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Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth

A Systematic Review of Benefits and Risks to Inform
Practice, Policy, and Research

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About This Report

Transgender and gender-expansive (TGE) youth often experience gender dysphoria, defined as distress related to a mismatch between one's gender identity and physical development. This report summarizes the rapidly evolving state of evidence on interventions for gender dysphoria and related health problems in TGE youth. We conducted a systematic review of studies that assessed interventions for gender dysphoria in TGE youth (age 25 or younger), published from 1990 to 2023, and summarized the amount, clinical significance, and certainty of evidence available. We reviewed and summarized the available evidence for beneficial and harmful outcomes associated with intervention categories currently recommended as the standards of care (i.e., gender-affirming psychosocial, hormonal, surgical, and reproductive health interventions) for addressing gender dysphoria and related health problems, as well as proposed alternatives to the standards of care (i.e., treatment for co-occurring mental disorders to reduce gender dysphoria, gender identity and expression change efforts). Across intervention categories and outcomes, limitations in the available evidence made it difficult to estimate with certainty the strength (and sometimes direction) of associations between intervention and outcome. Yet practitioners and policymakers can incorporate the best available science when making decisions about health care for TGE youth using evidence-informed approaches to account for these conditions of uncertainty. We also discuss implications for researchers seeking to improve this body of evidence so that it provides greater certainty about intervention effects and has greater practice and policy relevance.

RAND Health Care and RAND Social and Economic Well-Being

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Summary

Background

Individuals who identify as transgender, gender expansive, or both (*gender expansive* includes nonbinary and other identities outside male or female) can experience clinically significant distress and impairment associated with sex-related characteristics inconsistent with their gender identity (i.e., gender dysphoria). Professional organizations have identified standards of care for gender dysphoria—typically, interventions that seek to address psychosocial or physical sources of dysphoria. However, the research evidence on interventions that are part of those standards is rapidly evolving. The purpose of this report’s systematic literature review was to summarize (1) the available research on the benefits and harms of interventions for gender dysphoria in transgender and gender-expansive (TGE) youth and (2) the amount and certainty of evidence available for outcomes, organized within broad intervention categories.

Systematic Review Methods

Following best practices for systematic reviews, we conducted a targeted search of studies cited in published clinical guidelines, reviews, and legal proceedings in the first phase of review (June 2023 through January 2024), which informed a broader search in PubMed (in April 2024). We included peer-reviewed studies reporting outcomes from interventions for gender dysphoria delivered to TGE youth, age 25 or younger, published between 1990 and 2023. We did not have a preregistered review protocol. Team members used a template to extract key details about study samples and recruitment, designs, and outcomes and assessed the methodological quality of each study using JBI’s critical appraisal checklists. We then summarized the effect estimates and clinical significance for each outcome within a given intervention category, including an assessment of four certainty-of-evidence criteria from GRADE (Grading of Recommendations Assessment, Development and Evaluation; the most widely used framework for summarizing research evidence to inform clinical standards of care). *Certainty of evidence* is the level of confidence—from very low to high—that an intervention’s estimated effect on an outcome (from reviewed research) represents the actual effects. In the main report, we present the findings from the review (study-level details and outcome-level synthesis) and an overall evidence map.

Findings

The review included 105 studies, representing seven intervention categories: TGE-affirming psychosocial, hormonal (puberty-suppressing hormones and hormone replacement therapy), surgical, and reproductive health interventions, plus two categories not recommended in current standards of care (i.e., gender identity and expression change efforts, treatment for co-occurring mental disorders to reduce gender dysphoria). Most evidence came from cross-sectional, pre-post, and cohort studies. In brief, the outcomes and certainty of evidence for intervention categories were as follows:

- **Psychosocial interventions** (e.g., social transition, professional psychological support; $k = 22$ studies) were associated with decreases in suicidality and depression (very low certainty).
- **Puberty-suppressing hormones** (e.g., gonadotropin-releasing hormone analogues; $k = 49$ studies) were associated with decreases in pubertal changes, and **hormone replacement therapy** (e.g., testosterone,

estrogen; $k = 56$ studies) was associated with increases in pubertal changes associated with the youth's gender identity (both with low certainty). Both interventions were associated with reductions in youth-reported gender dysphoria in some studies; that outcome was measured infrequently, and evidence was rated very low certainty.

- **Gender-affirming surgeries** ($k = 18$ studies) were associated with reductions in gender dysphoria for mastectomy (low certainty) and other surgery types (very low certainty).
- Across these first four intervention categories, findings indicated low regret, low dissatisfaction levels, and low side effects and complications (all with very low certainty). For example, bone health metrics decreased relative to age-based reference values during puberty suppression; this outcome showed improvement after starting hormone replacement therapy (both very low certainty).
- Some studies found mental health improvements following hormones and surgeries, but others found no effects (very low certainty for all instances of the outcome, because of inconsistent study findings).
- **Reproductive health interventions** ($k = 9$ studies) were found to result in successful fertility preservation of viable oocytes, embryos, or semen (very low certainty).
- We did not identify relevant evidence for outcomes in youth for two intervention categories that are part of the standards of care: voice therapy and support for detransition.
- **Treatment of co-occurring mental health or developmental disorders** ($k = 7$ case reports) was not associated with improved mental health for interventions targeting eating disorders or depression and anxiety; for interventions targeting autism spectrum disorder, there was some evidence for improved autism symptoms but not gender dysphoria (all very low certainty).
- **Gender identity and expression change efforts** (sometimes referred to as *conversion therapy* or *reparative therapy*; $k = 4$ studies) were associated with increases in suicidality (low certainty) and increases or no change in mental health symptoms (very low certainty).

Implications

Despite the low certainty of the available evidence, practitioners and policymakers can use evidence-informed approaches that account for uncertainty in their decisions about health care for TGE youth, such as routinely updating the standards of care or developing relevant legislation. Researchers can use our findings to inform efforts to strengthen the evidence base by producing higher-certainty evidence with greater practice and policy relevance.

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Background

Transgender and Gender-Expansive Identity Development

This report examines existing evidence about interventions designed to address the health care needs of youth with transgender and other expansive gender identities. Humans display a diverse variety of *gender identities*, a psychological concept defined as one’s self-concept within the spectrums of masculinity and femininity (Ashley, 2023; Bilodeau and Renn, 2005). Broadly, gender identities consist of such categories as male, female, and gender-expansive identities that fall between or outside the male-female binary (e.g., nonbinary, genderqueer), with considerable nuanced variation in gender identities found among individuals and between cultural groups (Nanda, 2014). Gender identity is distinct from legal gender or sex assigned at birth (with the latter two terms often used interchangeably). Legally assigned gender is often limited to male or female and based entirely on visible sex characteristics, such as genitals and gonads—even in the case of intersex individuals, who are born with intermediate or inconsistent sex characteristics, for whom medical professionals and parents may “assign” a gender through medical interventions soon after birth (Fisher et al., 2016). Some individuals (not just those born intersex) have a gender identity that differs from their legally assigned gender, an experience referred to as *transgender*—in contrast to *cisgender*, the experience when one’s gender identity matches their legally assigned gender (Ashley, 2022a; Bilodeau and Renn, 2005).

Scholars of gender identity conceptualize transgender and gender-expansive (TGE) identities through a lifespan development model (Bussey, 2011; Renn and Bilodeau, 2005) in which gender identity is constructed by an individual over time by incorporating a combination of biological, psychological, and social influences (see also Ashley, 2023; Bhargava et al., 2021). Therefore, numerous factors contribute to gender identity development, although the precise contributions of the various factors remain unclear and likely vary between individuals. Inborn biological factors may play an important role in TGE identity formation, but so may key life events, such as reactions to physical changes during puberty, cognitive or emotional reactions to being treated as a certain gender, and messages from caregivers, peers, and society supporting or discouraging gender nonconforming behavior. Furthermore, *minority stress* (Frost and Meyer, 2023; Lefevor et al., 2019) interacts with identity development in societies and communities in which TGE youth experience discrimination and marginalization (Cyrus, 2017; Chodzen et al., 2019; Norton and Herek, 2013); those experiences, in turn, are associated with poorer mental health (Austin et al., 2022; Wilson et al., 2016). A recent review (Wittlin, Kuper, and Olson, 2023) concluded that associations between mental health problems and TGE identity are best explained by minority stress, because the review found no evidence that mental disorders cause or explain TGE identity.

Proportion of Youth Identifying as TGE

TGE population estimates are challenging to obtain (Lett and Everhart, 2022), but the best estimate from a national survey indicated that approximately 1.6 million people age 13 or older in the United States identify as TGE (Herman, Flores, and O’Neill, 2022)—with similar proportions of male, female, and nonbinary gender identities. When stratified by age, the percentage of people identifying as TGE is much higher for

youth ages 13 to 17 (1.4 percent) and 18 to 24 (1.3 percent) than for adults age 25 or older (0.3–0.5 percent). These estimates are consistent with findings that the average age of TGE populations is lower than that of cisgender populations (Feldman et al., 2021), which may be attributed to (1) lower life expectancy in this marginalized population (Hughes et al., 2022) but also to (2) more-inclusive attitudes toward gender diversity in younger generations (Jones, 2024).

The proportion of youth identifying as TGE has been increasing over the past two decades (as of 2024) (Zhang et al., 2021), but the evidence for which youth characteristics are associated with this increase varies among studies. Evidence from multiple studies in the United States, Canada, and European countries shows a clear shift toward greater numbers of TGE youth legally assigned female at birth presenting for interventions (Aitken et al., 2015; Arnoldussen et al., 2020; de Graaf et al., 2018; Zhang et al., 2021; Zucker, 2019). The reasons for this shift remain unclear; some observers believe that it may relate to social processes, such as lower stigmatization toward gender-nonconforming behaviors in individuals legally assigned female (Aitken et al., 2015; de Graaf et al., 2018; Zucker, 2019) or changes in referral patterns (Ashley, 2019). Furthermore, peer-reviewed evidence of significant changes over time in other characteristics of the population of TGE youth presenting for interventions is more limited. One study conducted with a sample of 1,072 adolescents in the Netherlands found no time trends—with the exception of those assigned female at birth—between 2000 and 2016 in demographics, level of dysphoria, and likelihood of needing treatment among TGE youth referred for services (Arnoldussen et al., 2020).

Such shifts in the proportion and gender characteristics of youth seeking health interventions related to their TGE identities have raised questions about potential implications for their clinical care. Some observers explain the increased prevalence of TGE identity in younger people as a reflection of social influence or pressure (Kaltiala-Heino et al., 2018; Zucker, 2019), especially when the identity is first disclosed in adolescence rather than earlier in childhood, among youth legally assigned female at birth, or both. These observers cite reports by caregivers to support their descriptions of the development of TGE identity among this group as “rapid” or “sudden” (Restar, 2020) and urge caution regarding intervention decisions for this group. In contrast, other observers do not share the concern regarding social influence and note (1) the multiyear lags that typically occur between an individual’s first recognition of TGE identity and their sharing it with others (Bauer, Lawson, and Metzger, 2022; Brumbaugh-Johnson and Hull, 2019; Turban et al., 2023), (2) that the speed at which TGE identity develops is not a reliable indicator of pathology or distress (Ashley, 2020; Coalition for the Advancement and Application of Psychological Science, 2021), and (3) that because of the multifactorial nature of gender identity development, experiences of social support and connection can influence TGE identity but are unlikely to singularly determine it (Lett et al., 2022).

All that said, youth characteristics are important to consider when selecting interventions that are individualized for a given TGE youth’s needs. For instance, another study in the Netherlands considered TGE youth referred for services between 2000 and 2018, dividing the sample into two groups: those who were referred before age 14 versus those who were referred at age 14 and older (Arnoldussen, de Rooy, et al., 2022). This study found significant differences between the two age groups in demographics, the extent of gender nonconformity in childhood, and such other factors as body dissatisfaction (Arnoldussen, de Rooy, et al., 2022). These findings highlight the importance of attending to demographic differences between TGE youth who seek interventions in childhood versus adolescence when understanding the health care needs of, and corresponding intervention responses to, the larger and more diverse recent cohorts of TGE youth patients.

Gender Identity Changes Within Individuals

TGE identities are rare but distinct developmental pathways for gender identity across the lifespan, and most TGE adults report beginning to develop the identity before age 10 (Turban et al., 2023; Zaliznyak, Bresee, and Garcia, 2020). Lifespan development models highlight that self-identification as TGE may change over

time, especially during key developmental phases (Bussey, 2011; Bilodeau and Renn, 2005). In childhood and adolescence, gender identity can be relatively fluid, and an individual's language capacities to articulate those identities are also still developing. Therefore, there is notable individual variation in the extent to which reporting the desire to change gender predicts long-term TGE identity, especially at younger ages (Ristori and Steensma, 2016; Steensma, McGuire, et al., 2013; Wallien and Cohen-Kettenis, 2008). Changes in TGE identity can include shifts to a cisgender identity (with such individuals often identifying as a sexual minority; e.g., Ristori and Steensma, 2016) and shifts among different TGE identities (e.g., nonbinary instead of a binary transgender identity; MacKinnon, Kia, et al., 2023).

The dynamic nature of TGE identity development has led observers to urge varied levels of caution in providing interventions to TGE youth. Some emphasize that significant numbers of youth identifying as TGE could age out of that identity and perhaps be harmed by premature intervention (Kaltiala-Heino et al., 2018; Levine, Abbruzzese, and Mason, 2022; Zucker, 2019). Other observers emphasize that clearer, more consistent self-report of TGE gender identity is associated with longer-term stability of that identity at any age—and therefore recommend that youth demonstrating stable identification over time should be prioritized for intervention to the extent that clinical judgment allows (Rae et al., 2019; Ristori and Steensma, 2016; Steensma, McGuire, et al., 2013). Still others argue that the available estimated rates of persistence in TGE identity are not representative of youth for whom these decisions need to be made in clinical contexts and that the greatest potential for harm lies in withholding intervention from TGE youth whose identities remain stable (Ashley, 2022b; Maung, 2024). These observers express concern toward restrictions that limit individuals' autonomy and access to interventions (Ashley, 2022b; Maung, 2024). To help reconcile these varied perspectives, clinical researchers have focused on evaluating the extent to which youth identifying as TGE experience benefits and harms (e.g., regret) after they receive—or do not receive—relevant interventions. Therefore, in this report we focused on understanding the available evidence about intervention benefits and harms, which offers valuable information to inform decisionmaking regardless of how questions about TGE identity development are resolved.

Standards for Transgender and Gender-Expansive Health Care

During the course of TGE identity development, the presence of sex-related characteristics inconsistent with gender identity (e.g., genitals, gonads, breasts, and secondary characteristics related to body size and shape, body and facial hair, voice) can cause distress and impairment. Such distress and impairment are currently referred to as “gender dysphoria” in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2022), the leading system for psychosocial diagnoses in the United States. The name and criteria for this diagnosis were updated in 2013 to reflect that the distress and impairment experienced by the individual, rather than their gender identity, are the source of the disorder and the target for treatment. The diagnostic category was called “transsexualism” when first introduced in 1980 and then “gender identity disorder” in a 1994 revision (American Psychiatric Association, undated). The diagnoses used from 1980 to 2013 represent a period during which medical consensus suggested that TGE identities were inherently pathological, in keeping with medical and mental health theories that considered TGE identity to be an expression of mental illness (de Vries and Cohen-Kettenis, 2012). Similar revisions were made in the International Classification of Diseases, which now uses the diagnostic category “gender incongruence” (World Health Organization, 2022). Given this history, medical diagnoses related to TGE identities remain controversial (Castro-Peraza et al., 2019), but the concept of gender dysphoria (relative to prior diagnoses) pushed the field to (1) focus on gender dysphoria as the appropriate target for treatment; (2) recognize that not all TGE people want or need interventions; (3) differentiate between gender dysphoria presentations in adults, adolescents,

and children; and (4) recognize intersex individuals' experiences of gender dysphoria by removing disorders of sexual development from the exclusion criteria.

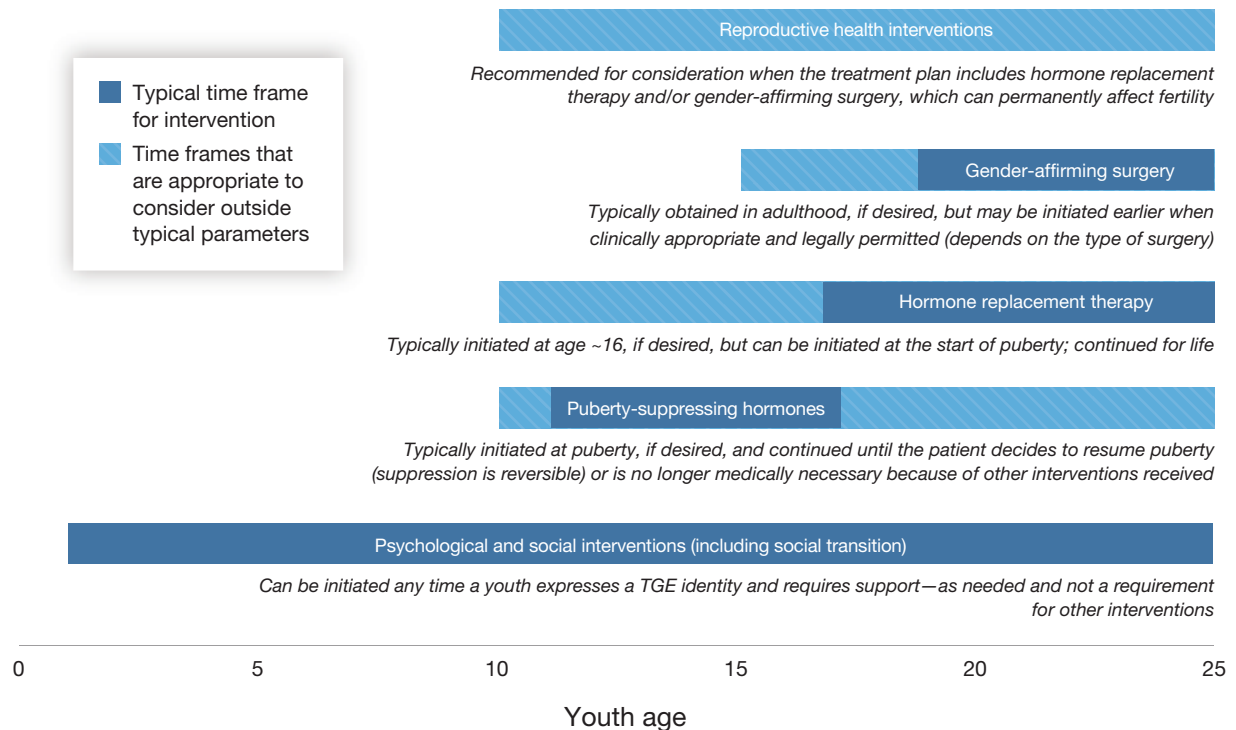
Drawing on the current understanding of gender dysphoria experiences within TGE identity development, two professional organizations have established guidelines for appropriate health care for patients who are TGE. Clinical practice standards of care, in general, are established and regularly updated by relevant professional societies based on the best available research evidence, professional experience and expertise, and patient experience and expertise (Shekelle et al., 1999). The latest guidelines for treating gender dysphoria are (1) version 8 of the “Standards of Care for the Health of Transgender and Gender Diverse People,” recently published by the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2022), and the (2) “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons,” which the Endocrine Society originally published in 2017 through its Clinical Practice Guideline series (Hembree et al., 2017) and began updating into a revised version in February 2024 (see Christensen, 2024). WPATH focuses broadly on transgender health; thus, its standards cover a wide variety of interventions designed to resolve gender dysphoria through the modification of sex-related characteristics, including hormonal therapies, surgeries, and voice and communication training—collectively referred to as *gender-affirming* interventions by WPATH and the Endocrine Society—and to address the needs of TGE patients in routine primary care, reproductive and sexual health care, and mental health care. The Endocrine Society guidelines focus on hormonal therapies in greater depth, with some attention to surgeries as well, consistent with the society's focus on endocrine-related disorders and treatments. Both organizations also delineate standards for adults, adolescents, and children; onset of puberty is used to distinguish adolescents from children. These guidelines are complemented by similar recommendations from discipline-specific organizations, such as the American College of Physicians (Serchen, Hilden, and Beachy, 2024), the American Academy of Pediatrics (Rafferty et al., 2018), and the American Psychological Association (2015, 2024). Figure 1.1 summarizes the typical time frames for each category of intervention for gender dysphoria and related health problems to illustrate how these interventions fit together within the standards of care for TGE youth (Coleman et al., 2022; Hembree et al., 2017). The standards of care also emphasize the need for careful assessment and individualized intervention selection, on the basis of needs of each TGE youth, when applying these standards in practice.

Policy Related to Gender Dysphoria Interventions

Since the mid-2010s, many jurisdictions in the United States have proposed or enacted policies that restrict or fully ban the use of some or all interventions for gender dysphoria that fall under the standards of care for TGE youth. In 2023, 22 states passed such bills (Trans Legislation Tracker, undated-b), marking the most legislative activity on this topic at any point in U.S. history. For example, Iowa Senate File 538 banned any use of TGE-affirming medical interventions for minors (under 18 years of age) (Iowa Legislature, 2023), and Montana Senate Bill 99 banned the same interventions and any social transitioning (i.e., living socially in ways that match the youth's gender identity) when supported by health care professionals (Montana Legislature, 2023). In January 2024 alone, 104 bills were introduced for consideration that year (Trans Legislation Tracker, undated-a). However, some states have passed legislation that promotes access to gender dysphoria interventions for youth—for example, ensuring insurance coverage for specific interventions and offering legal protections to youth who travel from states penalizing the interventions to receive care—resulting in wide variation in policy contexts for TGE-affirming care (Reed, 2024). Legal challenges to restrictive laws have resulted in an active U.S. Supreme Court case (*L. W. v. Skrmetti*; see American Civil Liberties Union, 2024). Federal legislation that restricts or bans the use of interventions that fall under standards of care for TGE youth is not currently under consideration but could be possible in the future (Dawson, Kates, and Musumeci, 2022), especially if the active state laws survive legal challenges. All state laws that have restricted

FIGURE 1.1

Typical Time Frame for Standard-of-Care Gender Dysphoria Interventions



SOURCES: Derived from the standards of care for TGE youth (Coleman et al., 2022; Hembree et al., 2017).

or banned gender dysphoria interventions thus far did so for legal minors (generally under the age of 18); however, legislative proposals have defined *youth* to include young adults age 25 or younger. Related policy decisionmaking is also unfolding in other countries. For example, in Europe, several national health systems have developed policies on health interventions for TGE youth; policies in some of those countries (e.g., the United Kingdom, Finland, Sweden) restrict interventions from the standards of care and diverge from the position of the European Academy of Paediatrics (Brierley et al., 2024).

It is important to summarize and evaluate the rapidly evolving evidence on gender dysphoria interventions for TGE youth so that relevant policies can reflect the most-robust available science. Multiple analyses of legislative proposals to ban or restrict gender dysphoria interventions have found that the proposals incorporate erroneous information to support the policy position—about such topics as gender dysphoria itself, the evidence for the benefits and safety of these interventions, and the standards of care (Lockmiller, 2023; McNamara et al., 2023, 2024; Meade et al., 2024). No comparable analysis of legislation promoting access to these interventions is available, but those proposals presumably could contain erroneous information as well (e.g., overstating the certainty or extent of known intervention benefits). Numerous considerations beyond research evidence also influence policymaking, but increasing the effective use of research evidence in policy decisions (i.e., evidence-based policymaking) has long been recognized as an important and underused approach to improving health outcomes (Brownson, Chiqui, and Stamatakis, 2009; Cairney and Oliver, 2017; Cookson, 2005; Dumont, 2019).

Purpose of This Systematic Review

We conducted a systematic review of literature on interventions for gender dysphoria and related health problems in TGE youth (age 25 or younger) to inform health care practice, policy, and research. Given that policies being proposed and enacted in the United States have largely focused on the benefits and risks of gender dysphoria interventions with youth specifically, we sought to understand the state of research with that age group. We defined *youth* as up to and including age 25 because, (1) as noted earlier, relevant legislation has already been proposed that included individuals of that age range in the definition of *youth*, and (2) many TGE individuals wait until legal adulthood to disclose their gender minority status and seek interventions for gender dysphoria (Bauer, Lawson, and Metzger, 2022; Turban et al., 2023), so many TGE young adults are seeking the same interventions as TGE adolescents. We also examined studies reporting a variety of health outcomes related to gender dysphoria, such as mental health and satisfaction with care.

The current review was designed to fill a specific gap in the available literature: the lack of a comprehensive systematic review of available interventions for gender dysphoria and related health problems in TGE youth. The available standards for TGE health interventions (e.g., Coleman et al., 2022; Hembree et al., 2017) considered research evidence for a much broader scope of practice recommendations than those specifically relevant to TGE youth. Even within the sections with youth-focused recommendations, those standards cite a variety of relevant research of sexual and gender minority populations, including studies of interventions for gender dysphoria with TGE adults, as well as studies of psychosocial interventions that are also provided to cisgender sexual minorities (i.e., gay, lesbian, bisexual, pansexual, and other minority sexual orientations). Therefore, from the published standards of care alone, it is difficult to fully assess the research evidence for interventions with TGE youth. Beyond the standards of care, systematic reviews have been published that focused on the research evidence for specific gender dysphoria interventions with TGE youth (e.g., Baram et al., 2019; Doyle, Lewis, and Barreto, 2023; Expósito-Campos, Pérez-Fernández, and Salaberria, 2023; Ludvigsson et al., 2023; Ramos et al., 2021; Thompson et al., 2023), but these reviews were conducted by different research teams and exhibited variation in approaches to compiling, assessing, and synthesizing evidence (including what evidence was ultimately included in the syntheses).

A related gap addressed by our review is the need for systematic assessment of the certainty of evidence for outcomes of gender dysphoria interventions with transgender youth. The concept of “certainty of evidence” (Hultcrantz et al., 2017) reflects the level of confidence that an intervention’s estimated effect on an outcome—on the basis of reviewed research—represents the intervention’s actual effects on that outcome. Certainty of evidence is a key consideration in GRADE (Grading of Recommendations Assessment, Development and Evaluation) (Guyatt et al., 2008, 2011), the most widely used framework for summarizing research evidence to inform clinical practice and policy. More than 100 professional organizations worldwide have endorsed the use of GRADE, and numerous resources are available to help guide its application, including a series of more than 30 papers (Siemieniuk and Guyatt, undated). Of the aforementioned systematic reviews, GRADE certainty-of-evidence assessments were reported in only one, a review of hormonal interventions for youth with gender dysphoria (Ludvigsson et al., 2023). Further, that review did not report details of how risk-of-bias assessments were completed, despite using those assessments to inform GRADE ratings and other key decisions (e.g., study inclusion and exclusion from the review), which made the review’s findings difficult to interpret.

In sum, a more comprehensive review is needed that uses a common approach to examine the available evidence for interventions targeting gender dysphoria and related health problems in TGE youth, including an assessment of the certainty of evidence. Relatedly, it is useful to consider whether viable alternatives to the standards of care have been identified for gender dysphoria in TGE youth. We therefore also sought to

examine proposed alternatives—that is, any interventions for TGE youth with gender dysphoria that have been studied but are not currently recommended as standards of care.

Research Questions

This systematic review sought to answer the following questions:

- What does available research suggest about the benefits and harms associated with interventions for gender dysphoria in TGE youth?
- What is the amount and certainty of evidence available for outcomes (gender dysphoria and related health problems) associated with each intervention category?

Systematic Review Methods

We conducted a systematic review of research studies examining outcomes of interventions for gender dysphoria and related health problems in TGE youth (both standard-of-care interventions and proposed alternatives). Our review documented the benefits and risks of identified interventions, including the amount and certainty of evidence for each outcome. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance (Page, McKenzie et al., 2021; Page, Moher, et al., 2021). PRISMA was designed to support the transparent, complete reporting of systematic reviews and is supported by a resource website (PRISMA, undated) and various PRISMA extensions (for a PRISMA search extension, see Rethlefsen et al., 2020; for the Synthesis Without Meta-Analysis guideline, see Campbell et al., 2020; for a PRISMA harms checklist, see Zorzela et al., 2016). However, we did not have a preregistered protocol for the review. See Appendix A for a completed copy of the PRISMA checklist and all relevant extensions.

Literature Search Strategies

To conduct our systematic review, we identified original research publications (e.g., journal articles, book chapters, and reports that report original data or analysis) across two phases of literature searches: (1) a targeted search of studies cited in published clinical guidelines, reviews, and legal proceedings, which then informed (2) a broader computerized database literature search using search criteria and an approach to reviewing results informed by our experience during the first phase (see Boell and Cecez-Kecmanovic, 2014, for more discussion of these review methods). Table 2.1 summarizes the sources used in our literature search process, including the number of citations reviewed per source.

For the initial targeted search, the first author developed a list of publications for review, drawing from literature cited in published clinical guidelines (e.g., Coleman et al., 2022; Hembree et al., 2017), several relevant reviews identified by the research team (Campbell, Tran, and Mann, 2023; Cass Review, 2022; Cornell University, What We Know Project, 2016, 2018; Doyle, Lewis, and Barreto, 2023; Eckert and Gorski, 2022; Tannehill, Gorski, and Eckert, 2022; Turban, 2022), and legal proceedings relevant to health care for TGE youth (e.g., *Emma Koe et al. v. Caylee Noggle*, 2023). These sources included non-peer-reviewed publications, but several were peer-reviewed and based on existing systematic reviews (Coleman et al., 2022; Doyle, Lewis, and Barreto, 2023; Hembree et al., 2017) and collectively offered a broad sampling (in terms of interventions, outcomes, etc.) of peer-reviewed literature for inclusion in our initial phase of the review. Review of these sources lasted from June through September 2023. We identified additional literature through an examination of reference lists and reviews cited in the original sources (backward searching), as well as an examination of studies that had cited the included studies (forward searching), with forward and backward searching continuing through January 2024; these processes enabled us to identify and include literature that had been published through 2023.

TABLE 2.1
Summary of Literature Review Sources

Phase 1: Initial Targeted Search, Reviewed June Through September 2023					
Source	Type	Topic	Youth Specific?	Peer Review?	Number of Citations ^a
Campbell, Tran, and Mann (2023)	Narrative review	GIECE	Yes	No	26
Cass Review (2022)	Narrative review	Gender dysphoria treatments	Yes	No	59
Coleman et al. (2022)	Clinical guideline	TGE health care	No	Yes	1,521
Cornell University, What We Know Project (2016, 2018)	Narrative review	SOGIECE; gender transition	No	No	119
Doyle, Lewis, and Barreto (2023)	Systematic review	HRT	No	Yes	46
Eckert and Gorski (2022)	Narrative review	Gender dysphoria treatment	Yes	No	137
<i>Emma Koe et al. v. Caylee Noggle</i> (2023)	Legal proceedings	Gender dysphoria treatment	Yes	No	78
Hembree et al. (2017)	Clinical guideline	Endocrine treatment	No	Yes	266
Tannehill, Gorski, and Eckert (2022)	Narrative review	Gender dysphoria treatment	Yes	No	134
Turban (2022)	Narrative review	Gender dysphoria treatment	Yes	No	16
Phase 2: PubMed Literature Search (Including Additional Identified Reviews), Conducted April 2024					
Source	Type	Topic	Youth Specific?	Peer Review?	Number of Citations ^a
PubMed search results ^b	Database search	n/a	n/a	n/a	3,134
Baram et al. (2019)	Systematic review	Fertility preservation	Yes	Yes	39
Expósito-Campos, Pérez-Fernández, and Salaberria (2023)	Systematic review	Psychosocial intervention	Yes	Yes	22
Kotamarti et al. (2021)	Systematic review	HRT; venous thromboembolism	No	Yes	11
Ludvigsson et al. (2023)	Systematic review	HRT	Yes	Yes	24
Mahfouda et al. (2019)	Narrative review	HRT; gender-affirming surgery	Yes	Yes	97
Ramos et al. (2021)	Systematic review	Puberty-suppressing hormone treatment	Yes	Yes	11
Thompson et al. (2023)	Systematic review	Gender-affirming hormone treatment and surgery	Yes	Yes	19
Wright, Candy, and King (2018)	Systematic review	GIECE	No	Yes	53

NOTE: GIECE = gender identity and expression change efforts; HRT = hormone replacement therapy; n/a = not applicable; SOGIECE = sexual orientation and gender identity and expression change efforts.

^a For systematic reviews, we reviewed citations of publications included in the review; for other source types, we reviewed all citations in the source.

^b See Table 2.2 for the search terms used in the PubMed literature search.

In the second phase of literature searching, we conducted a broader computerized database search using PubMed—a scientific database of biomedical literature from the National Library of Medicine, life science journals, and online books—to identify additional studies that met our inclusion criteria but had been previously missed, thus counteracting any bias in our sample of studies that could have been caused by our choice of literature sources for the first phase. Our search criteria, derived from our experience in the first phase and the criteria used in prior systematic reviews, are reported in Table 2.2. The second phase was completed in April 2024. As the purpose of this phase was to supplement the first phase, we focused on more-recent publications that we were most likely to have missed. We searched for studies from 2014 through 2023 but then screened the PubMed search results by publication date, starting with 2023. We stopped screening after we reached a year for which no new publications were identified for inclusion (2018). Furthermore, the PubMed results included another eight relevant literature reviews published in the same time frame, and we identified additional publications for inclusion that were cited in those reviews (including a small number of studies published prior to 2018). We again incorporated forward and backward searching into our literature search strategy for all publications identified through PubMed and the reviews.

TABLE 2.2
PubMed Literature Search Terms

Field ^a	Search Terms Specified
Query box	(“transgender”[Title/Abstract] OR “trans-gender”[Title/Abstract] OR “transfeminine”[Title/Abstract] OR “trans-wom*”[Title/Abstract] OR “transwom*” “transmasculine”[Title/Abstract] OR “transman”[Title/Abstract] OR “trans-man”[Title/Abstract] OR “transpeople”[Title/Abstract] OR “trans-people”[Title/Abstract] OR “transpeople”[Title/Abstract] OR “transsexual”[Title/Abstract] OR “trans-sexual”[Title/Abstract] OR “assigned female*”[Title/Abstract] OR “assigned male*”[Title/Abstract] OR “male to female”[Title/Abstract] OR “female to male”[Title/Abstract] OR “cross gender”[Title/Abstract] OR “gender expansive”[Title/Abstract] OR “gender diverse”[Title/Abstract] OR “gender fluid”[Title/Abstract] OR “nonbinary”[Title/Abstract] OR “non-binary”[Title/Abstract] OR “gender non-conform*”[Title/Abstract] OR “bigender”[Title/Abstract] OR “bi-gender”[Title/Abstract] OR “agender”[Title/Abstract] OR “bi-gender”[Title/Abstract] OR “gender dysphor*”[Title/Abstract] OR “gender incongru*”[Title/Abstract] OR “gender identity disorder”[Title/Abstract]) AND (“intervention”[Title/Abstract] OR “treatment”[Title/Abstract] OR “health care”[Title/Abstract] OR “therapy”[Title/Abstract] OR “hormone*”[Title/Abstract] OR “GnRH”[Title/Abstract] OR “puberty suppression”[Title/Abstract] OR “HRT”[Title/Abstract] OR “surgery”[Title/Abstract] OR “reproductive”[Title/Abstract] OR “fertility preservation”[Title/Abstract] OR “social transition”[Title/Abstract] OR “gender transition”[Title/Abstract] OR “gender reassignment”[Title/Abstract] OR “sex reassignment”[Title/Abstract] OR “gender confirm*”[Title/Abstract] OR “gender change”[Title/Abstract] OR “sex change”[Title/Abstract] OR “gender affirm*”[Title/Abstract])
Filter terms	Publication date: from 2014/1/1 to 2023/12/31 Species: Humans Age: Child: birth–18 years OR young adult: 19–24 years Other: excluded preprints

NOTE: The search was completed using a PubMed advanced search (see National Library of Medicine, undated). GnRH = gonadotropin-releasing hormone.

^a Query box terms are specified before initiating the search in PubMed. Filter terms are selected from prespecified options after the PubMed search is initiated to further filter the results.

Inclusion and Exclusion Criteria

In brief, we included literature that met the following five eligibility criteria:

1. The study reported findings from TGE participants.
2. TGE participants were youth (up to and including age 25).
3. A health intervention related to recipients' TGE identity (i.e., targeting gender dysphoria, related health problems, or both) was provided to at least one subsample.
4. Youth recipients' outcomes were measured following their receipt of the health care intervention (and comparison conditions, if relevant).
5. The source was published via peer review from 1990 to 2023.

Within these criteria, we captured a variety of study designs (from quasi-experimental trials to case studies) and research methods (a range of quantitative and qualitative methods), representing the breadth of research used to inform standards of care (Shekelle et al., 1999). We did not explicitly exclude non-English publications, but we identified only one such publication (in Spanish). Appendix B lists the inclusion and exclusion criteria in full detail. The first author conducted the initial screening of titles and abstracts from all search results for initial eligibility, conducted forward and backward searching, then assigned each potentially eligible publication to a research team member for review. That team member also verified the inclusion and exclusion criteria and discussed any discrepancies with the first author to reach consensus.

To illustrate the rationale behind our eligibility criteria, it is helpful to consider examples of the types of studies that did not meet the criteria. The most common reason for exclusion was that the sample did not include TGE youth (criterion 1 or 2). There were many instances in which a subset of participants in the sample were TGE youth, but information about their receipt of the health intervention or outcomes of the intervention conditions (criteria 3 and 4) could not be discerned for youth as a subpopulation. This is a common issue in research on sexual and gender health interventions, making interpretation of outcomes for TGE youth complex and reliant on assumptions that findings from the overall sample generalize to TGE youth recipients (Expósito-Campos, Pérez-Fernández, and Salaberria, 2023). For example, Nolan et al. (2023) evaluated the effects of immediate versus delayed testosterone in a randomized trial with 64 TGE participants ages 18–70 but reported outcomes (depression, suicidality, dysphoria) for only the full sample. Similarly, in a sample of 245 sexual and gender minority participants, Ryan et al. (2020) included 21 transgender young adults (8.6 percent) who experienced sexual orientation change efforts during adolescence but did not report outcomes separately for transgender versus cisgender participants. We excluded such studies because they did not help us evaluate health interventions for TGE youth specifically, which was the focus of the research questions.

It was less common for studies with TGE youth samples not to meet eligibility criterion 3 or 4, but this did sometimes occur. One example is an investigation of trends from the Amsterdam Cohort of Gender Dysphoria study (Wiepjes et al., 2018) that stratified findings by age group but reported only receipt rates (i.e., not outcomes) of gender-affirming hormonal treatment. (The authors did examine rates of regret for gonadectomy, but these were not stratified by age group because they were very low [≤ 0.6 percent].) Finally, for eligibility criterion 5, we chose a cutoff of 1990 because, prior to that date, limited credible research was published on interventions for TGE youth. Indeed, sufficient research did not become available for the WPATH standards of care to include a section on children and adolescents until 1998 (Levine et al., 1998). An example of an older study that met the first four criteria for inclusion but would not be useful for making health care decisions today is Barlow, Abel, and Blanchard's (1977) account of an "exorcism" of transsexual identity by a faith healer, which documented changes using unvalidated observations of "gender-specific motor behavior" and scores on a "card-sort measure of gender identity." Such approaches were mainstream in behavioral sci-

ences until the 1980s (Davison, 1982) but lacked the scientific rigor or cultural sensitivity expected because of improved knowledge of TGE identities in the subsequent decades. A task force from the Association for Behavioral and Cognitive Therapies (a leading organization supporting research on and practice of cognitive behavioral therapy) recently voted to add a “black box” disclaimer to 24 publications on sexual orientation and gender identity change efforts, all of which were published before 1990, indicating that the articles contain potentially harmful research that conflicts with current ethical standards (Comer et al., 2024). Given these issues, focusing on publications from 1990 onward was most useful.

Data Extraction and Critical Appraisal

We developed a summary template to guide the extraction of data from each publication, capturing PICOTSS information: **population** (e.g., sample size, gender identities, age at intervention, eligibility criteria), **interventions** for gender dysphoria, **comparisons** made between or within groups (including comparison interventions), **outcomes** among TGE youth (e.g., gender dysphoria, physical and mental health, side effects, regret) and how outcomes are measured, **timing** of the intervention and data collection, **settings** for intervention and study recruitment and participation, and **study design** (e.g., how intervention groups were created or assigned and how outcomes were analyzed). We recorded all reported outcomes (including multiple measures, time points, or analyses when relevant) from each publication, rather than preselecting certain outcome categories or measures for inclusion. We recorded point estimates, as well as confidence intervals and information about statistical significance and clinical significance (i.e., practical benefit to patients; see Kraemer et al., 2003), whenever available. We did not convert measures to a standard metric because we were not quantitatively synthesizing them, but we recorded effect sizes when reported (or when we could calculate them from reported information using the Campbell Collaboration effect size calculator; see Wilson, 2023) to help assess clinical significance. See Appendix C for a blank copy of the template used to summarize each publication.

Throughout the review period, the research team met biweekly to receive training and supervision from the first author in completing publication summaries. In early meetings, the team members each summarized three representative publications and synthesized the findings into a single summary. Later meetings focused on discussing issues encountered during the review process and ensuring that reviewers maintained a consistent approach. Once each initial summary was complete, the first or fifth author also reviewed the summary and the original publication to verify key details, providing feedback to team members as needed to ensure the accuracy and consistency of the summaries. We did not contact study authors to verify details or request additional information; instead, we noted unclear or missing details in the summary. Once all summaries were complete, we transferred the data into tables that included all relevant studies for an intervention category, with specified details of the samples, study design and interventions, and outcomes. Studies were grouped together by study design within each table. Generally, we followed the same categories of interventions detailed in the WPATH and Endocrine Society standards of care for TGE health interventions (Coleman et al., 2022; Hembree et al., 2017). However, we also included interventions not found (or contraindicated) in the standards when our review identified relevant evidence to assess. We also grouped together publications from the same study into unified entries for each summary table, so that studies could serve as the unit of analysis for the remainder of the review process.

For each study (including all relevant publications), we then assessed its methodological quality using the critical appraisal checklist from JBI that was appropriate for the study research design (Aromataris et al., 2024). The critical appraisal checklist tools were developed by JBI, an international research organization that supports the use of research evidence to improve health care practice and outcomes (Barker et al., 2023). The purpose of these checklists is to determine the extent to which a study has addressed the possibility of bias in

its design, conduct, and analysis so that risks of bias can be considered during the synthesis and interpretation of results across studies. For each study, two reviewers independently assessed the criteria and agreed on a final rating of yes, no, unclear, or not applicable for each. Appendix D summarizes the JBI critical appraisal checklist criteria for all study design types included in this review; four criteria produce quantitative estimates of the direction and magnitude of intervention effects on specific outcomes (cross-sectional, cohort study, quasi-experimental, and randomized controlled trial), and two provide information about effect direction only (qualitative study and case report).

Data Synthesis and Certainty-of-Evidence Assessment

As a final step, we synthesized all identified studies for each intervention into a summary of effect estimates for each outcome that had been studied (i.e., gender dysphoria, related health problems, or both). The first author and one co-author created the outcome summaries for each intervention category and came to an agreement on the final synthesis and ratings.

Summaries of effect estimates are a form of synthesis without meta-analysis that present the direction (i.e., increase, decrease, no change) and distribution of observed effects (Campbell et al., 2020). As before, we grouped interventions based on categories from the standards of care (Coleman et al., 2022; Hembree et al., 2017) or proposed alternatives; furthermore, we generally grouped clinically related outcomes for synthesis (e.g., gender dysphoria and body dissatisfaction together and depression and anxiety measures together under mental health) because there was considerable variation in which specific outcomes were measured in a given study. We took an inclusive approach to summarizing the variety of outcomes reported but prioritized by only summarizing outcomes that were (1) documented in multiple studies, (2) the primary or only outcome reported for an intervention (i.e., important to report regardless of the amount or certainty of evidence), or (3) documented by a quasi-experimental or cohort study that met every relevant JBI criterion (i.e., sufficiently low risk of bias to justify summarizing a single study).

We developed summaries of effect estimates by reviewing all reports of the outcome across studies. We determined the overall direction for an effect by (1) considering the distribution of statistical and clinical significance among the findings and (2) giving stronger consideration to effects from studies with more-rigorous designs, on the basis of the study design (in order from most to least rigorous: randomized controlled trial, quasi-experimental, cohort study, cross-sectional, qualitative, case report), plus any risks of bias noted in the relevant JBI checklist. Interpretation of clinical significance was based on the most-relevant metrics for a given measure (Kraemer et al., 2003), including the minimum effect size for a meaningful effect (e.g., $d \geq 0.2$, r and $\beta \geq 0.1$, odds ratio ≥ 1.5 ; see Chen, Cohen, and Chen, 2010; Nieminen, 2022), and established normative reference ranges for the outcome. Qualitative and case report study designs do not produce quantitative estimates of intervention effects and therefore were given the least weight in our summaries of effect estimates, but we still considered those findings because they provided information about the direction of effects. When there was heterogeneity in outcomes, we examined the distribution of effects for patterns related to the interventions and populations included in the studies, and we reported certain outcomes separately for specific interventions and populations as needed to adequately convey the heterogeneity observed. For example, in some cases it was necessary to create separate summaries of specific mental health outcomes (e.g., when effects differed for suicidality versus depression versus other mental health outcomes) rather than presenting a unified summary of mental health outcomes. We also differentiated whether summaries of evidence described findings for TGE youth generally or for specific age ranges, defined as children prior to the onset of puberty, adolescents (youth under age 18 after the onset of puberty), and young adults (youth ages 18–25). For measures of harms (such as adverse events), we assumed that no events for a measured outcome represented actual *zero events* (i.e., provided evidence that no harm had occurred; see Zorzela et al., 2016).

However, if a harm was not measured systematically—for example, recorded only whether a patient spontaneously reported the outcome—we did not assume that no reported events represented zero events and instead treated the outcome as unknown.

We then created a second summary table for each intervention category that lists each outcome—noting the direction of the outcome and when findings were specific to certain interventions, populations, or both—and presents a detailed narrative summary of evidence, including the distribution of clinically and statistically significant findings. Within each table, we listed targeted beneficial outcomes first, followed by potential harms, such as regret and side effects. Each summary table entry also reports the number of relevant studies (with citations) and our ratings of the certainty of evidence criteria, which apply to the body of evidence synthesized for that outcome. Our ratings for certainty of evidence used criteria from GRADE (Balslem et al., 2011; Hultcrantz et al., 2017; Schünemann et al., 2019, 2023). Table 2.3 presents the criteria for certainty of evidence that we assessed in our summaries of evidence and provides definitions of the ratings used for each criterion and the overall (outcome-level) certainty ratings. The certainty ratings are based on the extent of concerns that the intervention’s estimated effect on an outcome—from the reviewed research—could meaningfully differ from its actual effects on that outcome. Meaningful differences could be due to the effect’s direction (beneficial, no effect, or harmful) or size (small, moderate, or large).

Note that because we incorporated case reports in our summaries of evidence, it was challenging to rate the certainty-of-evidence criteria when all evidence for a given outcome came from case report study designs. In those instances, our approach to rating certainty of evidence was as follows. We always rated concerns for risk of bias and indirectness as very serious because, by design, case reports are meant to produce detailed

TABLE 2.3
Certainty-of-Evidence Criteria and Ratings

Criteria and Ratings ^a	Definitions
Criteria	
Risk of bias	Risk that outcome estimates are not accurate because of methodological limitations of the evidence
Imprecision	Extent of variation in outcome estimates <i>within</i> studies
Inconsistency	Extent of variation in outcome estimates <i>between</i> studies
Indirectness	How well findings can generalize from study samples, interventions, and measures to real-world equivalents
Criteria-level ratings	
Minimal concerns	Criterion has few or no concerns that lower certainty
Serious concerns	Concerns with criterion decrease certainty below high for the outcome
Very serious concerns	Concerns with criterion cap certainty for the outcome at low or very low
Outcome-level rating^b	
High certainty	High confidence that estimated effect (from reviewed research) and actual effect are close
Moderate certainty	Some confidence that estimate and actual effect are close
Low certainty	Estimate could differ meaningfully from actual effect in its size or direction
Very low certainty	Estimate likely differs meaningfully from actual effect in its size or direction

SOURCES: Features information from Balslem et al., 2011; Hultcrantz et al., 2017; Schünemann et al., 2019, 2023.

^a Ratings are determined by the overall body of evidence for a specified clinical outcome, from a specified intervention, in a specified population.

^b The overall-level rating accounts for all criteria-level ratings on risks to certainty of evidence across the full body of evidence assessed.

descriptions of phenomena rather than generalizable findings on the effects of interventions. We also considered the imprecision criterion as not applicable, since case studies did not provide quantitative estimates of intervention effects for which precision would be relevant. Lastly, we described the level of inconsistency as unclear in these instances because case report studies focused on clinical description of case-specific outcomes, which made it difficult to compare outcomes across studies. (Note that these same considerations would have applied to summaries of evidence that included only qualitative studies, but we found no such outcomes.)

Finally, it is important to note two ways in which we did not replicate the full GRADE process that produces clinical recommendations (see Schünemann et al., 2023). First, we did not use meta-analysis methods to create pooled estimates of effect sizes for each outcome. Our research questions required only *noncontextualized* ratings on the certainty of whether an intervention offers benefits, harms, or both (Zeng et al., 2021), rather than a specific effect size estimate used when GRADE ratings inform decisionmaking in a specific context (e.g., guidelines). Second, there was one GRADE certainty-of-evidence criterion we did not estimate, risk of publication bias, which is the extent to which a body of evidence is likely to represent selective publication of results. Such bias is widely acknowledged as common in biomedical research, but methods to directly measure it remain underdeveloped and frequently debated (Ayorinde et al., 2020; Lin and Chu, 2018). Thus, although some level of publication bias may be present in our findings, we did not attempt to quantify it or otherwise incorporate it into our certainty-of-evidence ratings.

Quality Assurance Process

Our systematic review and report-writing process went through an extensive quality assurance process to ensure consistency with RAND standards for high-quality and objective research and analysis. There were four phases of the quality assurance process. First, three peer reviewers with expertise in systematic reviews ensured complete and rigorous completion and reporting of all aspects of the review methods. This phase included one internal reviewer from RAND and one external reviewer, who both focused on the overall report, as well as a second internal reviewer who focused specifically on the study and outcome summary tables. Second, two peer reviewers with topic-specific content expertise (again, one internal and one external) reviewed and provided feedback on the version of the report approved by all method reviewers to ensure accuracy and completeness of the report content and conclusions. Third, six managers across two research divisions (RAND Health Care and RAND Social and Economic Well-Being) reviewed the next draft of the report and provided additional feedback; in parallel, another internal reviewer provided a tone review specifically focused on maximizing objectivity of the report. Finally, following all peer review and management approvals, we provided a near-final report draft to representatives from two organizations that have strong advocacy positions regarding access to TGE-affirming care for youth (one advocates for increased access, the other for restricted access) and requested their confidential comments on the report. This was not a peer review process but instead allowed us to revise aspects of the report considering how it would be interpreted by a variety of parties. We received comments from the organization that advocates for restricted access to TGE-affirming care but not from the organization that advocates for increased access. We made targeted revisions to the report based on the comments to maximize clarity and completeness of the report.

Findings

We organized our review findings into seven categories of interventions, reflecting the standards of care for TGE youth and proposed alternatives. Each section in this chapter contains a brief description of the intervention category, followed by details of the research studies reviewed for that category and a summary of the documented outcomes. Two annex files, available at www.rand.org/t/RRA3223-1, contain spreadsheets with tables detailing the studies (Annex I, containing Appendix G) and outcome summaries (Annex II, containing Appendix H); each annex contains seven tables on separate tabs, one per intervention category.

Figure 3.1 presents a flow diagram of the search results, including the number of publications screened and assessed for eligibility per phase. See Appendix E for an overview of all 105 studies (and 118 associated publications) included in the review. For each study, the appendix details which intervention categories were evaluated; many studies reported outcomes for multiple interventions, so they are discussed in this chapter under each relevant intervention category. See Appendix F for a list of 21 publications excluded after our full-text review and the reason for ineligibility.

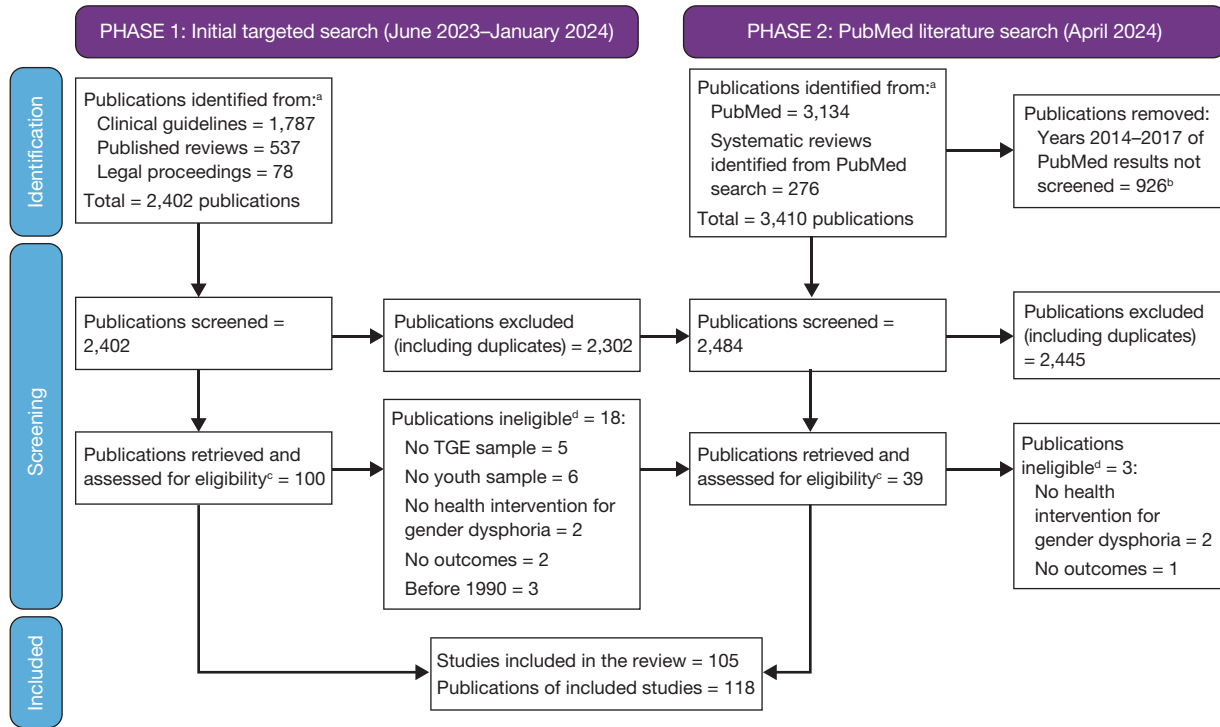
Figure 3.2 presents an evidence map (drawing from Miake-Lye et al., 2016) that provides a visual representation of the review findings. For each intervention row, outcomes are presented as bars that are organized by outcome category (columns). Each bar indicates the number of studies with evidence for the intervention and outcome, the certainty of evidence (the pattern of the bar), and whether the evidence suggests benefits, no clinically significant effects, or harms (the color of the bar). The evidence map illustrates that evidence was almost entirely very low certainty across intervention and outcome categories. The map also indicates benefits (or lack of harms in the case of such outcomes as regret or side effects) in most cases. Two proposed alternatives, listed last in the evidence map, had evidence of no effects or harmful effects on gender dysphoria and related health problems. The map also presents two intervention categories identified in the standards of care (Coleman et al., 2022; Hembree et al., 2017) that did not have any relevant evidence for outcomes in youth—voice therapy and support for detransition (i.e., reversal of social or medical gender transition steps)—so there are ten rows total.

Psychosocial Interventions

We identified 22 studies (21 percent of studies reviewed), reported across 24 publications, that examined outcomes of psychological or social (i.e., psychosocial) interventions for TGE youth. The individual studies are described and assessed in Annex I's Table G.1, and summaries of the findings across studies are presented in Annex II's Table H.1.

Standards of Care

TGE standards of care (Coleman et al., 2022; Hembree et al., 2017) recommend several interventions for TGE youth that involve psychosocial support. The format and content of these interventions vary, but all share a common purpose of supporting the TGE youth's transition into living as their gender identity rather than

FIGURE 3.1**Flow Diagram of Study Identification, Screening, and Inclusion**

^a See Table 2.1 for details of the number of records identified (i.e., citations reviewed) from each source.

^b We screened search results by publication date, starting with 2023, until we reached a year (i.e., 2018) for which no new publications were identified for inclusion; however, we also identified studies from before 2018 in this phase from the systematic review of reference lists and backward citation searching.

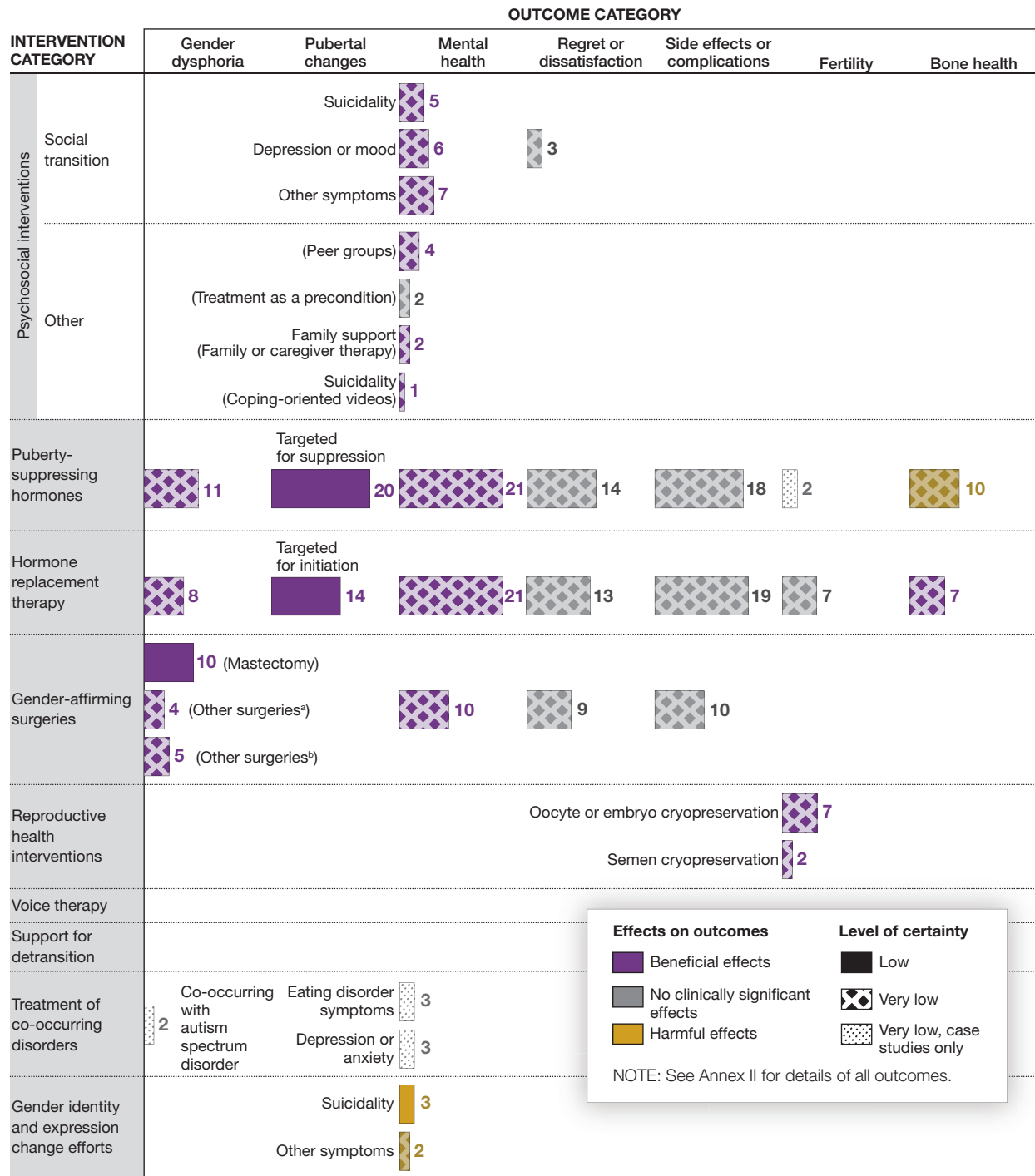
^c At this step, we performed forward and backward citation searching on records from the previous step assessed as eligible; records identified from forward and backward searching are included in this step's total (we did not track the number of publications identified this way separately, but they were a small proportion of the total).

^d See Appendix B for full details of eligibility criteria and Appendix F for a list of ineligible studies.

their legally assigned gender. One broad type of psychosocial intervention is social transition—the process by which a TGE individual starts living as their gender identity in one or more key domains of their life, such as with friends or at home, school, or work. Specific elements of the transition may include name change, pronoun change, change in legal gender markers (e.g., birth certificate, identification cards), participation in gender-segregated activities (e.g., sports) and settings (e.g., bathrooms), and gender expression, such as hair, clothes, jewelry, and makeup (Ehrensaft et al., 2020). Social transition is a highly variable and personalized process, rather than a routinized intervention, and it may take place with or without professional guidance and services. Nevertheless, we included it in this review because it is specifically addressed in the standards of care and is the primary intervention recommended prior to puberty (Coleman et al., 2022; Hembree et al., 2017).

Other, more-formalized psychosocial interventions involve professional psychosocial support (e.g., consultation, psychotherapy) for TGE youth and their caregivers and family to support well-being, development, and resilience, as well as provide psychoeducation about gender identity development. The standards indicate that these supports should affirm the youth's gender identity and are not intended to modify their gender identity or expression. These supports can be delivered in individual, family, or group settings and include youth, caregivers and family, or youth and family together. The standards of care do not specifically require psychosocial support to accompany other gender-affirming interventions (such as hormones and surgeries)

FIGURE 3.2
Evidence Map of Outcomes for Youth Gender Dysphoria Interventions



NOTE: Bars represent the number of studies with evidence for each intervention and outcome. When needed for clarity, labels next to bars specify outcome categories outside parentheses, and intervention categories are in parentheses. $k = 105$ studies.

^a Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty.

^b Vaginoplasty and/or mammaplasty.

but do recommend that mental health concerns be addressed during the preparation, initiation, and aftercare of those interventions.

Overview of Evidence

As shown in Annex I's Table G.1, studies examined a variety of aspects of social transition, professional psychosocial support, and coping-oriented brief videos. Community samples were used in most studies, but several studies focused on youth seeking medical services for gender dysphoria at a gender clinic. The most-common study designs were cross-sectional ($k = 9$) and quasi-experimental ($k = 6$),¹ but we also found one randomized controlled trial, two cohort studies, one qualitative study, and three case reports. Studies generally measured mental health outcomes (e.g., depression, suicidality, anxiety, substance use) through some combination of youth, caregiver, and clinician rating scales and interviews.

There was wide variation in how these studies rated on the relevant JBI critical appraisal checklist. For the cross-sectional studies, the most-common issues were self-reported intervention exposure and issues with addressing confounder variables; the only studies that met all criteria for the cross-sectional design checklist examined social transition in samples from gender clinics (Morandini et al., 2023; Sievert et al., 2021). Littman's (2021) cross-sectional survey of youth who detransitioned met almost none of the criteria (see Table G.1) and did not provide useful estimates of intervention effects, although the findings were qualitatively useful for illustrating diverse experiences with detransition. The quasi-experimental studies never met all JBI checklist criteria, because the study either included only pre-post measurement (i.e., no comparison group) or, when there were multiple groups, had a direct association between intervention assignment and outcomes (e.g., assignment was based on mental health status, and mental health outcomes were measured). For the other study designs, most studies were also missing at least one relevant JBI checklist criterion, although one case report met all criteria.

Synthesis and Certainty of Evidence

Annex II's Table H.1 summarizes findings across studies for four outcomes from social transition: suicidality, depression or mood symptoms, other mental health symptoms (e.g., anxiety, general functioning), and regret or dissatisfaction. These outcomes had the largest evidence bases, with five to seven studies contributing to each except for regret or dissatisfaction (three studies). We found that social transition was associated with decreases in suicidality (particularly in unsupportive family and school environments), decreases or maintenance of nonclinical depression or mood symptoms, inconsistent effects on other mental health symptoms, and low rates of regret and dissatisfaction (e.g., detransition)—all rated very low certainty. The certainty ratings were lowered by concerns about risk of bias (serious for suicidality and very serious for other outcomes), compounded by overlapping samples between studies for the depression and mood and other mental health symptom outcomes. There were also serious concerns with inconsistency for some outcomes; some studies or ratings within a study showed benefits, whereas others found no effects (no studies found increases in mental health symptoms or decreased functioning [i.e., harms]). Studies of social transition had two serious concerns with indirectness: First, because social transition is not a standardized intervention, effects may differ based on the approach used; second, effects may vary based on whether other interventions were received for gender dysphoria.

Table H.1 presents summaries for two other outcomes from professional psychosocial interventions (general psychological functioning outcomes and family support for TGE youth) and one outcome from brief

¹ Throughout the report, k is the number of studies.

coping-oriented videos (suicidality). We further differentiated the general psychological-functioning outcomes resulting from peer-support interventions versus professional psychosocial support as a precondition for additional interventions for gender dysphoria (e.g., hormonal therapy). Peer-support interventions were associated with increased functioning across four studies, whereas support as a precondition was associated with no effects in two studies. The outcome of family support for TGE youth showed increases specifically associated with family or caregiver therapy in two studies. The evidence for these three outcomes was rated as very low certainty because of the small number of studies (all with serious or very serious risks of bias) and high imprecision because of small samples. There was also one notable inconsistency in the evidence for peer interventions: Brandsma et al. (2022) found that a group intervention for youth with autism spectrum disorder and gender dysphoria was associated with increases in gender dysphoria, suggesting a potential risk of harm. Finally, Kirchner et al. (2022) found short-term decreases in suicidality following viewing It Gets Better Project videos. Although this study was a rigorous randomized controlled trial, we still rated the evidence for this outcome as very low certainty because only one study was available; furthermore, the decreases found for suicidality had minimal clinical significance. Regarding indirectness concerns (rated serious), these findings might not generalize beyond intervention delivery or family settings that support receipt of TGE-affirming psychosocial services.

Puberty-Suppressing Hormones

We reviewed 49 studies (47 percent, the second most frequent intervention category after hormone replacement therapy), reported across 56 publications, that examined outcomes of puberty-suppressing hormones for TGE youth. The studies are described and assessed in Annex I's Table G.2, and summaries of the findings across studies are presented in Annex II's Table H.2.

Standards of Care

Puberty-suppressing medications are a class of hormones or synthetic hormone analogues used to suppress the release of gonadotropins (Coleman et al., 2022; Hembree et al., 2017); these medications are also referred to as *puberty blockers*, *hormone blockers*, and other similar names. The physical changes of puberty will not occur as long as these hormones suppress gonadotropins. The intervention is generally reversible (to the extent that long-term effects have been studied); puberty can be initiated later, as is done when these medications are used to delay precocious puberty in cisgender youth, which has been the standard of care for decades (Bangalore Krishna et al., 2019). Examples of such medications include gonadotropin-releasing hormone analogues (GnRHa)—such as leuporelin, triptorelin, and buserelin—and some non-GnRHa medications. The medications are typically delivered by injection, implants, or nasal spray in various formulations. Given that puberty is a pivotal phase for gender identity development in TGE youth (Horton, 2024; Steensma, Kreukels, et al., 2013), TGE standards of care recommend use of puberty-suppressing hormones with youth who have initiated puberty and experienced increased gender dysphoria because of puberty-related physical changes (Coleman et al., 2022; Hembree et al., 2017). The standards indicate that puberty-suppressing hormones may continue to be used as a supplemental treatment after hormone replacement therapy is initiated, which is discussed in the next section.

Overview of Evidence

As shown in Table G.2, most studies in this review examined the use of GnRHa (most commonly triptorelin, when specified) for puberty suppression. Non-GnRHa medications used included antiandrogens, menstrua-

tion suppressors, and progestins (e.g., cyproterone acetate, lynestrenol). In most studies, patients participated in research as part of the TGE-focused health care through which the puberty-suppressing hormones were prescribed and monitored; however, a few community samples were included as well, in which case receipt of puberty-suppressing hormones was self-reported. About half of the studies used quasi-experimental study designs ($k = 25$; nearly all pre-post), but there were also eight cross-sectional studies, seven cohort studies, eight case reports, and one qualitative study (several other studies reported both quantitative and qualitative data but provided few details about the qualitative measures). The studies measured varied outcomes associated with puberty-suppressing hormones, typically examining within-youth changes in outcomes over the first two years (sometimes longer) after initiating the hormones. Many youth initiated other TGE-affirming interventions (commonly, hormone replacement therapy) during follow-up, further complicating the interpretation of outcomes.

Almost none of the quasi-experimental studies met the criteria on the full JBI critical appraisal checklist, because the studies used a pre-post design (i.e., no comparison group). Other common limitations for these designs were high rates of attrition or missing data and sample sizes that were too small for statistical significance testing. For the cross-sectional studies, there were issues with addressing confounder variables and retrospectively reported measures; McGregor et al. (2023) was the only study that met all cross-sectional checklist criteria. None of the cohort studies met all JBI checklist criteria, because the studies did not include a matched group, did not address confounding, or retrospectively self-reported intervention receipt (and sometimes a study missed multiple criteria); one study (Brik et al., 2020) met all applicable checklist criteria, although several were not applicable. Most other studies did not meet some of the relevant JBI checklist criteria, although several case reports did meet all. Two studies—Littman (2021) and Hisle-Gorman et al. (2021)—met so few criteria that they could not provide useful estimates of intervention effects (see Table H.2).

Synthesis and Certainty of Evidence

Table H.2 summarizes findings across studies for seven outcomes from puberty-suppressing hormones in TGE adolescents and young adults: pubertal changes targeted for suppression (20 studies), improved gender dysphoria (11 studies), improved mental health functioning (21 studies), low regret or dissatisfaction (14 studies), low side effects and complications (18 studies), decreased bone health (ten studies), and no effects on fertility (two studies). Overall, the available evidence suggested that puberty-suppressing hormones did suppress the pubertal changes targeted. Associated reductions in gender dysphoria were measured less consistently and almost never in the same study as pubertal changes. The latter studies instead tended to include general measures of satisfaction or focus on risks. Because pubertal changes were more commonly measured and had fewer concerns for risk of bias (rated serious) and imprecision (rated minimal), that outcome had low certainty but also did not provide a direct measure of changes in gender dysphoria or other clear indicators of clinical significance. The evidence for gender dysphoria and mental health outcomes was rated as very low certainty—but for different reasons. Gender dysphoria had very serious imprecision because it was measured in fewer and smaller studies, but the findings were consistent. Mental health outcomes varied widely based on details of the sample and setting (i.e., serious inconsistency), with the greatest benefits associated with receipt of puberty-suppressing hormones when psychosocial interventions were not available or desired. Other studies examining mental health outcomes found no effects; none found harms.

There was minimal evidence of regret or dissatisfaction and side effects or complications for puberty-suppressing hormones. The evidence for these outcomes was rated very low certainty given the very serious risk of bias and serious concerns with indirectness, although inconsistency and imprecision were minimal. Potential harms were identified related to bone health metrics, which tended to remain stable during puberty suppression but as a result showed decreases relative to age-based reference ranges; as growth rates are slowed during puberty suppression, reference ranges based on chronological age become less relevant,

and the clinical significance of these effects is unclear. These metrics showed improvement after beginning hormone replacement therapy, although it is unclear what the effects would be in cases in which puberty suppression is continued as long-term monotherapy. All evidence related to bone health metrics was rated very low certainty. Fertility-related side effects were examined in case studies, which documented successful oocyte preservation in two cases with histories of puberty suppression (rated very low certainty). Indirectness concerns for this body of research were rated as serious and primarily related to the samples coming from gender clinics in a subset of high-income countries and often receiving a combination of interventions, limiting generalizability.

Hormone Replacement Therapy

We reviewed 56 studies (53 percent, the most represented intervention category), reported across 63 publications, that examined outcomes of hormone replacement therapy (HRT) for TGE youth. The studies are described and assessed in Annex I's Table G.3, and summaries of the findings across studies are presented in Annex II's Table H.3.

Standards of Care

HRT involves the administration of sex hormones (masculinizing androgens or feminizing estrogens) to initiate desired changes in secondary sex characteristics and reduce gender dysphoria (Coleman et al., 2022; Hembree et al., 2017). HRT is also described as *gender-affirming hormonal therapy*, *cross-sex hormone treatment*, *masculinizing or feminizing therapy*, and other similar names. The type and dosage of sex hormones are matched to the TGE person's gender identity, sex, age, and current development of sex characteristics. Administration of HRT is typically via injection, pellet, or transdermal patch in various formulations. Unlike puberty-suppressing hormones, HRT produces physical changes that are not always reversible, and therefore the medical criteria for initiating HRT are stricter. For example, stopping HRT may result in complete reversal of some of the physical changes induced by HRT, such as body hair growth, redistribution of body fat, and changes in voice pitch. However, the changes might not always reverse, and other changes are typically only partially reversible (e.g., breast development from estrogens). The standards of care specify 16 as the age when typically developing adolescents are mature enough to assent to HRT, drawing from clinical expertise and legal considerations; however, age 16 is not a strict minimum age for initiating HRT (Coleman et al., 2022; Hembree et al., 2017). HRT is typically maintained over the patient's lifetime, although this depends on their treatment goals. Puberty-suppressing hormones are not always needed once a maintenance dose of HRT is reached, but in some cases the medications are maintained together to achieve desired treatment effects.

Overview of Evidence

As shown in Table G.3, most studies in this review examined HRT with both masculinizing androgens (testosterone) and feminizing estrogens (typically estrogen/estradiol, often combined with antiandrogen medication), although some samples included only one type of HRT. Because of the gendered nature of HRT, samples tended to be mostly youth with binary transgender male or female identities, but some nonbinary and other gender-expansive youth were included. As in studies of puberty-suppressing hormones, patients mostly participated in research on HRT as part of the TGE-focused health care through which the hormones were prescribed and monitored; however, a few community samples were included as well, with receipt of HRT self-reported by participants. About half of the studies used quasi-experimental study designs ($k = 26$; nearly all pre-post), but we also identified eight cross-sectional studies, ten cohort studies, 11 case reports,

and one qualitative study. These studies measured varied outcomes from HRT, largely the same outcomes measured for puberty-suppressing hormones. Participants often received other interventions for gender dysphoria before or after HRT, which further complicated interpretation of the outcomes for HRT specifically.

No quasi-experimental studies met the full criteria on the JBI critical appraisal checklist, for similar reasons as the studies of puberty-suppressing hormones (pre-post design, high rates of attrition, and small sample sizes). There was also a notable subset of studies in which effects of HRT were confounded with puberty-suppressing hormones, complicating interpretation of cause and effect. Similar issues were seen again for the cross-sectional and cohort studies, such as lack of attention to confounder variables and retrospectively reported measures; one cross-sectional study did meet all checklist criteria (Grannis et al., 2021, 2023; Olsavsky et al., 2023). Most other studies did not meet all relevant JBI checklist criteria (with the same issues noted for Littman, 2021, and Hisle-Gorman et al., 2021, precluding the identification of intervention effects); however, as before, several case reports did meet all the criteria.

Synthesis and Certainty of Evidence

Table H.3 summarizes findings across studies for seven outcomes from HRT: increases in pubertal changes targeted for initiation (14 studies), decreases in gender dysphoria (eight studies), increases in mental health functioning (21 studies), low rates of regret or dissatisfaction (13 studies), low rates of side effects or complications (19 studies), increases in bone density following puberty-suppressing hormones (seven studies), and no effects on fertility (seven studies). Overall, the available evidence suggests that HRT produced expected changes in hormone levels and related physical changes targeted for initiation, with associated improvements in body satisfaction and gender dysphoria in each of the eight studies measuring that outcome. However, the changes were not always to the same extent as when cisgender youth experience puberty with their endogenous hormones, and participants often desired additional physical changes.

As with puberty-suppressing hormones, gender dysphoria and pubertal changes were almost never measured in the same study of HRT. Pubertal changes were measured more frequently, typically in studies that also examined side effects and complications. The evidence that use of HRT was associated with pubertal changes (that is, initiated the desired physical effects) was rated low certainty, but with serious indirectness concerns. The certainty ratings (and reasons for each) with other outcomes largely paralleled puberty-suppressing hormones as well, with evidence for all outcomes rated as very low certainty. For mental health functioning, improvements in depression symptoms and general functioning were more consistent than for other mental health measures. Regarding bone health, studies found that bone density metrics showed increases (but only sometimes to pretreatment levels or expected levels for one's chronological age) after initiating HRT and following decreases relative to age-based reference ranges during treatment with puberty-suppressing hormones. A subset of studies also examined bone growth markers and found no changes after initiating HRT. Indirectness concerns for the research on HRT outcomes (rated serious) primarily related to the samples coming from gender clinics in a subset of high-income countries and often receiving a combination of interventions, limiting generalizability.

Gender-Affirming Surgeries

We identified 18 studies (17 percent), reported across 22 publications, that examined the outcomes of gender-affirming surgeries for TGE youth. The studies are described and assessed in Annex I's Table G.4, and summaries of the findings across studies are presented in Annex II's Table H.4.

Standards of Care

Surgeries for TGE identity affirmation consist of a wide variety of surgical procedures used to modify physical sex-linked characteristics to reduce gender dysphoria (Coleman et al., 2022; Hembree et al., 2017). Examples include genital reconstruction, or “bottom,” surgery (e.g., metoidioplasty or phalloplasty, scrotoplasty, or penile and testicular prostheses; penectomy, orchiectomy, vaginoplasty, or vulvoplasty); breast or chest, or “top,” surgery (e.g., mastectomy, mammoplasty), removal of internal reproductive organs (e.g., hysterectomy, salpingo-oophorectomy or ovariectomy), gender-affirming facial or body shape surgery, and voice surgery. These surgeries can also be used with cisgender and intersex people, both as gender-affirming care or for other medical reasons. Given that gender-affirming surgeries are intensive and irreversible (without further surgery) and require considerable aftercare, they are generally not recommended until adulthood. Thus, in this report, these interventions mostly apply to youth ages 18 to 25—but exceptions may be provided in cases of younger people with sufficient emotional and cognitive maturity to assent to the procedure, and these exceptions would generally require parent or guardian consent as well. As with HRT, this age-related guidance appears to be based on legal considerations and clinical judgment, not research evidence. Legal requirements are generally strictest for surgical procedures that affect fertility, as those effects are completely irreversible. Among TGE adults, desire for and access to these surgeries vary widely (Nolan, Kuhner, and Dy, 2019), and they represent a small but significant part of interventions for gender dysphoria. In most cases, HRT is continued following gender-affirming surgery.

Overview of Evidence

Of the research summarized in Table G.4, the most widely studied gender-affirming surgery type is mastectomy (“top” surgery) for individuals legally assigned female at birth; more than half the studies reviewed ($k = 10$) focused on this type of surgery. Four studies also examined vaginoplasty (“bottom” surgery) for those legally assigned male at birth (with a notable subset also receiving mammoplasty)—but always in samples that also included mastectomy recipients as well. Other surgeries were rarely reported. Most participants were recruited from TGE-focused health care settings, typically specialty gender clinics in major metropolitan areas and sometimes clinics that specialized in gender-affirming surgeries; in rare cases, participants were self-identified from community samples or reported receiving their gender-affirming surgery at a health care setting different from the research site. The most-common study designs were cross-sectional ($k = 6$) and quasi-experimental ($k = 7$), but we also found one cohort study, one qualitative study, and three case reports. Most studies measured outcomes specific to the surgeries received (e.g., gender dysphoria, satisfaction, side effects and complications), but some also examined global measures of mental health functioning. Youth typically received other TGE-affirming interventions prior to or concurrent with gender-affirming surgery (especially HRT), which made it difficult to interpret outcomes not specific to that surgery.

We noted several issues across studies of gender-affirming surgery based on the criteria in the relevant JBI critical appraisal checklist. Among cross-sectional study designs, the most prevalent issue was lack of attention to confounding variables. Other study-specific issues were noted as well (e.g., retrospective report of intervention, unclear outcomes, the previously noted serious limitations of Littman, 2021). Almost all quasi-experimental studies had notable design limitations (e.g., pre-post measurement only, differential attrition between groups, attrition of more than 50 percent). The only exception was Ascha et al. (2022), which used a propensity matching approach to increase rigor of the design (its only major limitation was that the groups produced were still not entirely comparable); that study specifically examined mastectomy. Regardless of design, no study met all JBI checklist criteria except for one of the case reports (reported in two publications: Cohen-Kettenis and Van Goozen, 1998; Cohen-Kettenis et al., 2011).

Synthesis and Certainty of Evidence

Table H.4 summarizes findings for six outcomes from gender-affirming surgeries, three of which were specific to certain surgeries and three of which were applicable across surgery types. Specific types of surgery were associated with decreases in gender dysphoria and related improvements with body satisfaction (for primary, and sometimes secondary, sex characteristics): mastectomy for TGE adolescents and young adults assigned female at birth ($k = 10$; rated low certainty), various “bottom” surgeries for TGE young adults assigned female at birth ($k = 4$; rated very low certainty), and vaginoplasty, mammaplasty, or both for TGE young adults assigned male at birth ($k = 5$; rated very low certainty). The evidence for mastectomy represented a larger number of studies, with minimal imprecision or inconsistency and lower risk of bias (rated serious rather than very serious concerns, because of the strengths of Ascha et al., 2022); mastectomy was also the only gender dysphoria outcome for this intervention category with a clear evidence base for adolescents. In contrast, the evidence bases for other gender-affirming surgeries had very serious concerns with risks of bias and imprecision, although consistency was high. Across outcomes, serious concerns with indirectness include lack of generalizability beyond gender clinics, a focus on patients with binary gender identities, and difficulty extrapolating beyond the specific combinations of interventions received.

The other three outcomes in Table H.4 applied across the types of gender-affirming surgery studied, and all were rated as very low certainty. There were low rates of regret or dissatisfaction, limited side effects and complications, and improved or stable mental health functioning; all these findings were based on a large number of studies ($k = 9$ or 10). Findings regarding regret or satisfaction and side effects or complications were largely limited by very serious risk of bias in the studies, making it difficult to determine the frequency of these outcomes with certainty. The harms noted would largely be addressed by improved surgical techniques (e.g., scarring, limited satisfaction with functioning or appearance); in the case of mastectomy, completion earlier in pubertal development more often permitted a less invasive procedure with fewer side effects. Otherwise, no major risks were documented. For mental health and general functioning outcomes, the evidence suggested that these improved or remained stable over time, but those outcomes were not clearly associated with receipt of gender-affirming surgery (as opposed to other TGE-affirming interventions received); for these studies, there were very serious concerns with risk of bias and imprecision, as well as serious concerns with inconsistency (and similar indirectness risks, again rated serious).

Reproductive Health Interventions

We identified nine studies (reported in nine unique publications) that examined the outcomes of interventions related to reproductive health in TGE youth. The studies are described and assessed in Annex I’s Table G.5, and summaries of the findings across studies are presented in Annex II’s H.5.

Standards of Care

Reproductive health is an important consideration for interventions targeting gender dysphoria, as hormones (puberty-suppressing hormones and HRT) and gender-affirming surgeries involving reproductive organs can temporarily or permanently affect fertility (Coleman et al., 2022; Hembree et al., 2017; see also Practice Committee of the American Society for Reproductive Medicine, 2019). Examples of reproductive health interventions for TGE individuals include fertility preservation (such as cryopreservation of embryos, eggs, or sperm), as well as support for preconception, pregnancy, delivery, and postpartum care. In all cases, the standards recommend that TGE patients should be fully informed of potential fertility impacts from their health care and supported in pursuing options that align with their parenthood goals; this may include decisions about when to start (or pause) HRT, as current recommendations are to discontinue for three months

to enable reproduction or fertility preservation. TGE youth need developmentally appropriate support for reproduction-related decisionmaking, especially if TGE hormonal interventions are initiated prepuberty (Nahata et al., 2019).

Overview of Evidence

Each study detailed in Table G.5 examined fertility preservation interventions, mostly with TGE individuals assigned female at birth (cryopreservation of oocytes [eggs] or embryos) but also cryopreservation of sperm in TGE individuals assigned male at birth. All data came from health care settings in which the participants sought fertility preservation services. The studies used cross-sectional or case report designs with small samples (one to 20 transgender youth per sample); in some studies, only some participants were age 25 or under at the time of fertility preservation. All studies included some consideration of the impact of prior puberty-suppressing hormones, HRT, or both on fertility preservation outcomes. Two studies included cisgender comparison groups (Amir et al., 2020; Dilday et al., 2022), and one randomized oocytes to two different preservation techniques, which were found to be equivalent (Lierman et al., 2017). We did not locate studies of other reproductive health interventions related to gender dysphoria in TGE youth.

According to our review of the criteria on the relevant JBI critical appraisal checklist, the most-common issues with the cross-sectional study designs were lack of attention to confounder variables and including sample sizes that were too small to make statistical significance testing appropriate. The case reports generally met all checklist criteria but occasionally lacked key details.

Synthesis and Certainty of Evidence

Table H.5 summarizes findings for fertility preservation outcomes. All studies demonstrated successful preservation of healthy and viable oocytes, embryos, or sperm, but descriptions of longer-term outcomes, such as pregnancy, were rare. Many participants were seeking fertility preservation prior to undergoing gender-affirming surgery that would cause them to be infertile and did not necessarily have immediate parenthood goals. As noted in the findings for HRT treatment, there was minimal evidence that a history of HRT affected fertility if the treatment was paused for at least three months prior to cryopreservation; it is less clear whether fertility preservation is possible during concurrent HRT treatment, as this was described only in a single case study (Gale et al., 2021). However, given the research designs and small sample sizes used in these studies, there were numerous concerns with the certainty of evidence criteria, resulting in ratings of very low certainty for both outcomes (oocytes and embryos and semen). These outcomes had very serious concerns for risk of bias, serious concerns for imprecision, and very serious concerns for indirectness (beyond small samples, other key issues with generalizability were samples coming only from large urban fertility clinics and the inability to assess long-term fertility outcomes). Consistency was a strength, as findings were similar across all studies.

Treatment of Co-Occurring Mental Health and Developmental Disorders

We identified seven studies (reported in seven unique publications) that examined the TGE-specific outcomes of treatment of co-occurring mental health or developmental disorders in TGE youth. The individual studies are described and assessed in Annex I's Table G.6, and summaries of the findings across studies are presented in Annex II's Table H.6.

Intervention Description

TGE standards of care (Coleman et al., 2022; Hembree et al., 2017) recommend that mental health concerns be addressed throughout the preparation, initiation, and aftercare of other gender-affirming interventions, such as hormones and surgeries. This means that it is important for intervention providers to be trained or otherwise equipped (e.g., work as part of a multidisciplinary team) to appropriately evaluate mental health needs in TGE youth and ensure that mental health treatment is available when needed. That said, the standards specifically recommend against using this type of care as a treatment for gender dysphoria itself, noting that it is not appropriate or evidence-based to conceptualize TGE identity as a symptom of an underlying mental or developmental disorder. The standards recognize that certain disorders have a higher prevalence in individuals with TGE identities, such as autism spectrum disorders (van der Miesen, Hurley, and de Vries, 2016) and eating disorders (Coelho et al., 2019), but that care must be taken to not conflate expressions of TGE identity with disorder symptoms or pathologize the patient's gender identity. The standards of care include limited discussion of research with TGE youth on this topic.

Overview of Evidence

As shown in Table G.6, all the studies on the treatment of co-occurring disorders used case report designs, with outcomes from a total of 14 individuals reported across seven studies. The treatments described targeted mental health problems (i.e., depression and suicidality, obsessive-compulsive disorder, or eating disorder), autism spectrum disorder (a developmental disorder), or both. Most treatments for co-occurring disorders were various types of psychosocial intervention, but some patients also received medications for mental health symptoms, and eating disorder treatments often included medical interventions to support weight gain. Most (but not all) cases also received some TGE-affirming interventions, and individuals' responses could be compared following those interventions versus after the treatment focused on co-occurring disorders. Only one case report (Ewan, Middleman, and Feldmann, 2014) met all criteria on the relevant JBI critical appraisal checklist for its presentation of treatment for co-occurring disorders. Generally, checklist criteria were not met because the case reports were brief and provided limited details (e.g., case history, presenting problem, assessment and intervention activities). Several studies did not consider the possible adverse events of the treatments presented, and the two studies that examined youth with autism spectrum disorders did not present implications of the cases for practitioners to consider (both of which are also checklist criteria for case reports).

Synthesis and Certainty of Evidence

Table H.6 summarizes the findings from case reports of treatment of co-occurring disorders without the provision of TGE-affirming interventions for three outcomes: eating disorder symptoms (and co-occurring mental health problems), depression or anxiety symptoms, and gender dysphoria co-occurring with autism spectrum disorder. Across all outcomes, certainty of evidence was rated very low because of the exclusive use of case report designs, which resulted in our rating all outcomes as having very serious concerns for risk of bias and indirectness, not applicable for the imprecision criterion, and unclear for the inconsistency criterion.

The case reports suggested that patients consistently did not benefit from typical treatment of co-occurring disorders (with some notable risks), whereas they did appear to benefit from TGE-affirming interventions in cases in which they received both types of interventions. In almost all cases involving treatment targeting mental health problems, patients showed continued symptoms throughout treatment—whereas receipt of TGE-affirming interventions led to notable improvements. This contrast was especially clear in the cases with eating disorders; most of these patients had engaged in disordered eating behavior to minimize puberty-related body changes that caused gender dysphoria and, therefore, found traditional eating disorder

treatment to be distressing. One case report with autism spectrum disorder described some change in autism symptoms, but none described change in TGE identity, contradicting the authors' suggestions that TGE youths' gender-nonconforming interests and behaviors were an expression of autism (i.e., a restricted, repetitive pattern of behavior, interests, or activities) rather than an indicator of their gender identity (Mukaddes, 2002). No participant in any case was reported to detransition or change gender identity. Instead, patients were consistently documented as expressing a desire for TGE-affirming interventions (studies varied in whether those interventions were provided and evaluated for a given case). Benefits were described in the cases that included those elements.

Gender Identity and Expression Change Efforts

We identified four studies (reported in four unique publications) that examined the outcomes of GIECE for TGE youth. The individual studies are described and assessed in Annex I's Table G.7, and summaries of the findings across studies are presented in Annex II's Table H.7.

Intervention Description

The WPATH standards of care (Coleman et al., 2022) describe GIECE as practices “aimed at trying to change a person’s gender and lived gender expression to become more congruent with the sex assigned at birth.” These practices are sometimes referred to as *conversion therapy* or *reparative therapy*, but these terms do not distinguish between GIECE and sexual orientation change efforts. WPATH and other professional organizations recommend against using these practices and consider their use unethical, given that TGE identities are not disorders (American Academy of Child and Adolescent Psychiatry, 2018; American Psychological Association, 2021; American School Counselor Association, 2022; Human Rights Campaign, undated; Serchen, Hilden, and Beachy, 2024). The term GIECE refers to a wide variety of practices that promote cisgender identities rather than well-defined interventions; techniques can be behavioral (e.g., aversive or punishment-based conditioning), cognitive (e.g., using thought restructuring or hypnosis), or social (e.g., emphasizing moral or religious norms as a rationale to change).

Overview of Evidence

As shown in Table G.7, three of the studies on GIECE outcomes used retrospective survey designs with community samples, which were analyzed using cross-sectional or quasi-experimental (specifically, event study and difference-in-differences) methods. In these studies, comparison groups included participants who reported never experiencing GIECE (in Turban, Beckwith, et al., 2020, they had to also report some previous receipt of therapy), and experience of GIECE was self-reported by participants as attempts to change their gender identity (the wording varied between the two surveys; see Annex I's Table G.7). The limitations found in our ratings of the criteria on the relevant JBI critical appraisal checklist for these three studies were all related to information about GIECE exposure or outcomes being self-reported and retrospective. The fourth study was a case report that discussed psychotherapy meant to “reverse the desire of belonging to the opposite sex” (Schneider et al., 2017). This study rated poorly on the JBI checklist for case reports (missing four of eight criteria) because receipt of GIECE was described as only part of the case history; many details about that intervention were lacking.

Synthesis and Certainty of Evidence

Table H.7 summarizes the evidence from studies of GIECE for two outcomes: suicidality ($k = 3$; rated low certainty) and mental health and substance use problems ($k = 2$; rated very low certainty). Across studies, there was an association between GIECE and increases in likelihood of suicidal ideation, likelihood, and frequency of suicide attempts (both immediately and long term after GIECE). Measures of psychological distress and substance use showed either increases or no change. No benefits were documented for any outcome in any study. Certainty of evidence was highest for suicidality because it had serious, rather than very serious, risk of bias; that outcome was examined in all three survey-based studies, and although the studies used retrospectively self-reported survey data, rigorous analytic approaches were also employed (especially in Campbell and Rodgers, 2023). Furthermore, there were minimal concerns with imprecision or inconsistency for the suicidality outcome. We rated certainty lower for mental health and substance use problems (very low) because of inconsistency among findings examined by the two relevant studies (which documented a mix of harm versus lack of improvement), serious concerns with imprecision in some findings, and very serious risk of bias. For the indirectness criterion, we noted serious concerns across outcomes (for example, findings might not generalize to youth who have died by suicide or youth who no longer identify as TGE).

Implications

This systematic review summarized and synthesized 118 peer-reviewed publications across 105 studies reporting outcomes from interventions for gender dysphoria and related health problems in TGE youth, up to and including age 25 (although outcomes were sometimes measured at older ages), that were published between 1990 and 2023. We sought to review the evidence associated with the standards of care for this population (gender-affirming interventions), as well as proposed alternatives. In total, we reviewed research on seven categories of interventions (five considered part of the standards of care and two alternatives) and assessed the study quality according to relevant JBI critical appraisal checklists (Aromataris et al., 2024). We then synthesized the evidence for each intervention category by outcome and characterized certainty of evidence using GRADE criteria (Guyatt et al., 2008, 2011; Hultcrantz et al., 2017). All outcomes were rated as having very low or low certainty of evidence. Overall, our findings were consistent with the results of previous reviews that summarized the research evidence for specific interventions related to gender dysphoria in TGE youth (e.g., Baram et al., 2019; Campbell, Tran, and Mann, 2023; Cornell University, What We Know Project, 2016, 2018; Doyle, Lewis, and Barreto, 2023; Eckert and Gorski, 2022; Expósito-Campos, Pérez-Fernández, and Salaberria, 2023; Ludvigsson et al., 2023; Mahfouda et al., 2019; Ramos et al., 2021; Tannehill, Gorski, and Eckert, 2022; Thompson et al., 2023; Turban et al., 2022; Wright, Candy, and King, 2018). The findings include consistency in the identification of benefits and potential harms across intervention categories, as well as the assessment of high risk of bias in this body of evidence from previous systematic reviews. Our review offers an up-to-date summary of evidence (through 2023) that used a common approach to compiling, assessing, and synthesizing available evidence on the major interventions for gender dysphoria in TGE youth.

On the other hand, our approach and findings showed important differences from reports that were undertaken to inform specific policy decisions by governments—particularly in cases that opted to ban or restrict interventions from the standards of care for TGE youth (see, e.g., Brierley et al., 2024). As one notable example, the final Cass Review (2024)—a report commissioned by the UK National Health Service to make policy recommendations for services provided to TGE youth in that system—was released while this report was in preparation. The Cass Review was another highly comprehensive effort to summarize research evidence on interventions for gender dysphoria in TGE youth, informed in part by systematic reviews of evidence for social transition (Hall et al., 2024), other psychosocial interventions (Heathcote et al., 2024), and hormonal interventions (Taylor, Mitchell, Hall, Langton, et al., 2024; Taylor, Mitchell, Hall, Heathcote, et al., 2024). (The Cass Review also incorporated input from professionals, both in the United Kingdom and other countries, as well as from youth and caregivers.) The systematic reviews conducted for the Cass Review used similar methods to our work, with some variations—for example, the reviews were restricted to studies with participants age 18 and younger, excluded case studies and non-English studies, used different risk-of-bias assessment tools, excluded studies meeting less than 50 percent of bias assessment criteria from syntheses in the hormonal intervention reviews, and did not provide certainty-of-evidence ratings for outcomes (Taylor, Mitchell, Hall, Langton, et al., 2024; Taylor, Mitchell, Hall, Heathcote, et al., 2024). Ultimately, the Cass Review recommended that the UK National Health Service implement greater restrictions on providing

gender dysphoria interventions to TGE youth. For example, the report recommended that the reviewed interventions be made available only through participation in a research trial—and noted the limitations of the available evidence as a key justification. Overall, it is important to recognize that the purpose and approach of the Cass Review report were guided by its mandate to make recommendations for UK National Health Service policy. Although policymakers elsewhere have begun considering how the Cass Review findings could inform their decisions, given its prominence and comprehensiveness, that mandate certainly affects the applicability of those findings for decisionmaking in other contexts. As one example, the Cass Review did not include evidence for gender-affirming surgery because the National Health Service had already restricted that intervention to individuals age 18 or older. In contrast, we sought to provide evidence summaries that practice and policy decisionmakers could more broadly consider across diverse contexts.

We now detail the implications of these findings across key domains: (1) practice and policy (specifically, making practice and policy decisions under conditions of uncertainty) and (2) research (to address gaps in the evidence base). Table 4.1 summarizes the implications by domain. Across all implications, we recognize the importance of incorporating the expertise of TGE people’s lived experience (Boylorn, 2008) into any efforts informed by these findings. *Lived experience* refers to the sources of evidence and expertise that come directly from individuals’ personal experiences. Those with lived experience may contribute through circumscribed activities, such as participation in qualitative research or advisory boards and also through representation among the workers and leaders engaged in practice, policy, and research. Scholars have articulated strategies for maximizing the value of lived experience for TGE health research and clinical practice (Scheim et al., 2019; Streed et al., 2023; Vaughan and Rodriguez, 2014), echoing more-general discussions of the role of lived experience in clinical practice (e.g., guideline development; see Institute of Medicine, 2011), policymaking (McIntosh and Wright, 2019), and research (Collins et al., 2018).

TABLE 4.1
Summary of Review Implications for Practice, Policy, and Research on Youth Gender Dysphoria Interventions

Domain	Implications
Practice and policy	• The GRADE Evidence to Decision framework can be used to balance the limited certainty of the evidence found in this review with other key considerations when developing or updating standards of care for youth with gender dysphoria to incorporate the best available science. • Interventions for youth with gender dysphoria for which we found low or very low certainty of evidence could still be considered for use in clinical practice with appropriate considerations, although guideline panels may refrain from making recommendations for certain interventions, populations, or outcomes because of insufficient evidence. • Policymakers can use evidence-based policymaking approaches to incorporate the evidence summarized in this review into solutions that address major risks of harm to TGE youth, whether from the provision or restriction of interventions.
Research	• New research can continue to inform and help refine the standards of care for gender dysphoria by addressing the gaps found in our evidence review. • Certainty of evidence can be increased from the levels found in this review, especially via rigorous quasi-experimental and mixed-method studies, improved length and rigor of follow-up assessments, and more attention to key outcomes (e.g., gender dysphoria). • Although the lack of prospective studies on interventions that seek to change, restrict, delay, or ignore TGE identity represents an evidence gap, such studies have serious ethical concerns that must be considered when building new evidence on this topic. • Recruiting larger, more-diverse samples of TGE youth for research would help improve the limited generalizability of the current evidence base. • Approaches from implementation science and quality improvement can evaluate impacts of adopting evidence-informed practices and policies for gender dysphoria interventions with TGE youth, as well as generate practice-based evidence on intervention effects. • More supports are needed for conducting rigorous research on these topics that can address the gaps identified in our review.

Implications for Practice and Policy: Making Decisions Under Conditions of Uncertainty

We produced a more focused review of the literature on interventions for gender dysphoria and related health problems in TGE youth than did the WPATH standards of care (Coleman et al., 2022) and the Endocrine Society’s clinical practice guideline (Hembree et al., 2017). Research specifically focused on TGE youth remains a small proportion of literature on this topic, and our certainty ratings of the available evidence were categorized as very low for 89 percent of outcomes and low for the other 11 percent. Furthermore, although we were unable to consider publication bias in our certainty ratings, we recognize that a given body of published evidence generally presents an incomplete account of the actual effects of an intervention for various reasons (Ayorinde et al., 2020; Lin and Chu, 2018). For example, published research may be biased by researchers’ and journal editors’ prior assumptions about care for TGE youth or general tendency to favor statistically and clinically significant findings over null findings.

Overall, the findings from this review pose a challenge for practitioners and policymakers seeking to make decisions that incorporate the best available evidence. There is clearly a need for more research on the effectiveness of interventions for gender dysphoria and related health problems in TGE youth, as we discuss in the “Implications for Research” section, below. That said, evidence-informed approaches—such as those offered by the GRADE framework—exist to help practitioners and policymakers incorporate the best available science into their decisions about health care for TGE youth while accounting for these conditions of uncertainty.

Practice Decisions

To develop GRADE recommendations for practice, a multidisciplinary guideline panel synthesizes evidence into actionable recommendations that are characterized by their direction—for or against—and being strong or weak (Andrews et al., 2013; Schünemann et al., 2023). It should also be noted that guideline panels can decide to refrain from making a recommendation for a given intervention, population, or outcome in cases of insufficient evidence. The GRADE Evidence to Decision framework (Alonso-Coello et al., 2016; Moberg et al., 2018) assists guideline panels in considering a variety of relevant criteria in their recommendation decisions, including such factors as the balance of risks and benefits, patient preferences, equity implications, and feasibility. Notably, all the evidence compiled in this review could potentially inform decisions about recommendations. GRADE recommendations do not require high-certainty evidence, and recommendations do not need to be strong to be clinically useful (e.g., weak recommendations can guide shared decisionmaking based on provider expertise and patient preferences). In fact, the GRADE Working Group has published guidance for how to consider making recommendations in cases in which only evidence with very low certainty is available, and the expertise of the guideline panel can supplement gaps in the evidence (Mustafa et al., 2021). Panels are especially encouraged to consider making recommendations under conditions in which providing no recommendation would be unhelpful to providers or could harm patients. As noted in GRADE guidance, “The certainty of the evidence is often low or very low, but decision-makers must still act” (Moberg et al., 2018). GRADE recommendations that incorporate all available research evidence on intervention benefits and harms, while considering the limitations of that evidence, maximize the use of evidence to inform practice.

Challenges with certainty of evidence are not unique to interventions for gender dysphoria and related health problems in TGE youth; many fields of study encounter such challenges when using research evidence to inform standards of care. In fact, systematic reviews of the application of GRADE (Fleming et al., 2016; Howick et al., 2020) have found that 22–24 percent of evidence summaries for the primary study out-

come were rated as very low certainty, and 81 percent of reviews included no outcomes with evidence that was high certainty. Research on associations between nutrition and outcomes, for instance, is generally of low or very low certainty per GRADE, presenting notable challenges for developing nutrition recommendations and guidelines (Tobias, Wittenbecher, and Hu, 2021). Yet such guidelines have been developed and are used to inform widely applicable population health assessments, food standards, and nutrition education or marketing interventions, all while accounting for uncertainty in the evidence (Neale and Tapsell, 2019). The systematic reviews of the application of GRADE we cite above (Fleming et al., 2016; Howick et al., 2020) did not distinguish between the certainty of evidence for interventions with adults versus youth, but it is worth noting that the latter interventions are often of lower certainty: There are particular challenges with ethically and safely conducting high-certainty research in pediatric medicine because of such factors as cost, feasibility, and recruitment limitations (van der Zanden et al., 2022).

Other areas of pediatric clinical practice similarly involve navigating limited evidence. For example, evidence with limited certainty guides the off-label prescription of medication (i.e., prescription for purposes other than those listed in the medication's formal approval) for a variety of pediatric conditions (e.g., musculoskeletal, cardiovascular, respiratory, pain; see Allen et al., 2018; Yackey et al., 2019). Such off-label uses are typically identified through clinical practice and lower-certainty research evidence but can still represent routine, appropriate care (Committee on Drugs et al., 2014). A recent systematic review of pediatric clinical guidelines identified 66 guidelines that recommended off-label medication as the standards of care (Meng et al., 2022). Many guidelines identified in that systematic review used GRADE, such as the guidelines for pediatric regional anesthesia (Suresh et al., 2018), treatment of venous thromboembolism (Monagle et al., 2018), and management of sepsis (Weiss et al., 2020). Given the prevalence of off-label prescription practices, Meng et al. (2022) encouraged more transparency in reporting when guidelines recommend use of off-label medications; in the authors' review, they needed to cross-reference recommendations with drug approval information from other sources to identify which involved off-label prescribing.

Ultimately, there will often be cases in which only weak or no recommendations can be made about a pediatric intervention because of limited certainty of evidence. However, this low or very low certainty should not be taken as an automatic advisement *against* use of the evidence. Absence of high-certainty evidence on effectiveness is not equivalent to evidence that effects are absent. A strong or even weak recommendation for or against the use of an intervention requires a full assessment of the evidence for benefits, lack of effects, or harms and the certainty of evidence for each (Andrews et al., 2013).

In the case of interventions for gender dysphoria and related health problems in TGE youth, we conclude that the available research evidence—although limited—can inform recommendations on interventions for gender dysphoria and related health problems in TGE youth through the GRADE Evidence to Decision framework. That conclusion is consistent with previous studies (McNamara et al., 2023; Meade et al., 2024). Updates to such recommendations are likely to be ongoing, as they would be for any clinical problem. For example, the WPATH and Endocrine Society guidelines are regularly revised (WPATH is in its eighth edition, and the Endocrine Society initiated a routine update to its guidelines in February 2024; see Christensen, 2024), and the World Health Organization (2023) is currently developing a guideline on the health of TGE people. However, the high uncertainty in this evidence base increases the likelihood that contradictory recommendations will result across decisionmaking contexts and processes (such as in the Cass Review, 2024).

Policy Decisions

When moving from practice decisions into policymaking, challenges with the certainty of evidence remain relevant. Clinical practice guidelines help to establish minimum standards of care that serves as a legal responsibility for medical providers, subject to policy oversight. However, that responsibility is not synonymous with providing care recommended in the guidelines, because the recommendations are never absolute

(Taylor, 2014). Thus, when clinical practice guidelines incorporate the best available scientific evidence, they also provide guidance for evidence-based policymaking (Alonso-Coello et al., 2016; Moberg et al., 2018). Evidence-based (or sometimes *evidence-informed*) policymaking recognizes the benefits of incorporating research evidence into policy decisions, such as regulations and legislation, that affect health outcomes (Brownson, Chriqui, and Stamatakis, 2009; Cairney and Oliver, 2017; Cookson, 2005; Dumont, 2019). Guidance is available for engaging in evidence-based policymaking (U.S. Government Accountability Office, 2023; World Health Organization, 2021), which policymakers can use to incorporate the evidence summarized in this review into policies relevant to provision of interventions for gender dysphoria in youth. The extent of alignment or misalignment between the evidence base and policy decisions can be influenced by a variety of factors—from existing legal requirements to policymaker and public values—and other factors may become more influential when the uncertainty of the evidence is higher. Influences of multiple factors are illustrated in the decisionmaking for the Cass Review’s (2024) recommendations for UK National Health Service policy. For example, recommendation 10 states that “all [TGE] children should be offered fertility counselling and preservation” prior to receiving hormonal interventions, although the Cass Review report was informed only by a systematic review of hormonal interventions—not the recommended fertility interventions themselves. Nevertheless, policy proposals to ban or restrict gender dysphoria interventions for TGE youth typically provide scientific justifications (Cass Review, 2024; Lockmiller, 2023; McNamara et al., 2023, 2024; Meade et al., 2024). Decisions regarding such proposals would benefit from careful consideration of the evidence review and implications detailed in this report.

Policies to ban or restrict interventions recommended in clinical guidelines would be most appropriate when they prevent serious risks of harm. One frequent point of contention in practice and policy decision-making is the extent of regret for gender dysphoria interventions (Meade et al., 2024). Our review found that the available evidence suggests low risks of harmful outcomes from gender-affirming interventions, such as regret, dissatisfaction, side effects, or complications. Potential harms, such as bone health and fertility effects of hormonal interventions, warrant ongoing clinical and research attention because of the very low certainty of evidence available, as well as limited evidence for adjunctive interventions that mitigate those harms (e.g., fertility preservation). Nevertheless, these interventions have not shown the serious risks of harm that would suggest the need for policies to restrict the interventions. The low regret rate—though again based on very low certainty of evidence—is consistent with a meta-analysis (Bustos et al., 2021), primarily of adult literature, that found that regret rates were under 2 percent for gender-affirming surgery (i.e., the most intensive TGE-affirming intervention). That finding continues to be replicated (e.g., Bruce et al., 2023). By comparison, a systematic review that explored a variety of other surgical procedures unrelated to gender dysphoria (Wilson, Ronnekleiv-Kelly, and Pawlik, 2017) found an average regret rate of 14 percent.

Evidence-based policymaking decisions about banning or restricting gender dysphoria interventions for TGE youth ought to consider the certainty of whether the policy is preventing harm that exceeds the potential harm of withholding clinical standards of care (Barbee, Deal, and Gonzales, 2022). In this review, the intervention for which harms were most clearly documented was GIECE, an alternative to the standards of care. This finding is consistent with a much larger body of research documenting the harmful mental health effects of a broader category of interventions called sexual orientation and gender identity and expression change efforts (SOGIECE; see, e.g., Comer et al., 2024; Daniel and Butkus, 2015; Forsythe et al., 2022; Goodyear et al., 2023; Panozzo, 2013; Przeworski, Peterson, and Piedra, 2021). Therefore, policymakers could consider policies regarding GIECE as a high priority for preventing harm to TGE youth.

Implications for Research: Addressing Gaps in the Evidence Base

The standards of care for gender dysphoria interventions with TGE youth (e.g., Coleman et al., 2022; Hembree et al., 2017) should be routinely updated to incorporate new research findings, given key limitations in the existing evidence base. The results of our review can help inform priorities for future research in this area. Generally, we found the body of literature available on interventions for gender dysphoria and related health problems in TGE youth to be growing but still modest, even when including transition-age adults ages 18 to 25. Research was especially limited for psychosocial interventions (22 studies), gender-affirming surgery (18 studies), and reproductive interventions (nine studies, all focused on fertility preservation), as well as for the proposed alternatives, and was completely absent for the topics of voice and communication therapy and interventions to support detransition (both of which are included in the WPATH standards; see Coleman et al., 2022), indicating important gaps that researchers can fill through more-focused attention on those topics. A notable subset of studies ($k = 7$) examined youth experiences retrospectively using data from the first U.S. Transgender Survey, the largest survey of transgender adults to date ($N = 27,456$; see James et al., 2016)—certainly a valuable source of data but also limited in its ability to examine youth experiences and outcomes. Recognizing that many institutions and researchers lack the resources to conduct pediatric health research (van der Zanden et al., 2022), especially with a small and vulnerable population such as TGE youth, funders and institutions should consider providing more resources to develop and conduct studies on these topics. In the short term, there would be considerable benefit to researchers stratifying their findings by age group whenever possible. We excluded from this review numerous studies with some TGE youth age 25 or under in the sample, which we could have included had results been reported specifically for those age groups.

Broadly, for all interventions targeting gender dysphoria and related health problems in TGE youth, researchers can expand knowledge by recruiting more-diverse study samples and focusing on a broader variety of youth across studies. These actions will help maximize the inclusiveness of interventions, services, and research teams and inform population-specific nuances for clinical recommendations. Regarding gender identity, nonbinary youth were often not included or represented only a small subset of study participants, despite nonbinary currently being the most prevalent TGE identity in the United States (James et al., 2016), and only a few studies reported the proportion of other gender-expansive identities in the sample. Within the diversity of gender identities, studies of transitions beyond binary male or female identities are lacking (MacKinnon, Kia, et al., 2023). All interventions in our review may be relevant to gender-expansive identities, although youth may vary in their level of interest or desired outcome from a given intervention. Inclusion of intersex youth was rarely reported and sometimes even listed as an exclusion criterion, despite the unique experiences of many intersex individuals in having their sexual characteristics modified soon after birth to match their legally assigned gender (Fisher et al., 2016; Roen, 2019). This exclusion reflects the lack of attention to the needs of intersex people in health research and practice (Zeeman and Aranda, 2020).

As another example, greater attention to the intersecting roles of race, ethnicity, and culture is essential for future research on gender dysphoria interventions, especially with TGE youth. Few of the reviewed studies provided any data on participant racial or ethnic identity, and most of those that did were majority-White samples (with most of the others being from majority-White countries); none of the studies examined such factors as systemic racism or culturally responsive approaches to care for minoritized groups in their results or implications (Howard et al., 2019; Kattari et al., 2015). However, the importance of these factors is recognized by the WPATH standards of care (Coleman et al., 2022) and other resources for practitioners (Brown and Mar, 2018; Oliphant et al., 2018; Telfer et al., 2018). As research increases across these important dimensions of identity, it would be beneficial to consider intersecting identities and power structures (e.g., religion). Finally, a challenge for generalizability is that TGE health expertise and research were concentrated in com-

prehensive gender-related service clinics, which may be difficult to access because of distance, waiting lists, or requirements to participate in research (Gridley et al., 2016; Horton, 2024). It would be useful to study the benefits and risks of treating gender dysphoria for TGE youth in such settings as pediatric primary care (Clark et al., 2018; Coleman et al., 2022; Radix, 2020) or specialty clinics for mental health conditions that have been conflated with gender dysphoria—especially for autism and eating disorders.

In addition to increasing the quantity and content of research on interventions for TGE youth, researchers can also take steps to maximize the certainty of evidence produced (Balshem et al., 2011; Andrews et al., 2013). More moderate- to high-certainty evidence would help strengthen and refine the current standards of care. We stress the importance of moderate- to high-certainty evidence because the GRADE criteria for high certainty of evidence prioritize randomized controlled trials or nonrandomized studies that achieve comparable levels of internal validity (Schünemann et al., 2019). Given the limitations of highly controlled research trials to generate evidence that can generalize into effective clinical practice (Frieden, 2017; Jones and Podolsky, 2015; Rothwell, 2005), treating them as a gold-standard research method is overly restrictive for guideline development. This point is particularly relevant in research on interventions for gender dysphoria in TGE youth, for which randomization can ethically be used only to compare key variations within or additions to the standards of care, because the safety risks of withholding the standards of care clearly outweigh the scientific knowledge to be gained (Ashley et al., 2024). Thus, we encourage researchers to consider the variety of quasi-experimental methods available for studying policy and practice without randomization (Palinkas, Mendon, and Hamilton, 2019; Shadish, Cook, and Campbell, 2002; Wing, Simon, and Bello-Gomez, 2018), which would produce evidence of moderate or even high GRADE certainty (e.g., by addressing observed and unobserved confounding variables). Such evidence would meaningfully raise the overall certainty of evidence for most areas of research that we reviewed, strengthening any GRADE recommendations that evidence subsequently informs. Applications of regression discontinuity, difference in differences, or similar methods already exist in transgender health research (see Campbell and Rodgers, 2022, 2023). Of course, randomized trials may be the ideal method for some research questions, when methodologically and ethically justifiable. For example, waiting lists for services may be leveraged for randomization to help control for the effects of time, repeated measurement, and attention.

The evidence base on interventions for gender dysphoria in TGE youth could also be improved by strengthening assessment of long-term outcomes, given the importance of understanding the developmental impacts of these interventions across the lifespan (Ludvigsson et al., 2023; Mahfouda et al., 2019; Ramos et al., 2021; Thompson et al., 2023). In our review, many cohort studies had follow-ups of two to five years, and quasi-experimental studies had follow-ups of one to three years (sometimes longer). Few studies for any intervention category followed youth beyond young adulthood, which may be the implicit meaning of *long term* in this research area (see, e.g., Ludvigsson et al., 2023), although the term is not consistently defined and does not represent professional consensus. Indeed, longitudinal follow-up for youth intervention studies is broadly challenging and requires intensive resources for participant engagement and retention (Broder et al., 2017; Field and Behrman, 2004), so the observed follow-up rates are not unusual. Lack of follow-up data was most notable for reproductive health interventions, psychosocial interventions other than social transition, and proposed alternatives to the standards of care (treatment of co-occurring disorders, GIECE). Overall, funders and institutions should consider ways to support researchers in extending follow-up lengths, as well as improving the certainty of evidence within the typical short- to moderate-term follow-ups.

Beyond study design, improving measurement also offers opportunities to maximize the certainty of evidence on interventions for gender dysphoria and related health problems. Whenever possible, mixed-methods research is ideal for balancing the strengths and limitations of various data sources (Palinkas, Mendon, and Hamilton, 2019): data can be gathered from multiple informants (e.g., youth, caregivers, health care providers) using both quantitative and qualitative methods. Of course, for some topics, a given indi-

vidual is the ideal informant. For example, youth are best positioned to share their gender identity and the history of how it developed, whereas caregivers can comment on observed behavior and early developmental periods. Discrepancy in reports between informants is to be expected and can be understood as reflecting the unique perspective and information offered by each informant (De Los Reyes et al., 2013; Weisz et al., 2017). Regarding mixed methods, quantitative measures were much more common in the reviewed studies, although the psychometrics (reliability and validity) of most measures was unclear—except for some well-established youth mental health measures, which still were not normed for TGE samples. This is an important limitation on our ability to assess key outcomes in a standardized manner. It would be beneficial to conduct rigorous measurement development studies for TGE health outcomes (Bowman et al., 2022) and to encourage wider use of these measures in research and clinical practice; for example, there were many missed opportunities to measure gender dysphoria outcomes in the studies we reviewed, despite this being the primary benefit for most of the interventions studied. Qualitative methods were not widely used in the research we reviewed, and when such methods were used, there was sometimes minimal reporting of data collection and analysis. Regardless of the method, following relevant reporting standards helps to ensure that complete and comparable information is available for synthesizing evidence across studies.

Another important limitation of research on gender dysphoria interventions for youth is that studies have largely focused on medical transition; indeed, desire to receive a specific medical service was the focus of recruitment or eligibility for many studies reviewed. However, supporting the health of TGE youth involves more than medical transition. The U.S. Transgender Survey found that a notable minority of TGE-identified people did not want to undergo the social and medical changes involved in “transitioning” or at least reported being uncertain; this was especially the case among nonbinary individuals (James et al., 2016). Some cases of transition regret and detransition could be attributable to TGE care pathways not being sufficiently responsive to individuals’ needs and goals (MacKinnon, Gould, et al., 2023). Rich descriptive research from surveys, qualitative interviews and focus groups, and other methods is equally valuable to research evaluating specific interventions, because it provides understanding of “[TGE] people’s lives without, before, and after medical gender affirmation” as called for in a research agenda developed by TGE researchers and experts in TGE health (Veale et al., 2022). We highlighted some such research in this review by including social transition interventions (which often occur outside formal medical intervention) and topics such as reproductive health that are affected by, but rarely studied along with, medical transition (again as suggested by Veale et al., 2022). More research would help ensure the effective and appropriate use of these interventions; for example, social transition is the only available intervention to support transition to the youth’s gender identity prepuberty and the only one that is generally reversible, but its wide applicability remains underexplored. In cases in which exploration of a youth’s gender identity is central to their treatment goals, psychotherapy may be beneficial, especially if provided in ways that are distinct from the proposed alternatives found in our review (which actively sought to change gender identity or treated it as a symptom of a co-occurring disorder). However, we found no research on the outcomes of any exploration-focused psychotherapy, so its effects remain unknown and the boundaries between beneficial exploratory psychotherapy and interventions such as GIECE remain undefined.

Any research designed to increase certainty of evidence regarding outcomes of proposed alternatives to the standards of care for TGE youth (i.e., GIECE and treating co-occurring mental disorders to reduce gender dysphoria), though valuable, should be approached with great care, given the existing evidence for harm and lack of evidence for benefits. Prospective research on interventions for gender dysphoria that seek to change, restrict, delay, or ignore TGE identity should be evaluated to ensure that the potential benefits of improved scientific knowledge outweigh the risks to participants because of the potential for serious ethical concerns. Institutions that set research priorities, such as health research funders and journals that publish health research, may consider issuing guidance on this topic. Funders regularly issue such guidance for varied rea-

sons; for example, the U.S. National Institute of Mental Health advised in recent requests for proposals on studies of adolescent social media use that “applications that only measure duration of time spent on screens or digital communications” would not be funded (National Institutes of Health, 2023), in line with expert recommendations that screen time is not a useful measure of social media use (Odgers, Schueller, and Ito, 2020). An example of guidance from journals is editorial policies around “candidate gene” studies for psychopathology (e.g., Hewitt, 2012); these policies reflect expert guidance that detecting discrete genetic markers is often not possible for complex behavioral phenomena, and findings from studies that potentially identified such markers are rarely replicated (Duncan and Keller, 2011). That said, a notable gap in this literature was the lack of data on patient preferences and perspectives regarding GIECE, which could be particularly informative, given that adults (including young adults) do voluntarily seek out such interventions.

A final issue for researchers to consider, in partnership with practitioners and policymakers, is how the implementation of evidence-based standards of care and policies influences their ultimate health impacts. Studies can evaluate the use of strategies from implementation science and quality improvement designed to help guide the adoption, with appropriate quality and safety levels, of standards of care or evidence-based health policies related to care for gender dysphoria in TGE youth. Implementation science is the study of contextual influences and strategies that affect the use of evidence-based interventions, tools, programs, and other practices in routine care settings (Mustanski and Macapagal, 2023; Price et al., 2024; Perry and Elwy, 2021) and can be combined with an ongoing examination of effectiveness when an intervention’s outcomes lack high certainty (Curran et al., 2022). Key concepts from implementation science have also been extended to the implementation of policy (Purtle et al., 2023; Crable et al., 2022) and deimplementation (i.e., discontinued implementation) of harmful or low-value services (McKay et al., 2018). Many strategies in the quality-improvement field overlap with those in implementation science, but quality improvement focuses more on the examination of local efforts through identifying, testing, and routinizing opportunities to improve high-priority processes or outcomes (Nilsen et al., 2022). Furthermore, studying these strategies can generate rigorous practice-based evidence on the clinical outcomes of implemented interventions, which would help strengthen the evidence base for gender dysphoria interventions with TGE youth. One example of useful research would be designing and evaluating the impacts of strategies for the education and training of medical and mental health providers in the standards of care (and the underlying evidence base) for gender dysphoria in youth; such training is typically absent, highly limited, or of unknown effectiveness (Korpaisarn and Safer, 2018; Nolan et al., 2020; Stryker et al., 2022).

Review Limitations

The results and implications of this review should be considered in the context of several limitations. First, our approach was designed to systematically identify and review a comprehensive pool of studies on interventions for gender dysphoria and related health problems in TGE youth, but we might have missed identifying certain studies—for example, studies published longer ago, cited infrequently, or conducted outside the United States. In any case, review findings will need to be regularly updated over time as new research is published, especially because there is currently a high level of research activity on health interventions for TGE youth (83 percent of the research we reviewed was published between 2014 and 2023). Second, our narrow focus on TGE youth meant that we excluded a wide variety of research with sexual minority individuals and TGE adults over age 25, as well as research with populations other than sexual and gender minorities (e.g., youth with precocious puberty), all of which have also been used to inform standards of care for TGE youth (Coleman et al., 2022; Hembree et al., 2017). A full understanding of the literature informing those standards requires, at a minimum, considering the reference lists included with each document. Third, although we used GRADE criteria to evaluate the certainty of evidence, we did not explicitly assess publication bias and

were able to synthesize only broad summaries of intervention effects rather than fully contextualized statements about certainty of effect sizes (Zeng et al., 2021). Finally, we did not review the evidence for various diagnosis and other assessment processes for gender dysphoria, which are critical to individualized intervention selection for a given TGE youth (as recommended in the standards of care; Coleman et al., 2022; Hembree et al., 2017).

Conclusions

Our focused review found evidence of benefits and low risks for interventions from the standards of care for TGE youth (i.e., gender-affirming interventions for gender dysphoria and related health problems). We also found evidence of risks and no benefits from proposed alternatives. Across all outcomes, the certainty of evidence was low or very low but still capable of informing practice and policy decisions with careful consideration of guidance on evidence-based decisionmaking under conditions of uncertainty. Continued research is needed to address gaps in the evidence base and inform updated practice and policy decisionmaking over time.

Completed PRISMA Reporting Checklist and Extensions

TABLE A.1
PRISMA 2020 Checklist for This Report

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page (i)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist [included on page 3 of this checklist document].	See below
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Ch. 1, "Purpose of This Systematic Review"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Ch. 1, "Research Questions"
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Ch. 2, "Inclusion and Exclusion Criteria"; Appendix B
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Ch. 2, "Literature Search Strategies"; Table 2.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Ch. 2, Table 2.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Ch. 2, "Inclusion and Exclusion Criteria"
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Ch. 2, "Data Extraction and Critical Appraisal"

Table A.1—Continued

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Ch. 2, “Data Extraction and Critical Appraisal”; Appendix C
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Ch. 2, “Data Extraction and Critical Appraisal”; Appendix D
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Ch. 2, “Data Extraction and Critical Appraisal”
Synthesis methods (see also the Synthesis without Meta-Analysis checklist below)	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Ch. 2, “Data Extraction” and “Data Synthesis”
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”; Table 2.3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Ch. 3, opening paragraphs; Figures 3.1 and 3.2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Ch. 2, “Inclusion and Exclusion Criteria”; Appendix F
Study characteristics	17	Cite each included study and present its characteristics.	Appendix E; Annex I, columns A–G

Table A.1—Continued

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Annex I, column K+
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Annex I, columns H–J
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Ch. 3, “Overview of Evidence” sections; Annex II, column F
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Ch. 3, “Synthesis and Certainty of Evidence” sections; Annex II, columns D, H
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Ch. 3, “Synthesis and Certainty of Evidence” sections; Annex II, columns E–I
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Ch. 4, opening paragraphs
	23b	Discuss any limitations of the evidence included in the review.	Ch. 4, opening paragraphs; “Implications for Research”; “Review Limitations”
	23c	Discuss any limitations of the review processes used.	Ch. 4, “Review Limitations”
	23d	Discuss implications of the results for practice, policy, and future research.	Ch. 4 “Implications for Practice and Policy”; “Implications for Research”; Table 4.1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Ch. 2, opening paragraph
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Ch. 2, opening paragraph
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	“About This Report”

Table A.1—Continued

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
Competing interests	26	Declare any competing interests of review authors.	“About This Report”
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendixes B, C, and D; Annexes I and II

SOURCES: Adapted from Page, McKenzie et al., 2021, Table 1 (CC BY 4.0), with the last column filled in for this study; also see Page, Moher, et al., 2021.

TABLE A.2
Abstract Checklist for This Report

Section and Topic	Item #	Checklist Item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each.	Yes
		If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Not applicable
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER INFORMATION			
Funding	11	Specify the primary source of funding for the review.	Yes, in “About This Report”
Registration	12	Provider the register name and registration number.	No, but noted that we did not preregister

SOURCES: Adapted from Page, McKenzie et al., 2021, Table 2 (CC BY 4.0), with the last column filled in for this study; also see Page, Moher, et al., 2021.

TABLE A.3
Search Checklist for This Report

Section/Topic	Item #	Checklist item	Location Where Item Is Reported
METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Ch. 2, "Literature Search Strategies"
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	Not applicable
Study registries	3	List any study registries searched.	Not applicable
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	Not applicable
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	Ch. 2, "Literature Search Strategies"
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	Not applicable
Other methods	7	Describe any additional information sources or search methods used.	Ch. 2, "Literature Search Strategies"
RESULTS			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Ch. 2, Table 2.2
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Ch. 2, Table 2.2
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	Ch. 2, Table 2.2
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	Ch. 2, "Literature Search Strategies"
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	Not applicable
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	Ch. 2, Table 2.1
PEER REVIEW			
Peer review	14	Describe any search peer review process.	Ch. 2, "Quality Assurance Process"
MANAGING RECORDS			
Total records	15	Document the total number of records identified from each database and other information sources.	Ch. 3, Figure 3.1
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Ch. 3, Figure 3.1

SOURCE: Adapted from Rethlefsen et al., 2021 (CC BY 4.0), with the last column filled in for this study.

TABLE A.4
Harms Checklist for This Report

Section/Topic	Item #	PRISMA Harms (Minimum) Checklist Item	Location Where Item Is Reported
TITLE/Title	1	Specifically mention “harms” or other related terms, or the harm of interest in the review.	Title page (p. i)
METHODS/ Synthesis of results	14	Specify how zero events were handled, if relevant.	Ch. 2, “Data Synthesis and Certainty-of-Evidence Assessment”
RESULTS/Study characteristics	18	Define each harm addressed, how it was ascertained (e.g., patient report, active search), and over what time period.	Ch. 3, “Synthesis and Certainty of Evidence” sections; Annex I, column K Annex II
RESULTS/ Synthesis of results	21	Describe any assessment of possible causality.	Ch. 3, “Overview of Evidence” sections; Annex II

SOURCE: Adapted from Zorzela et al., 2016, with the last column filled in for this study.

TABLE A.5
Synthesis Without Meta-Analysis (SwiM) Checklist for This Report

Section/Topic	Item #	Checklist Item	Location Where Item Is Reported
METHODS			
Grouping studies for synthesis	1a	Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	Ch. 2, "Data Synthesis and Certainty-of-Evidence Assessment"
	1b	Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	Not applicable
Describe the standardized metric and transformation methods used	2	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	Ch. 2, "Data Extraction and Critical Appraisal"
Describe the synthesis methods	3	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	Ch. 2, "Data Synthesis and Certainty- of-Evidence Assessment"
Criteria used to prioritize results for summary and synthesis	4	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	Ch. 2, "Data Synthesis and Certainty- of-Evidence Assessment"
Investigation of heterogeneity in reported effects	5	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Ch. 2, "Data Synthesis and Certainty- of-Evidence Assessment"
Certainty of evidence	6	Describe the methods used to assess the certainty of the synthesis findings	Ch. 2, "Data Synthesis and Certainty- of-Evidence Assessment"; Table 2.3
Data presentation methods	7a	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots)	Ch. 2, "Data Extraction" and "Data Synthesis" sections
	7b	Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	Ch. 2, "Data Extraction and Critical Appraisal"; Annex I
RESULTS			
Reporting results	8	For each comparison and outcome, provide a description of the synthesised findings and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Ch. 3 "Synthesis and Certainty of Evidence" sections; Annex II
DISCUSSION			
Limitations of the synthesis	9	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis and how these affect the conclusions that can be drawn in relation to the original review question	Ch. 4, "Review Limitations"

SOURCE: Adapted from Campbell et al., 2020 (CC BY 4.0), with the last column filled in for this study.

Review Inclusion and Exclusion Criteria

1. **INCLUDE IF** sample includes *transgender and/or non-binary (TGE) participants*
 - a. *EXCLUDE IF* participants are not TGE, gender identity is not specified, or gender identity is combined with other factors (e.g., sexual orientation)
 - b. *EXCLUDE IF* opinion piece, guidelines, or other publication other than original research (i.e., there are no participants)
2. **INCLUDE IF** sample of TGE participants are *youth or young adults*, up to and including age 25
 - a. *EXCLUDE IF* participants are adults age >25 or age is not specified
 - b. *EXCLUDE IF* participants include a wide age range without clear differentiation of results for youth/young adults
3. **INCLUDE IF** a *health care intervention related to recipients' TGE identity* was provided to at least one subsample; interventions can be medical (e.g., hormones, surgery) or behavioral (e.g., therapy, support groups, "social transition" like use of preferred name/pronouns), affirming or nonaffirming (e.g., "gender exploration therapy," gender identity change practices/"conversion therapies")
 - a. *EXCLUDE IF* none of the participants received a health care intervention (but note that "watchful waiting" under medical supervision counts as an intervention)
 - b. *EXCLUDE IF* participants received an intervention that was not health care (e.g., supportive housing, income assistance)
 - c. *EXCLUDE IF* participants received an intervention that was not intended to be related to their TGE identity (e.g., care for a disability, substance use treatment)
4. **INCLUDE IF** the *recipients' outcomes* were measured following their receipt of the health care intervention (and comparison condition, if relevant); outcomes can be quantitatively and/or qualitatively measured
 - a. *EXCLUDE IF* publication only reports descriptive information or process information (e.g., sample demographics, number of intervention recipients/completers)
 - b. *EXCLUDE IF* outcomes are described without a clear description of how they were measured (how administered, who provided info, when collected, etc.)
5. **INCLUDE IF** the source was published via peer review, in 1990 or later only
 - a. *EXCLUDE IF* published without peer review
 - b. *EXCLUDE IF* published with peer review, but subsequently retracted
 - c. *EXCLUDE IF* published in 1989 or earlier

Publication Summary Template

Article Details

Reviewer initials	Date reviewed
Publication title	
Link to full text	
Publication outlet	
Author(s) and their affiliations	
Funding source(s)	
Peer reviewed?	

Sample and Recruitment Details

Record this info for each sample or subsample reported in the publication.

- A *sample* is a group of participants included in a study; many publications only have one sample, but some report results from multiple studies with different samples. Copy the table below as needed for multiple samples.
- A *subsample* is part of a larger sample (for example, if youth who received a treatment are compared to youth who didn't, that is a sample with two subsamples). Add or remove columns in the tables as needed so you have the right number of subsamples for each sample.

In some cases, only data for the entire sample will be reported; in others, only subsamples; in others, both will be reported. Just record whatever the publication reported (no need to try to calculate anything else). Put "NR" for any info not reported.

SAMPLE #1	Full sample	Subsample #1	Subsample #2
Name/description:			
How this sample was recruited to participate:			
Eligibility criteria (aka inclusion/exclusion criteria)			
Note potential sources of bias from recruitment			
Sample/subsample size (n)			
Gender identity: use the categories reported in the study, examples include: • n or % identify male • n or % identify female • n or % identify nonbinary • etc. etc. <i>*not sex assigned at birth*</i>			
Also record details of how gender identity was assessed/ defined (e.g., DSM gender identity disorder/ dysphoria?)			
Sex assigned at birth: Note details here when relevant; e.g., if sample includes intersex individuals			
Sexual orientation: use the categories reported in the study, examples include: • n or % homosexual and/or gay and/ or lesbian • n or % heterosexual • n or % bisexual • n or % pansexual • n or % asexual • etc.			
<i>If SO reported:</i> details of age reported, and whether reported pre- or post-beginning transition			
Age when health care of focus for study started: • Mean/average • Standard deviation • Minimum • Maximum • Grade level(s) <i>(record all reported)</i>			
[IF DIFFERENT] Age when provided data to the study: • Mean/average • Standard deviation • Minimum • Maximum • Grade level(s) <i>(record all reported; record each follow-up separately)</i>			

NOTE: DSM = *Diagnostic and Statistical Manual of Mental Disorders*; SO = sexual orientation.

Study Design

Record this info for each sample or subsample reported in the publication. Copy the table below and/or add or remove columns as needed, so that the samples and subsamples match what is presented in “Sample and Recruitment Details.”

In some cases, only data for the entire sample will be reported; in others, only subsamples; in others, both will be reported. Put “NR” for any info not reported.

SAMPLE #1	Full sample	Subsample #1	Subsample #2
Intervention name/brief description: Specify elements below and put “NA” for any elements not applicable (NOTE: interventions include “treatment as usual” or control/waitlist groups)			
Elements focused on trans identity: (medication/hormones, affirming psychotherapy, surgery, etc.)			
Gender orientation change efforts: (such as “conversion therapy,” “gender exploratory therapy,” etc.)			
Elements focused on access to medical care: insurance, transportation, etc.			
Elements focused on related issues: mental health, substance use, education and occupation, housing, legal, social services, etc.			
Any other elements			
How groups were created/assigned (put “NA” if only one group)			
Comparisons made: • Between groups • Within groups at different time points (specify group, time for each)			
Note potential sources of bias from study design			

Outcomes

Record info about the measures administered and the findings from any comparisons listed under “Study Design,” above. Sometimes there can be a lot of information due to a study including many measures and/or testing many different comparisons. Do your best to copy/paste relevant info, and try to just focus on the details asked for here (you do not need to record every statistic reported in the paper). When in doubt, ask for a second opinion of what is relevant!

MEASURES	Name	How Administered	Who Provided Info for Measure	When Collected (relative to start of intervention)
1.				
2.				
3.				
4.				
5.				
Note potential sources of bias from measures:				

(add more rows as needed for number of measures)

How administered = survey, interview, medical record, etc. (note if online or in person)

Who provided info = youth, parent, medical provider, etc.

When collected = # of days, months, years, etc. after intervention started

Outcome Type	Summary of Findings
Beneficial: intervention produced an outcome better than the comparisons	
No effect: intervention outcome was the same as the comparisons	
Harmful: intervention produced an outcome worse than the comparisons (or no improvement for an outcome that could have improved without intervention)	
Level of certainty about the outcomes (based on study design/bias concerns)	

Summary of Tools Used to Assess Methodological Quality, by Study Design

The research team followed published JBI guidance (Aromataris et al., 2024; Barker et al., 2023) when applying the JBI critical appraisal checklist tools. Specifically, we used the JBI critical appraisal checklist tools to critically appraise risk of bias for each study included in our review of interventions for gender dysphoria and related problems in TGE youth. Please refer to the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2024) for full details of how to apply the checklists, and an accompanying publication by Barker et al. (2023) for details of how the critical appraisal checklists have been developed over time.¹

For each study summarized, research team members followed these steps to complete the appropriate JBI checklist:

1. Confirm the study design.
2. Review the checklist criteria that correspond to the study design. Use the guidance provided in the *JBI Manual for Evidence Synthesis* for rating each criterion; the criteria are summarized on the following pages with notes about considerations specific to this review. Ratings always take one of the following four values:
 - a. **Yes:** all aspects of the criterion are clearly met
 - b. **No:** some or all critical aspects of the criterion are clearly not met
 - c. **Unclear:** difficult to judge the criterion and/or whether unmet aspects are critical
 - d. **Not applicable:** depending on the specifics of the study design, the criterion is irrelevant.
3. Specify ratings of the study for each checklist criterion. For any rating of “yes,” no additional information is needed; this should be evident from the study entry. For all other ratings, provide an explanation of the rating using the format below:
 - a. **format for ratings: rating; explanation**
4. A second reviewer completes the first three steps independently; for each rating, the second reviewer either confirms agreement or identifies a discrepancy. In cases of discrepancy, the first and second reviewer discuss to achieve consensus on a rating.

The study design types included in this review are cross-sectional studies, cohort studies, quasi-experimental studies, randomized controlled trials, qualitative studies, and case reports.

Cross-sectional studies and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 7, Appendix 7.5, of the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2024). The critical appraisal checklist criteria consist of the following:

¹ The manual is available to download on JBI’s website: <https://jbi-global-wiki.refined.site/space/MANUAL>; the accompanying article is available at the *Journal of JBI Synthesis*’s website: https://journals.lww.com/jbisrir/fulltext/2023/03000/revising_the_jbi_quantitative_critical_appraisal.4.aspx.

- inclusion criteria
- participants and setting
- intervention measure
- condition measure²
- confounding identified
- confounding addressed
- outcome measures
- statistical analysis.

Cohort studies and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 7, Appendix 7.1, of the *JBIManual for Evidence Synthesis* (Aromataris et al., 2024). The critical appraisal checklist criteria consist of the following:

- comparable groups
- group assignment
- intervention measure
- confounding identified
- confounding addressed
- free of outcome
- outcome measures
- observation period
- follow-up rate
- attrition addressed
- statistical analysis.

Quasi-experimental studies and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 4, Appendixes 4.3 and 4.4, of the *JBIManual for Evidence Synthesis* (Aromataris et al., 2024).³ The critical appraisal checklist criteria consist of the following:

- cause and effect
- group assignment⁴
- comparable care
- control group⁵
- pre-post measurement
- follow-up rate
- comparable outcomes
- outcome measures
- statistical analysis.

² For interventions that do not require a formal gender dysphoria diagnosis, such as social transition, this criterion is not applicable.

³ Under the JBI critical appraisal checklist criteria, pretest/posttest studies in which the patients are the same (the same single group) are rated as quasi-experimental studies.

⁴ In one single group, pretest/posttest studies in which the patients are the same (the same single group) in any pre-post comparisons, the answer to this question should be “yes.”

⁵ The control group should be an independent, separate control group, not the pre-test group in a single group pretest/posttest design.

Randomized controlled trials and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 4, Appendixes 4.1 and 4.2, of the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2024). The critical appraisal checklist criteria consist of the following:

- randomization
- concealed allocation
- comparable groups⁶
- participants masked
- interventionists masked
- comparable care
- assessors masked
- comparable outcomes
- outcome measures⁷
- follow-up rate⁸
- intent-to-treat⁹
- statistical analysis
- trial design.

Qualitative studies and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 3 of the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2024). The critical appraisal checklist criteria consist of the following:

- congruent philosophy
- congruent questions
- congruent methods
- congruent analysis
- congruent interpretation
- positionality
- researcher influence
- participant voice
- ethical approval
- conclusions.

Case reports and the corresponding JBI critical appraisal checklist tool are detailed in Chapter 7, Appendix 7.4 of the *JBI Manual for Evidence Synthesis* (Aromataris et al., 2024). The critical appraisal checklist criteria consist of the following:

⁶ Do not consider only the *p*-value for the statistical testing of the differences between groups with regard to the baseline characteristics.

⁷ Two other important threats that weaken the validity of inferences about the statistical relationship between the cause and the effect are low statistical power and the violation of the assumptions of statistical tests. These other two threats are explored within statistical analysis.

⁸ Question 10 is NOT about intention-to-treat (ITT) analysis; question 11 is about ITT analysis.

⁹ This analysis is a type of statistical analysis recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement on best practices in trials reporting, and it is considered a marker of good methodological quality of the analysis of results of a randomized trial. The ITT is estimating the effect of offering the intervention, that is, the effect of instructing the participants to use or take the intervention; the ITT is not estimating the effect of receiving the intervention of interest.

- demographics
- case history
- presenting condition
- assessment described
- intervention described
- post-intervention condition
- adverse events
- implications.

Overview Table for Included Studies and Publications

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Achille et al. (2020)		✓	✓				
Akgul et al. (2019)		✓					
Allen et al. (2019)			✓				
Amir et al. (2020)			✓		✓		
Arnoldussen, van der Miesen, et al. (2022)		✓	✓	✓			
Ascha et al. (2022)				✓			
Austin, Craig, and D'Souza (2018)	✓						
Barnard et al. (2019)		✓	✓		✓		
Barrett et al. (2022)					✓		
Becker-Hebly et al. (2021); Nieder et al. (2021)	✓	✓	✓	✓			
Bodlund and Kullgren (1996)			✓	✓			
Boskey et al. (2023)				✓			
Brandsma et al. (2022)	✓						
Brik et al. (2020)		✓					
Bungener et al. (2020)				✓			
Burke et al. (2016)			✓				
Caanen et al. (2017)		✓	✓				

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Campbell, Mann, Nguyen, and Rodgers (2023)			✓				
Campbell, Mann, Rodgers, and Tran (2023)	✓						
Campbell and Rodgers (2023)							✓
Cantu et al. (2020)			✓				
Carmichael et al. (2021); McPherson and Freedman (2023)		✓					
Chen et al. (2023); Millington et al. (2021)			✓				
Cohen-Kettenis and Van Goozen (1998); Cohen-Kettenis et al. (2011)	✓	✓	✓	✓		✓	
Cohen-Kettenis and Van Goozen (1997); Smith, Van Goozen, and Cohen-Kettenis (2001); Smith, Cohen, and Cohen-Kettenis (2002)				✓			
Coleman and Cesnik (1990)	✓					✓	
Costa et al. (2015)	✓	✓					
de Castro Peraza et al. (2023)	✓						
DeChants et al. (2022)	✓						
Delemarre-van de Waal and Cohen-Kettenis (2006)		✓	✓				
de Nie et al. (2023)			✓		✓		
de Vries et al. (2011)		✓					
de Vries et al. (2014)			✓	✓			

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Dilday et al. (2022)					✓		
Donaldson et al. (2018)		✓	✓	✓		✓	
Durwood, McLaughlin, and Olson (2017)	✓						
Durwood et al. (2023)	✓						
Ewan, Middleman, and Feldmann (2014)		✓				✓	
Gale et al. (2021)			✓		✓		
Grannis et al. (2021); Grannis et al. (2023); Olsavsky et al. (2023)		✓	✓				
Green et al. (2020)							✓
Green et al. (2022)			✓				
Grimstad, Knoll, and Jacobson (2021)			✓				
Gupta et al. (2023)			✓				
Hill et al. (2010)	✓						
Hisle-Gorman, Ginsburg, and Srouji (2021)		✓	✓				
Insogna, Ginsburg, and Srouji (2020)			✓		✓		
Jarin et al. (2017)			✓				
Joseph, Ting, and Butler (2019)		✓					
Kaltiala et al. (2020)			✓				
Khatchadourian, Amed, and Metzger (2014)		✓	✓				
Kirchner et al. (2022)	✓						
Klaver et al. (2018); Klaver et al. (2020)		✓	✓				

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Klink et al. (2015)		✓	✓				
Kuper et al. (2020)		✓	✓	✓			
Laurenzano et al. (2021)			✓				
Lavender et al. (2023)		✓	✓				
Lee et al. (2023)		✓	✓	✓			
Lierman et al. (2017)			✓		✓		
Littman (2021)	✓	✓	✓	✓			
López de Lara et al. (2020)		✓	✓				
Marinkovic and Newfield (2017)				✓			
Martin, Lewis, and Omurtag (2021)		✓	✓		✓		
McGregor et al. (2023)		✓					
Mehringer et al. (2021)			✓	✓			
Morandini et al. (2023)	✓						
Moussaoui et al. (2023)		✓					
Mukaddes (2002)						✓	
Mullins et al. (2021)			✓				
Navabi et al. (2021)		✓					
Neyman, Fuqua, and Eugster (2019)		✓					
Olson et al. (2014)			✓				
Olson et al. (2016)	✓						
Olson et al. (2022)	✓	✓	✓				
Olson-Kennedy, Okonta, et al. (2018)			✓				
Olson-Kennedy, Warus, et al. (2018)				✓			

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Pang et al. (2020)		✓					
Perera, Gadambanathan, and Weerasiri (2003)						✓	
Perl et al. (2020); Perl et al. (2021)		✓	✓				
Pollitt et al. (2021); Russell et al. (2018)	✓						
Ristori et al. (2019)		✓	✓			✓	
Schagen et al. (2016); Hannema et al. (2017)		✓	✓				
Schagen et al. (2020)		✓	✓				
Schneider et al. (2017)		✓					✓
Schwartz et al. (2023)		✓					
Sievert et al. (2021)	✓						
Skorochood, Rysin, and Wolf (2023)				✓			
Stanley and Cooper (2018)			✓				
Stoffers, de Vries, and Hannema (2019)			✓				
Tack et al. (2016)		✓	✓				
Tack et al. (2017)		✓	✓				
Tack et al. (2018)		✓					
Tang et al. (2022)				✓			
Tordoff et al. (2022)		✓	✓				
Turban, Carswell, and Keuroghlian (2018)	✓		✓				
Turban, Beckwith, et al. (2020)							✓
Turban, King, et al. (2020)		✓					

Citation(s) for Study Publications	Intervention Categories Evaluated						Gender Identity and Expression Change Efforts ^g
	Psychological and Social Interventions ^a	Puberty-Suppressing Hormones ^b	Hormone Replacement Therapy ^c	Gender-Affirming Surgeries ^d	Reproductive Health Interventions ^e	Treatment of Co-Occurring Disorders ^f	
Turban et al. (2021)	✓						
Turban et al. (2022)			✓				
van de Grift et al. (2020)		✓					
van der Loos et al. (2022)		✓	✓				
van der Loos et al. (2023)		✓	✓				
van der Miesen et al. (2020)		✓					
Vlot et al. (2017)		✓	✓				
Vrouenraets et al. (2022)		✓					
Weinhardt et al. (2021)	✓						

^a See Annex I's Table G.1 and Annex II's Table H.1 for findings.

^b See Annex I's Table G.2 and Annex II's Table H.2 for findings.

^c See Annex I's Table G.3 and Annex II's Table H.3 for findings.

^d See Annex I's Table G.4 and Annex II's Table H.4 for findings.

^e See Annex I's Table G.5 and Annex II's Table H.5 for findings.

^f See Annex I's Table G.6 and Annex II's Table H.6 for findings.

^g See Annex I's Table G.7 and Annex II's Table H.7 for findings.

Overview Table for Ineligible Publications Reviewed

Citation	Reason for Ineligibility
Abernathy et al. (2023)	No health intervention for gender dysphoria (outcomes not reported separately for contraception versus menstrual suppression)
Barlow, Reynolds, and Agras (1973)	Published before 1990
Barlow, Abel, and Blanchard (1977)	Published before 1990
Barlow, Abel, and Blanchard (1979)	Published before 1990
Bauer et al. (2015)	No youth sample (outcomes not reported separately for youth participants)
Cardoso da Silva et al. (2016)	No youth sample
Di Ceglie and Thümmel (2006)	No youth sample
Dromer et al. (2022)	No TGE sample (outcomes not reported separately for TGE participants)
Fennell et al. (2023)	No youth sample
Kinitz et al. (2022)	No TGE sample (outcomes not reported separately for TGE participants)
Lee et al. (2020) ^a	No outcomes
Malpas (2011)	No outcomes
Nelson, Whallett, and McGregor (2009)	No youth sample (outcomes not reported separately for youth participants)
Nolan et al. (2023)	No youth sample (outcomes not reported separately for youth participants)
Russon et al. (2022)	No TGE sample (outcomes not reported separately for TGE participants)
Ryan et al. (2020)	No TGE sample (outcomes not reported separately for TGE participants)
Sevlever and Meyer-Bahlburg (2019)	No health intervention for gender dysphoria
Vance et al. (2023) ^a	No health intervention for gender dysphoria
van de Grift (2018)	No TGE sample (outcomes not reported separately for TGE participants)
Wiepjes et al. (2018)	No outcomes
Williams, Allard, and Sears (1996)	No health intervention for gender dysphoria

NOTE: See Appendix B for the full details of eligibility criteria.

^a These publications were identified as ineligible in phase 2 of the review (i.e., the PubMed literature search); all other publications were identified as ineligible during phase 1 (i.e., the initial targeted search).

Abbreviations

GIECE	gender identity and expression change efforts
GnRHa	gonadotropin-releasing hormone analogues
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRT	hormone replacement therapy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
SOGIECE	sexual orientation and gender identity and expression change efforts
TGE	transgender and gender expansive
WPATH	World Professional Association for Transgender Health

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