studies considering other clinical outcomes or non-trans groups (i.e. LGBT-focused studies).

[#] Quality of included reviews was assessed using AMSTAR2 criteria. Reviews are graded “high” to “critically low” based on number of critical weaknesses as per the AMSTAR2 guidance.

* General: Used where reviews provided an overview and addressed multiple mental health outcomes, or where mental health was described in its entirety. More detail on the sub-topics addressed in each of these reviews is included in the supplements.

Panel 1. Key themes from included reviews reporting methodological limitations and literature gaps in primary studies describing mental health and neurodevelopmental outcomes in trans and non-binary people.

Measurement issues

• Heterogeneity in assessment of gender identity:
  ○ Differing definitions of TNB population.
  ○ Evolving terminology describing gender identity over time.
• Heterogeneity in assessment of mental health outcomes:
  ○ Self-reporting or use of electronic health records
  ○ Use of various screening/diagnostic tools – validation unclear in TNB populations.
• Small sample sizes.
• Aggregation of TNB population with other minority groups (e.g. LGBT populations or combining men who have sex with men with trans women).

Selection issues

• Sampling methods introducing selection bias:
  ○ Snowballing and convenience sampling commonly utilised.
  ○ Recruitment through gender identity clinics (only captures a subset of gender minority population able to access to gender-affirming care).
• Lack of appropriate control or comparison groups.

Factors limiting generalisability
• Importance of cultural, legal and religious context in lived experience of TNB people. • Sampling frame of individuals accessing gender identity health services or engaged with TNB community. • Predominantly white/Caucasian participants.

• Majority of evidence from US. • English language restriction applied in search strategy.
Evidence gaps and recommendations for future research
• Limited research considering intersectionality (especially considering role of ethnicity). • Lacking evidence from rural contexts. • Limited evidence describing gender sub-groups, including non-binary identities. • Limited evidence capturing older people's mental health. • Limited longitudinal research. • Lack of engagement with people from TNB community during research process.

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