



Review article

Non-HIV chronic disease burden among transgender populations globally: A systematic review and narrative synthesis

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ARTICLE INFO

Keywords:

Transgender persons
Chronic disease
Health
Systematic review

ABSTRACT

Chronic disease is a growing concern for research, policy and clinical care. While the global burden of HIV for transgender populations has been comprehensively covered in recent systematic reviews, the same is not true for the burden of other chronic disease. The objective of this study was to review the literature on non-HIV chronic disease burden for transgender populations worldwide. A systematic review was conducted of Medline, Embase, CINAHL, PsycINFO and LGBT Life bibliographic databases for peer-reviewed scientific studies with non-HIV chronic disease prevalence data for transgender populations published any date up to February 15, 2019 without restriction on country or study design. A total of 93 studies and 665 datapoints were included in this review, comprising 48 distinct chronic disease outcomes in seven groups (cancer, cerebro/cardiovascular conditions, chronic liver and kidney disease, mental health and substance use conditions, metabolic and endocrine disorders, musculoskeletal and brain disorders, respiratory conditions, and unspecified and other conditions). The empirical literature on chronic disease among global transgender populations focuses on mental health morbidity, demonstrating an evidence gap on chronic physical health morbidity, particularly beyond that of sexual health. This review identified important gaps including in age-related conditions, inflammation-related disease and studies designed explicitly to investigate chronic disease burden among transgender populations. There is a need for high quality evidence in this area, including longitudinal population-based studies with appropriate comparison groups, and consistent measurement of both transgender status and chronic conditions.

1. Introduction

1.1. Chronic disease as a public health issue

Chronic disease is a leading cause of morbidity and mortality globally, accounting for 63% of deaths annually— with cardiovascular disease, diabetes, cancer, and chronic respiratory conditions responsible for much of the disease burden (80%) (World Health Organization. *Global Status Report on Noncommunicable Diseases, 2010*). In addition to premature mortality, consequences of chronic disease include medical complications, elevated risk of other co-morbidities, and disability (World Health Organization, 2010; Forouzanfar et al., 2016). At the population level, chronic disease morbidity impacts growing healthcare system burden and cost, healthcare-cost related poverty, and larger economic effects (World Health Organization, 2010), such that each 10% increase in chronic disease burden corresponds with a 0.5% lower

rate of annual economic growth globally (Stuckler, 2008). Despite advances in medicine, technology and healthcare systems that have eradicated many serious threats to human health, chronic disease burden continues to rise worldwide, increasingly so in middle and low-income countries (Forouzanfar et al., 2016). Mounting chronic disease burden is further fueled by population growth and ageing as the global population increasingly lives in a post epidemiologic transition context (Kivimäki et al., 2015). Importantly, key drivers of chronic disease include modifiable risk factors such as environmental exposures (e.g. workplace risks, sanitation services), access to social and material resources (e.g. healthy food, freedom from violence, adequate income) and health behaviours (e.g. substance use, exercise), and thus may be more intervenable than risk factors for acute and other illnesses. (Forouzanfar et al., 2016) This is therefore an important area for public health focus.

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<https://doi.org/10.1016/j.pmedr.2020.101259>

Received 9 June 2020; Received in revised form 9 November 2020; Accepted 15 November 2020

Available online 28 November 2020

2211-3355/© 2020 The Authors.

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1.2. Transgender populations and chronic disease

While chronic disease for transgender populations has been recognized as a priority research area (IOM, 2011), there is scarce literature in this area, particularly outside of HIV and mental health conditions (Reisner et al., 2016; Marshall et al., 2019). HIV among transgender populations has been well reviewed recently and globally (Reisner et al., 2016; Baral et al., 2013; Poteat et al., 2016; Reisner and Murchison, 2016; Herbst et al., 2008; Becasen et al., 2019; MacCarthy et al., 2017). A review of research on the global health burden of transgender populations published from 2008 to 2014 found only 7% of included data on general health (e.g. chronic disease, mortality), mostly in the United States (US) (Reisner et al., 2016). Of the limited research, there is evidence transgender people experience poorer physical health compared to cisgender people (Reisner et al., 2016). Much of the existing research, beyond sexual and mental health, has focused on cardiovascular conditions among transgender people accessing gender affirming hormone therapy (GAHT), again largely in the US, although also in Europe (Streed et al., 2017). Studies have shown that transgender people have higher prevalence of any chronic disease (Witten, 2014) as well as multimorbidity, compared to cisgender groups (Downing and Przedworski, 2018). Chronic disease burden may also be exacerbated for transgender people who are racialized (Seelman et al., 2017; Brown and Jones, 2014), older (Swartz et al., 2019), of lower socioeconomic status (Seelman et al., 2017), have poor access to other social determinants of health (Blosnich et al., 2017), and live with co-morbidities (Proctor et al., 2016).

1.3. Rationale and objectives for this review

No systematic review of the literature has been conducted of chronic disease burden for transgender populations. This study sought to systematically review and synthesize all available epidemiologic data on chronic disease burden, primarily prevalence in this case, among transgender populations, to identify areas for future research, and inform healthcare practice, policy focus and action. Initially, we also aimed to assess whether chronic illness burden was greater for transgender populations living with HIV compared to those living with HIV as data were available; however, the number of studies reporting HIV chronic co-morbidities for transgender people captured in this review was too few to warrant a sub-analysis.

2. Methods

2.1. Protocol and registration

The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, <https://www.crd.york.ac.uk/prospéro>), registration number CRD42020104077. The review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

2.2. Eligibility criteria

This review included peer-reviewed journal articles reporting quantitative data on the prevalence of chronic disease among transgender people. Studies with a very small transgender sample sizes ($n < 10$) and those published in languages other than English, French, Spanish, Italian, or Portuguese were excluded. Given the evidence need, no restrictions were placed on publication date, study country, or type of study design. If multiple publications reported the same chronic disease outcomes from a single study, the article reporting the most chronic disease data was included. For reported mental health and substance use outcomes, those based on symptomology assessments were excluded (e.g. psychometric scales for depression), for consistency with study

outcomes in other chronic disease groups.

2.3. Information sources

MEDLINE, Embase, CINAHL, PsycINFO, and LGBT Life bibliographic databases were electronically searched for peer-reviewed literature published through February 15, 2019.

2.4. Literature search

The search strategy was developed in consultation with a research librarian at the University of British Columbia and included Medical Subject Headings (MeSH terms) and keywords related to the two main search concepts: transgender persons and chronic disease. Commonly used terms for both concepts were included as subject headings and keywords, such as “transsexual”, or “gender minority” for transgender; and “long-term illness”, “chronic disease”, or “diabetes” for chronic conditions. The MEDLINE search strategy is included in [Supplementary material](#).

2.5. Study selection

Studies were screened in parallel by two independent reviewers (AJR, AIS) using Covidence (Veritas Health Innovation, Melbourne). Reviewers rated studies for inclusion or exclusion at the title and abstract level first, then at the full text level. Disagreements at each screening phase were resolved through discussion and reasons for exclusion recorded.

2.6. Data extraction

Data elements extracted included participant characteristics, study design, sample size, and outcomes. One reviewer (AJR) extracted data from included publications using a predetermined extraction form. The second reviewer (AIS) assessed a 10% sample of extracted data for accuracy and any discrepancies were resolved through discussion between the two reviewers (Inter-rater reliability, percent agreement: 97%). Both the number of unique studies and the number of relevant datapoints reported in each study were captured. For example, a study reporting cancer outcomes for transgender people counted as $n = 1$ at the study level. If this study reported the prevalence of multiple cancer types (e.g. lung cancer and skin cancer), it counted as $n = 2$ at the datapoint level. Further, if the study reported cancer outcomes for multiple transgender sub-groups (e.g. by gender, race), each reported outcome was counted as a unique datapoint. For mental health and substance use outcomes, only diagnoses based on self-report, provider-report, or structured clinical interviews were included as most reliable measures of chronic disease conditions; assessments of symptomology (e.g., depression symptom scales) were excluded.

3. Results

3.1. Study selection

As shown in [Fig. 1](#), 11,272 unique records were identified from the electronic database search. After title and abstract screening, 10,848 records were excluded with 424 articles assessed for eligibility via full text review. Of these, 93 articles were eligible for the review.

3.2. Study characteristics

The 93 studies included 665 datapoints, reporting 48 unique chronic disease outcomes. Outcomes were grouped into seven chronic condition groups, adapted from the (World Health Organization. [Global Status Report on Noncommunicable Diseases, 2010](#)), for the purpose of narrative synthesis ([Fig. 2, Supplementary material](#)) (Popay et al.,

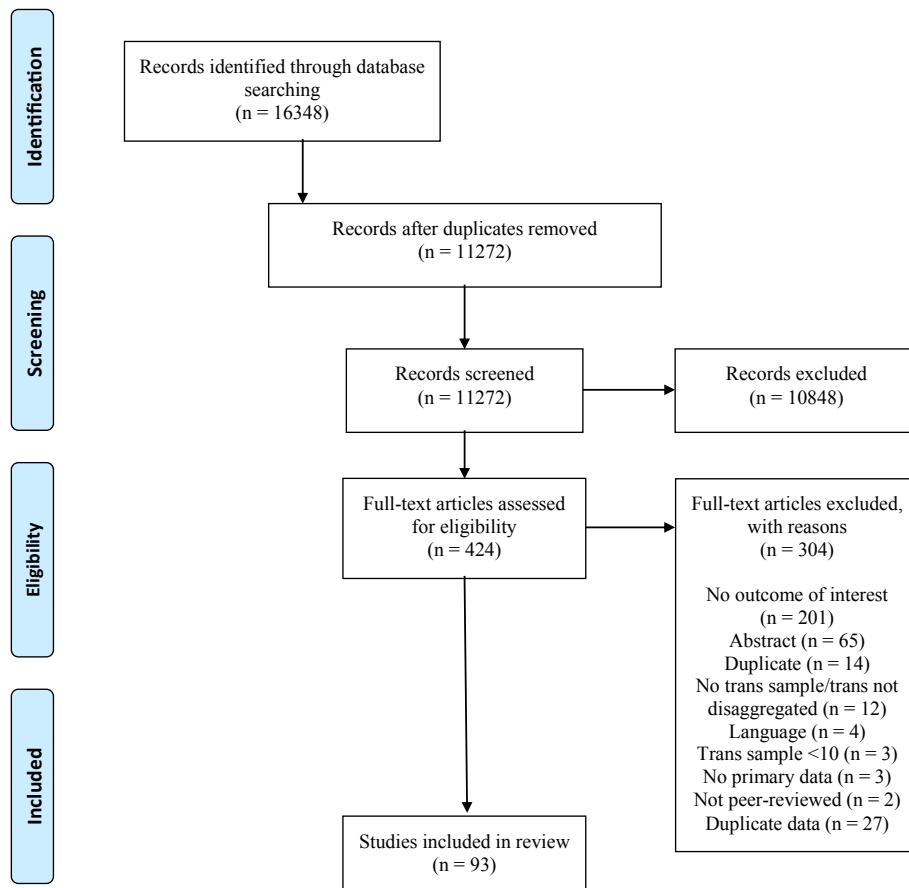


Fig. 1. PRISMA flowchart for study screening for systematic search.

Figure 2. Chronic disease groups captured in the systematic review, proportion by study and datapoint

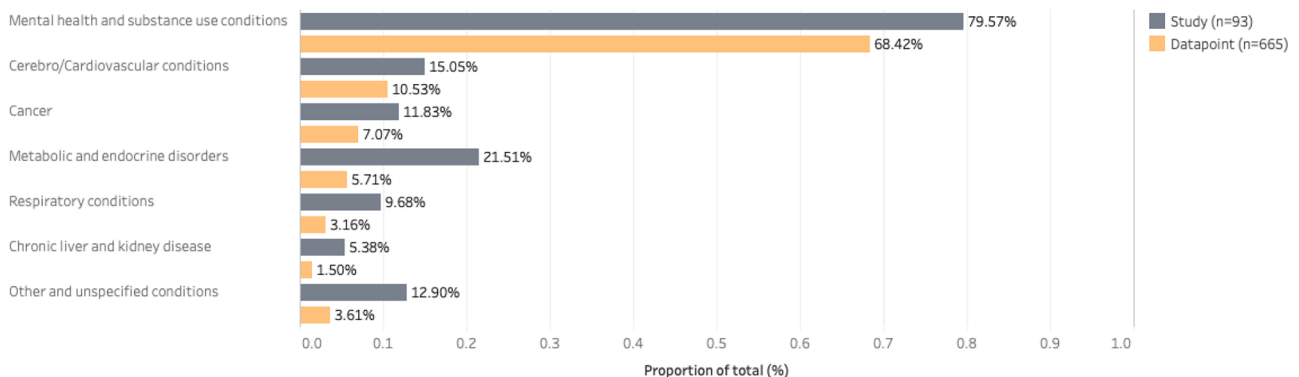


Fig. 2. Chronic disease groups captured in the systematic review, proportion by study and datapoint.

2006).

As summarized in Table 1, articles were published between 1980 and 2019: 57% were published in the five years preceding the search (2015–2019) and 85% in the decade preceding the search (2010–2019). Nearly half of included studies were clinical samples (44%), nearly one-quarter convenience samples (23%), 22% electronic medical record (EMR), 6% respondent-driven sampling (RDS) or snowball sampling methods, and 5% probability-based samples. A majority of studies employed cross-sectional designs (77%), nearly one-fifth longitudinal designs (17%), one a case-control design, and one a randomized controlled trial (RCT). Only 6.46% employed matching of any kind. Study design was classified based on analytic design (e.g. if a study used

data from a retrospective cohort but treated the sample as cross-sectional in analysis, it was categorized as cross-sectional).

Studies were conducted primarily in the US (46%), with 6% published in Canada, 5% each in Spain and The Netherlands, and all other countries contributing less than 5% of included studies (Fig. 3). The global distribution of studies spanned Asia (6%), Europe (28%; including one study conducted in multiple countries in the region), Latin America (2%), the Middle Eastern and North African (MENA) region (6%), North America (53%), Oceania (3%; including one study conducted in multiple countries in the region); and one study spanning multiple regions (1%) conducted in 24 countries including primarily the US, Canada, Australia, Sweden and the United Kingdom. None were

Table 1
Studies and study characteristics included in systematic review.

Study ID	Study sample	Country	Sampling method	Study design	Trans sample size	Chronic condition outcomes
ASIA						
(Chen et al., 2019)	Transgender people	China	Convenience	Cross-sectional	1309	Mental health and substance use disorders
(Kalra and Shah, 2013)	Hijras accessing an STI clinic	India	Clinical	Cross-sectional	50	Mental health and substance use disorders
(Baba et al., 2011)	Transgender men patients at a GID clinic	Japan	Clinical	Cross-sectional	178	Metabolic and endocrine disorders
(Hoshiai et al., 2010)	GID clinic patients	Japan	Clinical	Cross-sectional	579	Mental health and substance use disorders
(Rutledge et al., 2018)	Transgender women	Malaysia	Convenience	Cross-sectional	199	Mental health and substance use disorders
(Lim et al., 2019)	Transgender OBGYN clinic patients	South Korea	EMR	Cross-sectional	54	Mental health and substance use disorders
EUROPE						
(Cuyper et al., 1995)	Applicants for GAS at a gender identity clinic	Belgium	Clinical	Cross-sectional	35	Mental health and substance use disorders
(Defreyne et al., 2017)	Transgender endocrine clinic patients starting GAHT	Belgium	Clinical	Cross-sectional	1081	Metabolic and endocrine disorders
(Weyers et al., 2009)	Transsexual women accessing GAS	Belgium	Clinical	Cross-sectional	50	Unspecified and other diseases
(Wierckx et al., 2013)	Transgender gender clinic patients accessing GAHT, with cisgender control group	Belgium	Clinical	Cross-sectional	352	Cerebro/Cardiovascular diseases
(Simonsen et al., 2016)	Transsexual people accessing GAS at a public GID clinic	Denmark	EMR	Retrospective cohort	104	Cancer; Cerebro/Cardiovascular diseases; Chronic liver and kidney disease; Other and unspecified diseases; Respiratory disease
(Simonsen et al., 2016)	Transsexual people accessing GAS at a public GID clinic	Denmark	EMR	Retrospective cohort	104	Mental health and substance use disorders
(Holt et al., 2016)	Youth referred to a gender identity clinic	England	Clinical	Cross-sectional	218	Mental health and substance use disorders
Judge et al. (Judge et al., 2014)	Endocrine clinic patients with suspected or confirmed GD referred for GAHT	Ireland	Clinical	Cross-sectional	218	Cerebro/Cardiovascular conditions; Metabolic and endocrine disorders; Mental health and substance use disorders
(Colizzi et al., 2014)	Transgender patients at a gender identity clinic	Italy	Clinical	Prospective cohort	118	Mental health and substance use disorders
(Fisher et al., 2013)	Patients with GID at a GID clinic, without previous GAS	Italy	Clinical	Cross-sectional	140	Mental health and substance use disorders
(Madeddu et al., 2009)	Transsexual GID psychiatric clinic patients seeking GAS	Italy	Clinical	Cross-sectional	50	Mental health and substance use disorders
(Heylens et al., 2014)	Adults with GID seeking GAHT/ GAS at gender clinics	Multiple (The Netherlands, Belgium, Germany, Norway)	Clinical	Cross-sectional	305	Mental health and substance use disorders
(Haraldsen and Dahl, 2000)	Transsexual patients with GAS history and cisgender personality disorder patients and cisgender healthy controls	Norway	Clinical	Cross-sectional	86	Mental health and substance use disorders
(Duišin et al., 2014)	Transgender psychiatric clinic patients and cisgender heterosexual comparison group	Serbia	Clinical	Cross-sectional	30	Mental health and substance use disorders
(Becerra-Fernandez et al., 2014)	Transgender men patients with GD diagnosis at GID clinic	Spain	Clinical	Cross-sectional	77	Metabolic and endocrine disorders
(Bergero-Miguel et al., 2016)	Transgender patients with GD at a public gender identity clinic	Spain	Clinical	Cross-sectional	210	Mental health and substance use disorders
(Gómez-Gil et al., 2009)	Transsexual patients with GD seeking GAS/GAHT	Spain	Clinical	Cross-sectional	230	Mental health and substance use disorders
(Guzmán-Parra et al., 2016)	Transsexual patients of a gender identity clinic	Spain	Clinical	Cross-sectional	197	Mental health and substance use disorders
(Vilas et al., 2014)	Transgender gender disorder clinic patients accessing GAHT	Spain	Clinical	Prospective cohort	157	Metabolic and endocrine disorders
(Bodlund and Kullgren, 1996)	Transsexual patients accessing GAS	Sweden	Clinical	Prospective cohort	19	Mental health and substance use disorders
(Hepp et al., 2005)	Psychiatric clinic patients with GID	Switzerland	Clinical	Cross-sectional	31	Mental health and substance use disorders
(de Vries et al., 2011)	Adolescent gender identity clinic patients with GID	The Netherlands	Clinical	Cross-sectional	105	Mental health and substance use disorders
(Gooren et al., 2013)	Transsexual patients accessing GAHT	The Netherlands	EMR	Retrospective cohort	3102	Cancer
		The Netherlands	EMR		2306	Cancer

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Table 1 (continued)

Study ID	Study sample	Country	Sampling method	Study design	Trans sample size	Chronic condition outcomes
(Gooren and Morgentaler, 2014)	Transsexual women gender clinic patients with history of GAHT and orchiectomy			Retrospective cohort		
(Van Kesteren et al., 1997)	Transsexuals receiving GAHT	The Netherlands	EMR	Retrospective cohort	1109	Cerebro/Cardiovascular diseases
(Wallien et al., 2007)	Dutch children referred to a GID clinic, and a comparison group of children referred to an ADHD clinic	The Netherlands	Clinical	Cross-sectional	120	Mental health and substance use disorders
LATIN AMERICA						
(Fontanari et al., 2018)	Transgender women patients at a GD clinic	Brazil	Clinical	Cross-sectional	289	Mental health and substance use disorders
(Lobato et al., 2007)	Transsexual patients in a GID program	Brazil	Clinical	Cross-sectional	138	Mental health and substance use disorders
MIDDLE EAST AND NORTHERN AFRICA REGION						
(Aghabikloo et al., 2012)	Patients with GID seeking GAS	Iran	Clinical	Cross-sectional	69	Mental health and substance use disorders
(Havar et al., 2015)	Patients with GID accessing GAS	Iran	Clinical	Cross-sectional	108	Mental health and substance use disorders
(Mazaheri Meybodi et al., 2014)	Transsexual psychiatric clinic patients with GID	Iran	Clinical	Cross-sectional	83	Mental health and substance use disorders
(Ibrahim et al., 2016)	Transgender and cisgender adult controls	Lebanon	RDS/Snowball	Cross-sectional	20	Mental health and substance use disorders
(Basar and Oz, 2016)	GD diagnosed psychiatric clinic patients	Turkey	Clinical	Cross-sectional	116	Mental health and substance use disorders
(Yildirim et al., 2017)	Children and adolescent psychiatric clinic patients with GID and a matched control group with non-GID diagnoses	Turkey	Clinical	Matched cross-sectional	20	Mental health and substance use disorders
NORTH AMERICA						
(Chiniara et al., 2018)	Adolescents presenting to a transgender youth clinic	Canada	Clinical	Cross-sectional	203	Mental health and substance use disorders
(Drummond et al., 2018)	Assigned female sex at birth patients referred to a gender identity clinic as youth	Canada	Clinical	Prospective cohort	25	Mental health and substance use disorders
(Heard et al., 2018)	Transgender youth patients of a GD program	Canada	Clinical	Cross-sectional	174	Mental health and substance use disorders
(Rotondi et al., 2011)	Transfeminine adults	Canada	RDS/Snowball	Cross-sectional	186	Mental health and substance use disorders
(Rotondi et al., 2011)	Transmasculine adults	Canada	RDS/Snowball	Cross-sectional	205	Mental health and substance use disorders
(Williams et al., 2017)	Women and transgender/gender liminal people	Canada	Convenience	Cross-sectional	193	Mental health and substance use disorders
(Becerra-Culqui et al., 2018)	Transgender youth patients	United States	EMR	Matched cross-sectional	1333	Mental health and substance use disorders
(Beckwith et al., 2017)	HIV-positive adults with criminal justice system involvement history	United States	Convenience	Randomized controlled trial	20	Mental health and substance use disorders
(Beckwith et al., 2017)	Transgender patients at an LGBT community clinic	United States	EMR	Cross-sectional	145	Mental health and substance use disorders
(Brooksmith et al., 2018)	Pediatric endocrine clinic patients with GD diagnosis	United States	Clinical	Cross-sectional	78	Metabolic and endocrine disorders
(Brown and Jones, 2016)	Veterans	United States	EMR	Matched case-control	5135	Cancer; Cerebro/Cardiovascular diseases; Chronic liver and kidney disease; Mental health and substance use disorders; Metabolic and endocrine disorders; Other and unspecified diseases; Respiratory disease
(Chen et al., 2016)	Pediatric endocrinology clinic patients referred for GD	United States	Clinical	Retrospective cohort	38	Mental health and substance use disorders
(Cole et al., 1997)	Individuals presenting to a gender clinic with GD or transsexualism	United States	Clinical	Cross-sectional	435	Mental health and substance use disorders
(Dai and Hao, 2019)	Adults	United States	Probability-based	Cross-sectional	669	Cancer; Cerebro/Cardiovascular diseases; Chronic liver and kidney disease; Mental health and substance use disorders; Metabolic and endocrine disorders; Other and unspecified chronic diseases; Respiratory conditions
		United States	Convenience	Cross-sectional	54	

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Table 1 (continued)

Study ID	Study sample	Country	Sampling method	Study design	Trans sample size	Chronic condition outcomes
(Dawson et al., 2017)	Amazon Mechanical Turk workers					Mental health and substance use disorders
(Dragon et al., 2017)	Medicare beneficiaries	United States	EMR	Cross-sectional	7454	Cancer; Cerebro/Cardiovascular conditions; Chronic liver and kidney disease; Mental health and substance use disorders; Metabolic and endocrine disorders; Other and unspecified diseases; Respiratory disease
(Flentje et al., 2014)	People entering publicly funded substance abuse treatment	United States	EMR	Cross-sectional	199	Mental health and substance use disorders
(Flentje et al., 2016)	Urban homeless sexual and gender minorities	United States	Convenience	Cross-sectional	49	Mental health and substance use disorders; Unspecified and other diseases
(Gaither et al., 2017)	Transgender women patients seeking GAS from a high-volume surgeon	United States	Clinical	Cross-sectional	330	Cerebro/Cardiovascular diseases; Mental health and substance use disorders; Metabolic and endocrine disorders; Respiratory disease; Unspecified and other diseases
(Hill et al., 2016)	Transgender veterans and active duty service members	United States	Convenience	Cross-sectional	106	Cancer; Cerebro/Cardiovascular diseases; Mental health and substance use disorders; Metabolic and endocrine disorders; Other and unspecified diseases; Respiratory disease
(Hutchison et al., 2018)	Transgender patients in a state cancer registry	United States	EMR	Retrospective cohort	230	Cancer
(Jarín et al., 2017)	Adolescent patients with GD on GAHT	United States	EMR	Retrospective cohort	116	Mental health and substance use disorders
(Katz-Wise et al., 2017)	Transgender and gender non-conforming adults	United States	Convenience	Cross-sectional	452	Mental health and substance use disorders
(Katz-Wise et al., 2018)	Transgender and gender non-conforming youth and their families	United States	Convenience	Cross-sectional	33	Mental health and substance use disorders
(Keuroghlian et al., 2015)	Transgender and gender non-conforming adults	United States	Convenience	Cross-sectional	452	Mental health and substance use disorders
(Klemmer et al., 2018)	Transgender women	United States	RDS/Snowball	Cross-sectional	233	Mental health and substance use disorders
(Lindsay et al., 2016)	Transgender veterans of Iraq or Afghanistan accessing the VHA	United States	EMR	Cross-sectional	332	Mental health and substance use disorders
(Liu et al., 2019)	College students	United States	Probability-based	Cross-sectional	301	Mental health and substance use disorders
(Lothstein, 1980)	Adolescent gender identity clinic patients seeking GAS	United States	Clinical	Prospective cohort	27	Mental health and substance use disorders
(Lytle et al., 2016)	College students	United States	Probability-based	Cross-sectional	123	Mental health and substance use disorders
(Mustanski et al., 2010)	LGBT youth	United States	Convenience	Cross-sectional	20	Mental health and substance use disorders
(Nahata et al., 2017)	Transgender adolescents at an urban clinical gender program, referred for GAHT	United States	EMR	Cross-sectional	79	Mental health and substance use disorders
(Nokoff et al., 2018)	Adults	United States	Probability-based	Cross-sectional	764	Cerebro/Cardiovascular diseases; Metabolic and endocrine disorders
(Nuttbrock et al., 2015)	Transgender women	United States	Convenience	Prospective cohort	230	Mental health and substance use disorders
(Odo and Hawelu, 2001)	Native Hawaiian transgender women HIV prevention program clients and general population comparison group	United States	Clinical	Cross-sectional	100	Metabolic and endocrine disorders
(Quinn et al., 2017)	Transgender health system patients, and cisgender matched comparison group	United States	EMR	Matched cross-sectional	6456	Cancer; Cerebro/Cardiovascular diseases; Mental health and substance use disorders; Metabolic and endocrine disorders
(Qureshi et al., 2018)	LGBT adults	United States	Convenience	Cross-sectional	27	Cerebro/Cardiovascular diseases
(Reisner et al., 2013)	Transmasculine adult attendees of a transgender health conference	United States	Convenience	Cross-sectional	73	Mental health and substance use disorders; Metabolic and endocrine disorders; Respiratory disease
(Reisner et al., 2014)	Transgender men accessing STI testing at an LGBT community clinic	United States	EMR	Cross-sectional	23	Mental health and substance use disorders
(Reisner et al., 2015)	Transgender youth/young adult patients of an adolescent urban community health center, and matched cisgender controls	United States	EMR	Matched cross-sectional	180	Mental health and substance use disorders
(Reisner et al., 2016)	Young transgender women	United States	Convenience	Cross-sectional	298	Mental health and substance use disorders

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Table 1 (continued)

Study ID	Study sample	Country	Sampling method	Study design	Trans sample size	Chronic condition outcomes
(Reisner et al., 2016)	Transmasculine adults who have sex with cisgender men	United States	Convenience	Cross-sectional	173	Mental health and substance use disorders
(Seelman et al., 2017)	Transgender and gender non-conforming adults	United States	Convenience	Cross-sectional	417	Cerebro/Cardiovascular diseases; Mental health and substance use disorders; Metabolic and endocrine disorders; Respiratory disease
(Silverberg et al., 2017)	Transgender health system patients, and cisgender matched comparison group	United States	EMR	Matched retrospective cohort	4889	Cancer
(Spack et al., 2012)	Children and adolescents with GID referred for care to a multidisciplinary gender clinic	United States	Clinical	Cross-sectional	97	Mental health and substance use disorders
(Vankim et al., 2014)	College students	United States	Probability-based	Cross-sectional	53	Metabolic and endocrine disorders
(Warren et al., 2016)	LGBT adults	United States	Convenience	Cross-sectional	208	Metabolic and endocrine disorders
(White Hughto and Reisner, 2018)	Transgender and gender non-conforming older adults	United States	Convenience	Cross-sectional	452	Unspecified and other diseases
(Wilson et al., 2015)	Transgender women	United States	RDS/Snowball	Cross-sectional	314	Mental health and substance use disorders
OCEANIA						
(Bolger et al., 2014)	Transgender men	Australia	Convenience	Cross-sectional	279	Mental health and substance use disorders
(Cheung et al., 2018)	New patients with GD at an endocrine and a primary care clinic	Australia	EMR	Cross-sectional	540	Cancer; Cerebro/Cardiovascular diseases; Chronic liver and kidney disease; Mental health and substance use disorders; Respiratory disease
(Pitts et al., 2009)	Transgender people	Multiple: Australia, New Zealand	Convenience	Cross-sectional	253	Mental health and substance use disorders
MULTIPLE/GLOBAL						
(Witten, 2014)	Transgender adults	Multiple (24 countries including primarily United States, Canada, Australia, Sweden, United Kingdom)	RDS/Snowball	Cross-sectional	1963	Unspecified and other disease

Abbreviations: STI = sexually transmitted infections; GID = Gender Identity Disorder; OBGYN = obstetrician/ gynecologist; EMR = electronic medical record; GAS = gender affirming surgery; GAHT = gender affirming hormone treatment; GD = gender dysphoria; ADHD = Attention-Deficit/ Hyperactivity Disorder; HIV = human immunodeficiency virus; LGBT = lesbian, gay, bisexual, trans; VHA = Veterans Health Administration

conducted in sub-Saharan Africa.

A third of studies (33%) reported results for transgender samples without disaggregating by gender. Of those that did disaggregate by gender, nearly all included transgender women (89%) while 21% were conducted exclusively with transgender women. More than three-quarters (77%) of studies included transgender men, while 13% were conducted exclusively with transgender men. Only one study reported disaggregated chronic disease outcomes for gender non-conforming or non-binary people (2%). Included studies employed a diversity of transgender status measures, but the predominant measure was diagnosis-based ascertainment using the Diagnostic and Statistical Manual of Mental Disorders (DSM III-IV; 54%), with an additional 5% using a combination of DSM diagnoses and clinical notes. A third of included studies used an identity measure and 8% used a two-step measure that assessed sex assigned at birth and current gender (The GenIUSS Group. Best Practices for Asking Questions to Identify Transgender and Other Gender Minority Respondents on Population-Based Surveys. The Williams Institute; 2014). The majority of studies sampled adult populations (67%), 16% were among youth, and 17% included mixed age groups.

3.3. Synthesis of results

3.3.1. Mental health and substance use disorders

Mental health and substance use disorders comprised the majority of included data (80% of studies, $n = 74$; 68% of datapoints, $n = 455$). Mood, anxiety, and substance use disorders were the most commonly

studied outcomes in this category (21%, 18%, and 10% of datapoints, respectively). Overall, the lowest prevalence for mood and anxiety disorders was reported in clinical studies with some finding no prevalence among the study samples. The highest prevalence was reported in EMR studies - specifically in US studies of transgender adolescents accessing gender affirming care in an urban center, Medicare beneficiaries, and Veteran Health Administration patients (mood disorder: up to 82%; anxiety disorder: up to 67%) (Nahata et al., 2017). However, substance use disorder estimates varied more by study type, with the highest prevalence (50%) reported by a lifetime measure among transgender women ($n = 20$) with a gender identity diagnosis in a Swiss cross-sectional clinical study of psychiatric morbidity (Hepp et al., 2005).

3.3.2. Cerebrovascular and/or cardiovascular diseases

A total of 15% of studies ($n = 14$) and 11% of datapoints ($n = 70$) included cerebrovascular and/or cardiovascular diseases. The most commonly reported outcomes in this area were cardiovascular disease (7%), hypertension (2%), and hyperlipidemia (1%). Most datapoints in this area were provided via clinical or EMR studies (43%), with 19% from the US probability-based Behavioral Risk Factor Surveillance System (BRFSS) study (Dai and Hao, 2019; Nokoff et al., 2018), and 6% from several convenience samples. Prevalence of cardiovascular disease ranged from no cases in some studies to as high as 30% among a sample of 7,454 transgender adults in an EMR study of Medicare beneficiaries (Dragon et al., 2017). Hyperlipidemia prevalence ranged from 9% to 64%, and hypertension from less than 1% to 60%, with no discernable pattern in terms of study design, sample, gender, or chronic condition

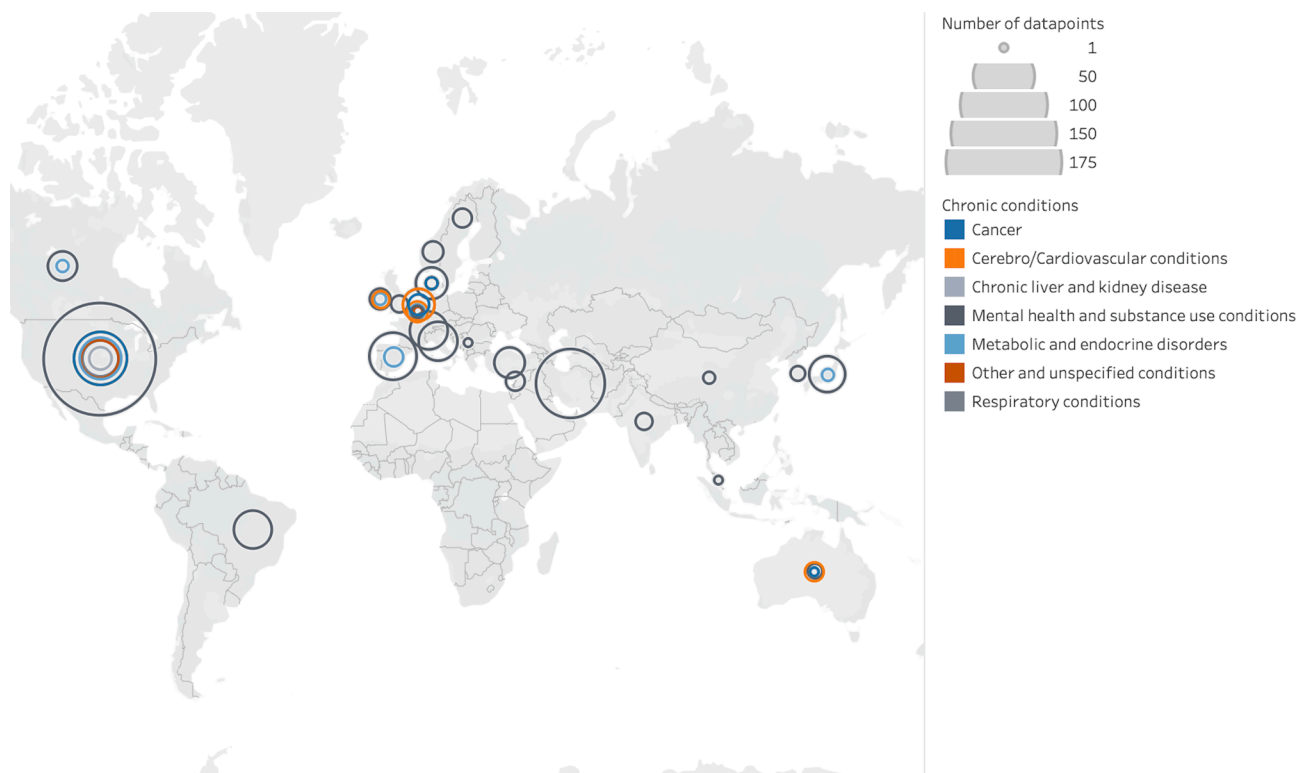


Fig. 3. Global distribution of chronic disease outcomes among transgender populations.

measures or definitions. Cerebrovascular disease comprised three datapoints (0.45%), and prevalence ranged from < 1% in a Netherlands EMR study of transgender people accessing GAHT (Van Kesteren et al., 1997) to 8% in a matched case-control EMR study of US veterans (Brown and Jones, 2016).

3.3.3. Cancer

Cancer outcomes were included in 12% of studies ($n = 11$) and 7% of datapoints ($n = 47$). The most reported cancer conditions were general or unspecified cancer, breast cancer, and viral infection-induced cancers, prostate cancer, and endocrine cancer (<2% of datapoints respectively). Three of the 11 studies reported incidence estimates for cancer outcomes, the remaining 73% reported prevalence exclusively. Of the studies in this area, 55% included cisgender comparators for transgender groups, with mixed evidence on the comparative cancer burden for transgender individuals, both for overall cancer morbidity and specific cancer types (i.e. some studies found cancer disparity for transgender compared to cisgender people, some did not). EMR studies provided the majority of cancer estimates (82%), and many were longitudinal studies (45%). Nearly all cancer outcomes were measured directly via provider diagnosis (i.e. in clinical or EMR studies; 91%), with the remaining measured via self-report diagnosis.

3.3.4. Metabolic and endocrine disorders

Metabolic and endocrine disorders represented 6% of datapoints ($n = 38$) and 22% of studies ($n = 20$). The most common outcome studied in this area was obesity (3% of datapoints), followed by diabetes (2%), and polycystic ovary syndrome (PCOS) and metabolic syndrome (<1% each). Diabetes prevalence ranged widely from <1% to 6% in clinical studies using self-report and provider diagnosis for condition ascertainment, to 27% to 31% in EMR studies relying on clinical diagnosis. Of the two clinical studies reporting PCOS prevalence for transgender men, one in Japan and one in Spain, estimates were comparable (32–36%) and both used the 2003 Rotterdam criteria for condition measurement (Baba et al., 2011; Becerra-Fernandez et al., 2014).

3.3.5. Respiratory disease

Respiratory diseases were included in 10% of studies ($n = 9$) and 3% of datapoints ($n = 21$). The most frequently reported respiratory outcomes were chronic lung disease (2% of datapoints) and asthma (1%). One-third of respiratory outcomes came from convenience samples, 29% EMR and probability-based samples respectively, and 10% clinical. Asthma prevalence was as high as 33% for an age-standardized estimate via self-report in a community-based convenience sample of 73 transmasculine adults attending a transgender health conference in the US (Reisner et al., 2013). Asthma prevalence was as low as 6%, via self-report in a clinical study of 330 transgender women seeking gender-affirming surgery from a high-volume US surgeon (Gaither et al., 2017).

3.3.6. Chronic liver and kidney disease

The lowest proportion of studies (5%, $n = 5$) and 2% of datapoints ($n = 10$) included chronic liver and kidney disease. All studies in this group were EMR-based except for one, using data from the probability-based BRFSS study in the US. Geographically, data was contributed from Europe, Oceania, and the US. Chronic kidney and liver disease were equally reported outcomes (0.75% of all datapoints), with prevalence estimates ranging widely from 3% by self-report provider diagnosis among transgender and gender non-conforming adults in a US probability sample (Dai and Hao, 2019), to 23% by provider diagnosis in an EMR study of transgender Medicare beneficiaries for chronic kidney disease (Dragon et al., 2017). Chronic liver disease was as high as 12% by provider diagnosis, in the same EMR Medicare study (Dragon et al., 2017). In studies that reported outcomes disaggregated by gender (40% of studies in this group), transgender women and men had a similar prevalence of chronic liver and kidney disease.

3.3.7. Other and unspecified diseases

Unspecified chronic diseases and other chronic diseases not otherwise grouped were included in 4% of datapoints ($n = 24$) and 13% of studies ($n = 12$). Arthritis and unspecified chronic diseases were the most commonly reported outcomes in this group (0.75% of datapoints

each). Remaining “other” chronic diseases not included in any other group included pain disorders, osteoporosis, organic brain disorders and injuries, musculoskeletal diseases, gastroesophageal reflux disease, epilepsy, and benign prostatic hyperplasia. Of the five available arthritis datapoints, most were based on self-report diagnosis in probability-based or convenience sample surveys (80%). The remaining arthritis datapoint was the highest prevalence estimate (39%) based on a direct provider diagnosis from an EMR study of Medicare beneficiaries that included 7454 transgender patients (Dragon et al., 2017). Studies providing prevalence estimates of unspecified chronic conditions (e.g. “any chronic condition”, “chronic health condition”) used a diversity of sampling strategies but the majority were self-report measures (53%). Estimates ranged from 26% in a clinical study of 50 Dutch transgender women accessing gender-affirming hormone and surgical care (Weyers et al., 2009), to 50% among transgender women in a convenience sample from a point-in-time population count survey of 1027 homeless sexual and gender minorities in the US (Flentje et al., 2016).

4. Discussion

4.1. Summary of evidence, gaps and future directions

4.1.1. Chronic conditions

This review of global chronic disease burden among transgender populations included 93 studies and 665 datapoints, reporting on 48 unique outcomes and spanning 23 countries and four decades of research. Findings include a predominance of research on mental health. This is consistent with known trends in transgender health research (Marshall et al., 2019), including a 2016 review of the global health burden for transgender populations that found mental health to be the most commonly studied area in transgender health (31% of articles published between 2008 and 2014) and called for research focused on neglected and urgent health areas for transgender populations (e.g. physical health) (Reisner et al., 2016). Our review indicates the focus on mental health research among transgender people persists to the exclusion of other chronic disease.

The continued focus on mental health in transgender research is in part a legacy of the historical psycho-pathologization of transgender status (Bockting, 2009). Transgender-related diagnoses were only recently removed from the World Health Organization International Classification of Diseases (11th edition) chapter on mental and behavioural disorders in 2018, taking effect clinically in 2022 (GATE - » [Joint Statement on ICD-11 process for trans gender diverse people. Published May 24, 2019](#)). Hopefully, this change will contribute to a growing shift away from a disproportionate focus on the mental health of transgender people.

There is a specific need for future research on understudied chronic physical health conditions in transgender populations. This review found gaps in research on age-related chronic conditions including dementia, cancer, hypertension and osteoporosis and inflammation-related chronic illness such as cardiovascular disease, diabetes, and arthritis. For example, in addition to the elevated prevalence of cardiovascular morbidity found in a previous review (Wierckx et al., 2013), there is evidence transgender women are more likely to experience cardiovascular risk factors as well as mortality compared to cisgender adults (Asscheman et al., 2011). Future research on inflammation-related chronic physical conditions is especially relevant for transgender populations. Inflammatory processes implicated in chronic disease morbidity may be compounded by exogenous sex hormone use (an important part of gender-affirming care for many transgender people) (Scheim and Bauer, 2015), by HIV disease that disproportionately affects transgender populations (Poteat et al., 2016), and by chronic disease drivers such as stress, stigma and discrimination (DuBois et al., 2017; Jackson et al., 2010; Busse et al., 2017). The impact of GAHT on health outcomes, including chronic disease, is an important area for future research (Poteat et al., 2014).

The prevailing focus on the sexual and mental health of transgender people has ignored some conditions with a high burden among transgender populations. For example, PCOS, which was reported by only two studies in this review, may affect a third of transgender men (Baba et al., 2011; Becerra-Fernandez et al., 2014). Even within the mental health group, there is a disproportionate focus on mood, anxiety and substance use disorders, to the exclusion of other conditions such as PTSD (affecting up to 23%, in an EMR study of transgender adolescents accessing gender affirming care in a US urban center) (Nahata et al., 2017). The current review found an increase in PTSD research compared to Reisner et al.’s 2016 global health burden review (n = 24, n = 3 datapoints, respectively), but there remains disproportionately little epidemiological evidence in this area. Many studies included in the current review were broad descriptive epidemiological studies characterizing the overall health of transgender samples that further highlights the limited number of studies (n = 3) with an explicit focus on investigating the burden of specific chronic disease among transgender people.

4.1.2. Sampling and study design

Caution is warranted when interpreting prevalence estimates from the existing body of evidence. The majority of included studies were cross-sectional, within-group analyses, using non-representative sampling. Fewer than a third (28%) included cisgender comparator groups to investigate health disparity by gender identity, with only five employing matching for more robust estimates. Much of the data in this review was based on transgender populations in the US, with a predominance of EMR-based studies, primarily those conducted among Medicare beneficiaries (Proctor et al., 2016), veterans receiving care through the Veterans Health Administration system (Blosnich et al., 2013), and those insured through the Kaiser Permanente system (Quinn et al., 2017). The health of transgender individuals in these systems may not reflect the health status of the transgender general population, either in the US or in other regions. There is the need for the inclusion of core gender identity measures in nationally-representative probability-based studies (Waite and Denier, 2017; Baker, 2019).

4.1.3. Chronic disease measurement

Consistent with findings from Reisner et al.’s 2016 review (Reisner et al., 2016), heterogeneity in chronic disease measures (e.g. DSM diagnosis, structural clinical interview for mental health conditions, ICD, treatment history, clinical thresholds for physical conditions) and definitions (e.g. variety in DSM editions, ICD revisions, structured clinical interview instruments) were found in the current review of the literature. Included studies also used varied recall periods (e.g. lifetime, current, past-year, past two-years, past six-months) and prevalence measures, with more than a third (37%) reporting only frequencies and proportions. Additionally, many outcome measures were developed for use with other populations and may not have been validated for use with transgender samples (King et al., 2020). This may affect chronic disease prevalence estimates, particularly prevalence of conditions defined by sex-based clinical measures for transgender people on GAHT.

4.1.4. Transgender status measurement

This review found heterogeneity of transgender status measures across studies (e.g. DSM diagnosis, self-report) with few employing recommended two-step measures (Bauer et al., 2017). The currently evolving context of transgender measurement in clinical and EMR studies is of particular relevance given the preponderance of EMR and clinical studies in this review (Ewald et al., 2019). Studies that reported results disaggregated by gender for transgender groups largely used binary operationalizations of gender. While gender minority health research generally suffers from small sample sizes, there is a growing recognition of the diversity of lived experience among transgender populations and an urgent need for evolution in how gender identity is measured to reflect the lived realities of gender diverse people (Lagos, 2018; Reisner and Hughto, 2019; Streed et al., 2018). Gender non-

conforming and non-binary people may experience mental health and substance use disparities even compared to binary-identified transgender groups (Reisner and Hughto, 2019; Streed et al., 2018). Rigorous, standardized transgender status measurement that reflects population gender diversity is key for future research.

4.2. Limitations

The results of this review should be considered in light of its limitations. Importantly, this review sought to map the available evidence in the area of chronic disease among global transgender populations, employing narrative synthesis largely at the datapoint level. As such, this review did not endeavor to synthesize or meta-analyze chronic disease prevalence estimates and thus results may be limited in the extent to which they can inform direct clinical practice. The primary intent was to identify research gaps and evidence needs. Findings may also have been skewed by the ability of one study with many datapoints to disproportionately contribute data to this synthesis. In this review of published studies reporting quantitative prevalence estimates for transgender populations, there was also heterogeneity of quality of evidence, including in study design and prevalence measures used across studies. As such, evidence from this review may be susceptible to information and selection bias, threatening study validity, speaking to the need for more rigorous epidemiological research. Though, importantly, the quality of the captured studies does not negate the identification of significant research gaps and evidence needs with regards to chronic disease, particularly physical chronic disease.

Finally, the focus of this synthesis was on chronic disease outcomes and not chronic disease risk factors. Only 40% (n = 37) of studies in this review reported significant correlates of chronic disease, including sociodemographics (e.g. sexual orientation, gender, age, race/ethnicity, socioeconomic status, country of origin) and psychosocial factors (e.g. history of violence, lifetime suicidal ideation), as well as trans-specific factors (e.g. experiences of transphobic victimization, access to a trans-affirming healthcare provider, social/medical transition status). A growing number of studies have demonstrated the importance of stigma, healthcare access, violence and syndemic or co-occurring factors in shaping health outcomes for transgender people (Reisner et al., 2016; Poteat et al., 2016; White Hughto et al., 2015). Future research is needed that can shed light on these drivers of disease burden, as well as the moderating and mediating impacts of intersecting social locations. Specifically, only approximately half (48%) of studies in this review reported race or ethnicity characteristics of the study sample, though, 22% of included studies were conducted in countries with majority or entirely non-white samples. Given evidence of racial disparities in chronic mental and physical health for transgender people, (Brown and Jones, 2014) the intersection of race, ethnicity, and gender diversity is an important area of focus for future chronic disease research.

4.3. Conclusions

This systematic review makes an important contribution as the first to focus on chronic disease among global transgender populations. Findings from this review point to a number of critical gaps in the existing transgender health literature landscape in terms of chronic disease burden knowledge, and important areas for future research. In particular, there is a need for research in areas other than sexual and mental health (Reisner et al., 2016), areas with unique vulnerability for transgender people such as inflammation-related disease, and areas with little evidence to date such as age-related chronic conditions. There is also a need for well-designed longitudinal studies (particularly important for incident cancer and other age-related conditions); research making use of large, population-representative data and appropriate comparison groups (Reisner et al., 2016), and use of consistent measurement for both transgender status (Reisner et al., 2016) and chronic disease ascertainment (Swartz et al., 2019). The alignment of funding

mechanisms to these research priorities is fundamental to continued progress in transgender chronic health research. Finally, research with an explicit focus on chronic disease in transgender populations, including multimorbidity, is warranted (Swartz et al., 2019), as well as studies designed to investigate multi-level drivers of chronic disease burden. Given links between factors such as poverty, stigma, discrimination and barriers to healthcare access for transgender people (Reisner et al., 2016; Poteat et al., 2016; White Hughto et al., 2015), future research in this area should be rigorously designed to enable disentangling of the effects of these important determinants of health and point to opportunities for multi-level interventions to attenuate their effects in transgender populations.

Funding

AJR is supported by a Frederick Banting and Charles Best Doctoral Research Award from the Canadian Institutes of Health Research (#152382).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmedr.2020.101259>.

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