Table 1 Articles on the epidemiology of gender dysphoria in children and adolescents.

Author **Year** **Ref** **Country**	**Age**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Arnoldussen et al 2019 [15] The Netherlands	**Mean** 14.6 years **Range** 10.1–18.1 years	Prevalence 2000–2016 N=1 072 (n=668 females)	To examine whether consecutively transgender clinic-referred adolescents between 2000 and 2016 differ over time in demographic, psychological, diagnostic, and treatment characteristics	Demographics. Intelligence: measured by Dutch version of the Wechsler Intelligence Scale for Children, or the Wechsler Adult Intelligence Scale. Psychological functioning: measured by the Child Behaviour Check List Gender dysphoria intensity: Youth Self-Report, intensity of gender dysphoria measured by the Utrecht Gender Dysphoria Scale. Percentage of referrals diagnosed with gender dysphoria Percentage of diagnosed adolescents that started with affirmative medical treatment (puberty suppression and/or gender-affirming hormones)
Becerra-Culqui et al 2018 [29] USA	**Range** 3–17 years	Electronic medical record (EMR) – based retrospective and prospective cohort study n=588 transfeminine n=745 transmasculine children 10 male and 10 female referent cisgender enrolees matched to each TGNC individual	To estimate the prevalence of mental health diagnoses among transfeminine and transmasculine children and adolescents at the time of their initial presentation (index date) and compare their mental health status to that of their cisgender counterparts.	Prevalence ratios of: Anxiety disorders attention deficit disorders Autism spectrum disorders Conduct and/or disruptive disorders Depressive disorders Eating disorders Self-inflicted injury Suicidal ideation

Author **Year** **Ref** **Country**	**Age**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Bränström et al 2019 [37] Sweden	**Mean** 31.5 years	Registry study, 3 linked registries 2005 -2015 n=2 679 Legal gender: n=1 284 male n=1 395 female Swedish Total Population Register National Patient Register Prescribed Drug Register.	To ascertain the prevalence of mood and anxiety disorder health care visits and antidepressant and anxiolytic prescriptions in 2015 as a function of gender incongruence diagnosis and gender affirming hormone and surgical treatment in the entire Swedish population.	Epidemiology **Mental health treatment** Mood disorder Anxiety disorder Health care visits, Antidepressant prescriptions Anxiolytic prescriptions Hospitalization after a suicide attempt. **Hormone treatment** Oestrogen or progesterone Androgen Androgen-suppressing or -blocking medication **Surgical treatment** Breast or dermatological chest surgery Surgery of the reproductive organs Dermatological surgery Laryngeal surgery
Chen et al 2016 [16] USA	**Mean** 14.4 ± 3.2 years	Retrospective chart review of referrals 2002–2015 n=38 n=22 natal females **Follow-up** 13 years	Frequency and characteristics of referrals	Numbers of referrals per year Timing of referral Comorbid conditions Hormonal therapy Eligibility for treatment. Pubertal status at presentation, Psychological evaluation for GD, History of RLE (real-life experience of living full-time in the identified gender). **Concurrent diagnoses** (depression, attention deficit/hyperactivity disorder, autism spectrum disorder, suicidality and/or self-harm, psychotropic medications)

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Chiniara et al 2018 [17] Canada	**Range** 12–18 years **Mean** 16 years	Retrospective review 2014–2016 n=203 n=156 natal females	Examine characteristics, including mental health comorbidities, among adolescents presenting to a transgender clinic	Demographic data: AFAB - assigned female at birth; AMAB - assigned male at birth; social transition; age at referral Clinical characteristics, Tanner stage, Bone age Utrecht Gender Dysphoria Scale Mental health comorbidities (depression, anxiety, autism spectrum disorder, suicidal ideation, self-harm, medication for mood disorder) Blood work
Connolly et al 2016 [38]		Review		
Costa and Colizzi 2016 [39] United Kingdom	**Range** 18–58 years	Systematic review up to 2016 17 included studies (cross-sectional studies and longitudinal studies)	Systematic review of all studies examining the effect of cross-sex hormonal treatment on mental health and well-being in gender dysphoria.	
de Graaf et al 2018 [18] United Kingdom	**Age at referral** **Mean** 8.72 years (SD 2.30) natal boys **Mean** 9.78 years (SD 2.15) natal girls	Extraction of health records 2000–2017 n=1 215 n=681 natal boys n=534 natal girls	Examine the sex ratio of children, age at referral and year of referral, for children referred to the Gender Identity Development Service in the UK.	Birth assigned gender Year of referral Age at assessment

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de Graaf et al 2018 [21] United Kingdom	**Range** 1–18 years	Retrospective review of referrals 2009–2016. N=4 506	Examine the sex ratio in the number of children and adolescents referred over the past 7 years.	Age at referral Birth assigned gender Sex ratio Psychological functioning (internalizing and externalizing problems: Child Behaviour Checklist)
de Graaf et al 2019 [40] United Kingdom	Under 18 years	Referrals between 2012–2014 N=995	Identify the ethnicities of children and young people referred to the UK Gender Identity Development Service.	Ethnicity
Drummond et al 2008 [11] Canada	**Age at assessment** Mean: 8.88 years Range: 3–12 years **Age at follow-up** Mean: 23.24 years Range: 15–36 years	Cohort 1975–2004 n=25 girls	This study provided information on the natural histories of 25 girls with gender identity disorder.	Cognitive functioning: assessed by Wechsler Adult Intelligence Scale Sex-typed behaviour Recalled childhood gender identity and gender role behaviour Concurrent gender identity. Sexual orientation in behaviour. Sexual identity self-labelling. Social desirability
Hisle-Gorman et al 2019 [27) USA	**Range** 2–18 years **Median** 11.6 years	Retrospective case-cohort study of GD diagnoses with and without ASD Health care records 2000–2013. n=48 762 diagnosed with ASD **Follow-up** 3 years	We investigated diagnosed GD in patients formally diagnosed with ASD in the Military Health System	Diagnosis of GD

Author Year Ref Country	Age	Study design n	Aims/ Research question(s)	Outcome measures
Kaltiala-Heino et al 2019 [10] Finland	**Mean** 15.7 years	Prevalence Data from a School Health Promotion Study 2017. N=135 760	To explore the susceptibility of gender identity to mischievous responding, and prevalence of cis-gender, opposite-sex and other/ non-binary gender identities as corrected for likely mischievous responding among Finnish adolescents.	Sex Perceived gender Disability Factitious responses (implausible, likely mischievous responding). The School Health Promotion Study (SHPS) by the National Institute for Health and Welfare is a school-based survey designed to examine the health, health behaviours and school experiences of teenagers.
Kaltiala-Heino et al. 2015 [20] Finland	**Mean** 16 years	Structured quantitative retrospective chart review of all Sex Reassignment applicants (2011–2013). N=47 n=41 natal girls n=6 natal boys	To describe the adolescent applicants for legal and medical sex reassignment during the first two years of adolescent gender identity team in Finland, in terms of sociodemographic, psychiatric and gender identity related factors and adolescent development.	Signs of gender dysphoria/ gender incongruence in childhood (< age 12) Age of onset of gender concerns Age convinced of being transsexual. Duration of living in desired gender role. Psychiatric history prior to entering gender identity service (anxiety, depression, suicidal behaviours, conduct problems, autism spectrum related problems, substance abuse, psychotic symptoms, other) Peer-related difficulties (bullying, isolation, before or after onset of gender dysphoria) Sociodemographic variables (age, natal sex, family structure, parental education)

Author Year Ref Country	Age	Study design n	Aims/ Research question(s)	Outcome measures
Kaltiala-Heino et al 2019 [9] Finland	**Range** 16–18 years	Survey on gender experience among junior high school students, during the 2012–2013 and 2017 school years. n=1 746 survey responders n=644 male n=1 102 female	Explore whether there has been an increase in prevalence and changes in sex ratio in feelings of gender dysphoria (GD) in an adolescent population in Northern Europe	Gender identity/Gender Dysphoria: measured with GIDYQ-A. Age
Landen and Innala 2000 [25] Sweden	**Range** 18–70 years	Questionnaire 1998 n=992 randomly selected national sample of Swedish residents (lay people) n=668 respondents	A general inventory of the ethical views on sex reassignment and attitudes toward transsexuals in Sweden.	Demographic Characteristics Possibility to undergo sex reassignment Bearing of expenses Right to get married in their new sex Right to work with children Right to adopt and raise children
Littman 2018 [23] Littman 2019 correction [24] USA	**At announced transgender identification** Mean age of 15.2 **At survey** Mean: 16.4 years	Descriptive, exploratory study, survey n=256 parent-completed surveys (82.8% natal females)	To collect data about parents' observations, experiences, and perspectives about their adolescent and young adult children showing signs of an apparent sudden or rapid onset of gender dysphoria that began during or after puberty, and develop hypotheses about factors that may contribute to the onset and/or expression of gender dysphoria among this demographic group.	Non-heterosexual sexual orientation Rapid onset gender dysphoria Pre-existing diagnosis of mental health disorder Pre-existing diagnosis of Neurodevelopmental disability Parent-child relationships Behaviours (distrust, asocial, isolation, social media/internet use)
Mann et al 2019 [30] United Kingdom	Up to 25 years	Systematic Review, 2000–2017 n=7 included studies	To investigate the prevalence of self-injurious thoughts and behaviours among children and young people in the UK identifying as a gender not typically associated with the sex they were assigned at birth and, further, to examine relevant prevalence rates of self-injurious thoughts and behaviours reported.	Prevalence of self-injurious thoughts and behaviours: Self-harm/ self-injurious behaviour Thoughts of self-harm Suicidal ideation Suicide attempt

Author **Year** **Ref** **Country**	**Age**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Nabbijohn et al 2019 [28] Canada	**Range** 6–12 years	Parent-report online questionnaire (anonymous survey) June to Dec 2016. n=2 445 n=441 clinical subgroup (mental health/ developmental diagnoses) n=2004 nonclinical (not seeking health care) subgroup	Gender variance in association with Autism Spectrum Disorder characteristics in nonclinical children and in children with developmental/ mental health diagnoses.	Gender Variance (GV): measured by Gender Identity Questionnaire for Children. Subdomains of ASD characteristics: measured by the Children's Social Behaviour Questionnaire. Clinical diagnoses: Autism Spectrum Disorder (ASD), Attention-deficit/hyperactivity disorder (ADHD), Obsessive–compulsive disorder (OCD), Sensory processing disorder (SPD), Oppositional defiant disorder (ODD), Mood and anxiety disorders, Learning disabilities, Neurodevelopmental conditions. Among nonclinical children: Parent-reported difficulties orienting socially, Stereotyped behaviours
Nordahl-Hansen et al 2019 [31]	Review update of Oien et al 2018 [32]		Update of previous review: Systematic map review on Gender Dysphoria, sexuality and Autism spectrum disorder (Øien et al. 2018)	
Øien et al 2018 [32]		**Systematic map review,** overview of systematic reviews, up to 2018 n=28 included quantitative studies n=19 included qualitative studies	To map the current empirical research on the co-occurrence of GD and ASD	Gender dysphoria Autism spectrum disorder

Author Year Ref Country	Age	Study design n	Aims/ Research question(s)	Outcome measures
Steensma et al 2013 [13] The Netherlands	**Age at referral and first diagnosis** Range: 6–12 years **Age at follow-up** Range: 15–17 years	Referrals 2000 and 2008 n=127 adolescents n=79 boys n=48 girls **Follow-up** 4-year period between 2008 and 2012	To assess Childhood Predictors of Persistence of GDiInto Adolescence	Demographics: natal sex, age at assessment, diagnosis (DSM-IV-TR GID), social role transition, parents' marital status, parents' social class, and Full-Scale IQ. Gender Identity and Gender Dysphoria: The Dutch version of the Gender Identity Interview for Children (GIIC). The Dutch version of the Gender Identity Questionnaire (GIQ) Psychological Functioning: assed through parental report, by the Dutch version of the Child Behaviour Checklist/ 4-18 (CBCL), and teacher report, by the Dutch version of the Teacher's Report Form (TRF). Quality of Peer Relations. Adolescence: Gender Identity: The Gender Identity Interview for Adolescents and Adults (GIAA) Gender Dysphoria: The Utrecht Gender Dysphoria Scale (UGDS) Body Image: The Body Image Scale (BIS) Sexual Orientation Parent Report.
Strang et al 2018 [14] USA	**Range** 13–21 years **Mean** 16.6 (SD 1.9) years	Interviews n=22 autistic gender-diverse adolescents **Follow-up** 12 and 22 months	To characterize the short-term gender trajectories of adolescents with the co-occurrence [autistic gender-diverse adolescents who have diagnostically-confirmed ASD); To identify salient themes in these young people's lives	Pre-pubertal gender nonconformity Gender dysphoria Social gender affirmation

Author Year Ref Country	Age	Study design n	Aims/ Research question(s)	Outcome measures
Sumia et al 2017 [8] Finland	**Mean** 17 years	Anonymously classroom questionnaire on current and childhood gender experience. n=719 n=401 girls n=318 boys	We studied current and recalled childhood gender identity	Dimensions of identity: Current gender identity: assessed with the Gender Identity/Gender Dysphoria Questionnaire for adolescents (GIDYQ-A) Recalled gender identity: assessed with the Recalled Childhood Gender Identity scale (RCGI)
Wallien et al 2008 [12] The Netherlands	**At referral** Mean: 8.4 years Range: 5–12 years **At follow-up** Mean: 18.9 years Range: 16–28 years	Retrospective 1989 and 2005 n=77 children n=59 boys n=18 girls **Follow-up** 10.4 ± 3.4 years	To establish the psychosexual outcome of gender-dysphoric children at 16 years or older and to examine childhood characteristics related to psychosexual outcome	Cross-gender identification Discomfort with their own sex Gender roles Gender dysphoria Sexual orientation
Van der Miesen et al 2018 [34] The Netherlands	**Mean** 16 years adolescents 32 years adults	Prevalence 2010–2014 n=573 adolescents with ASD n=807 adults with ASD n=1 862 controls	The self-reported wish to be of the opposite gender of adolescents and adults with ASD	Emotional and behavioural problems: measured by DSM-oriented scales of the Youth Self-Report and the Adult Self-Report. Subdomains of the ASD spectrum: measured by Children's Social Behaviour Questionnaire and the Adult Social Behaviour Questionnaire.
Wiepjes et al 2018 [36] The Netherlands www.sbu.se/307	**Range** 7–81 years **Three age groups** <12 years 12–18 years >18 years	Retrospective review of medical files, 1972–2015 n=6 793 n=2 361 natal females n=4 432 natal males **Follow-up** 46–271 months after initiation of hormone treatment	To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment.	Number who applied for transgender health care, Percentage starting with gender-affirming hormonal treatment (HT) Prevalence of transgender people receiving gender-affirming treatment Percentage who underwent gonadectomy Percentage who regretted gonadectomy

Author Year Ref Country	Age	Study design n	Aims/ Research question(s)	Outcome measures
Zucker KJ 2017 [41]		Review		

ASD = autism spectrum disorder, GD= Gender dysphoria.

Table 2 Articles on regret of gender affirmative treatment.

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Blanchard et al. 1989 [44] Canada	**At surgery** **Range** 29–41 years	Questionnaire 1981–1985 n=111 postoperative **Follow-up** >1 year after surgery	Whether heterosexual males are more likely to regret sex reassignment surgery than homosexual males or females.	Regret
Defreyne et al 2017 [49] Belgium www.sbu.se/307	Not reported	Systematic Review 1960–2017 29 articles included	The impact and outcomes of gender affirming hormonal treatment and gender affirming surgery on the quality of life of trans men.	Regret Hormonal therapy: quality of life, sexual functioning; Gender affirming surgery: Chest reconstructive surgery Hysterectomy and oophorectomy Gender affirming genital surgery Fertility; Effects of gender affirming surgery: Satisfaction, Regret, quality of life, sexual functioning

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Dhejne et al. 2014 [42] Sweden	**Age at application** **Range** 16–75 years **Median** 27 years FtM 32 years MtF	Review of application files 1960–2010 n=767 n=289 natal females n=478 natal males **Follow-up** 50 years	Incidence and prevalence of applications in Sweden for legal and surgical sex reassignment examined over a 50-year period (1960–2010), including the legal and surgical reversal applications.	Regret, for surgical conversion to original sex Assigned sex at birth, Date of first visit to a healthcare provider with a documentation of gender dysphoria, Date and outcome of the decision (with reasons if refused), Date of new legal gender, Sex reassignment abroad (if applicable). Age of the applicants calculated based on the date of the first application.
Imbimbo et al 2009 [45] Italy	**Range** 21–59 years **Mean** 31.36 ± 5.1 years	Questionnaire 1992–2006 n=163 MtF patients who had undergone gender-transforming surgery **Follow-up** 12–18 months after surgery	Clinical and psychosocial profile of male-to-female transsexuals in Italy, personal and clinical experience and evaluation of their postsurgical satisfaction levels.	Regret Suicidal ideation/suicide before SRS Emotional support Presurgical preparation Surgical procedure Postsurgical discomfort Postsurgical sex life Overall satisfaction. General demographic data (employment status, family status, personal relationships)

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Johansson et al 2010 [46] Sweden	**Age at index** **Male-to-female** Range: 21–60 years Mean: 37.3 **Female-to-male** Range: 18–46 Mean: 27.8 **Age at SRS** **Male-to-female** Range: 22–57 Mean: 38.2 **Female-to-male** Range: 22–49 Mean: 31.4	Follow-up study, semi-structured interview. Prospective and longitudinal n=60 patients approved for sex reassignment n=25 MtF (5) n=17 FtM (51) **At follow-up** n=32 completed sex reassignment surgery n=5 in process n=abstained from genital surgery **Follow-up** >5 years in the process, or >2 years after sex reassignment surgery	Evaluation of the process of sex reassignment	Regret Early-onset transsexualism Late-onset transsexualism Global outcome of sex reassignment Satisfaction with the sex reassignment process Work, partner relationships, and sex life
Landen et al 1998 [43] Sweden	**At request for intervention** Mean: 24–25 years	Retrospective review of inception cohort, 1972–1992 n=218 **Follow-up** 4–24 years from application to evaluation	Evaluate the features and calculate the frequency of sex-reassigned subjects who had applied for reversal to their biological sex, and to compare these with non-regretful subjects.	Regret Applications for surgical conversion to original sex
Lawrence et al 2003 [47] USA.	**Age at SRS** **Mean** 44 years (SD 9) **Range** 18–70 years	Questionnaire, 2000–2000 n=232 MtF **Follow-up** >1-year postoperative	This study examined factors associated with satisfaction or regret following sex reassignment surgery (SRS), operated by one surgeon using a consistent technique.	Regret Preoperative Predictor Variables Related to Transsexual Typology Preoperative Predictor Variables Related to Compliance with Established Treatment Regimens Mental, Physical, and Social Factors Satisfaction

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Nelson et al 2009 [48] United Kingdom	**Range** 20–45 years **Mean** 31 years	Retrospective review, postal questionnaire n=17 FtM **Follow-up** **Range:** 2–23 months **Mean:** 10 months	Intervention: Reduction mammaplasty	Regret Patient satisfaction Surgical outcome Psychological morbidity Complications (haematomas, wound infection, wound dehiscence, hypertrophic scars) Secondary surgery (scar revision, nipple reduction/realignment, dog-ear correction, nipple tattooing)
van de Grift et al 2018 [50] The Netherlands	**Range** 17–63 years **Mean** 36.3 years	Multi-centre, cross-sectional follow-up study, applications for medical interventions 2007–2009 n=201 responded n=136 had undergone GAS **Follow-up** 4 to 6 years after first clinical contact	We assessed the outcomes of gender-affirming surgery (GAS, or sex-reassignment surgery) and the associations between postoperative (dis)satisfaction and quality of life. **Intervention** Genital, chest, facial, vocal cord and/or thyroid cartilage surgery	Regret Procedure performed, self-reported complications, satisfaction with surgical outcomes (standardized questionnaires), quality of life (Satisfaction with Life Scale, Subjective Happiness Scale, Cantril Ladder), gender dysphoria (Utrecht Gender Dysphoria Scale), psychological symptoms (Symptom Checklist-90)
Wiepjes et al. 2018 [36] The Netherlands www.sbu.se/307	**Range** 7–81 years **Three age groups** <12 years 12–18 years >18 years	Retrospective review of medical files 1972–2015 n=6 793 people n=4 432 birth-assigned male n=2 361 birth-assigned female **Follow-up** 46–271 months after initiation of hormone treatment	To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment.	Regret of gonadectomy Number applied for transgender health care, Number starting with gender-affirming hormonal treatment Number receiving gender-affirming treatment Number undergone gonadectomy (all 25 years or older)

Table 3 Articles on psychosocial effects of puberty suppression and gender affirming hormonal treatment.

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Bränström et a 2019 [37] Sweden	**Mean** 31.5 years	Registry study, 3 linked registries 2005 and 2015 n=2 679 Legal gender: n=1 284 male n=1 395 female Swedish Total Population Register National Patient Register Prescribed Drug Register.	To ascertain the prevalence of mood and anxiety disorder health care visits and antidepressant and anxiolytic prescriptions in 2015 as a function of gender incongruence diagnosis and gender affirming hormone and surgical treatment in the entire Swedish population.	Epidemiology: Mental health treatment: Mood disorder Anxiety disorder health care visits, antidepressant prescriptions anxiolytic prescriptions hospitalization after a suicide attempt.
Costa et al 2016 [39]		Systematic review		
de Vries et al. 2014 [52] The Netherlands	**Range** 13.6–20.7 years **Before the start of puberty suppression** Mean: 13.6 years; **When cross-sex hormones were introduced** Mean: 16.7 years; **>1 year after gender reassignment surgery** Mean: 20.7 year	Follow-up study. Individuals receiving puberty suppression during adolescence 2004–2011 n=55 n=22 natal males, n=33 natal females **Follow-up** >1 year after gender reassignment surgery	Longer-term longitudinal evaluation of puberty suppression by means of gonadotropin-releasing hormone analogues	Psychological functioning: gender dysphoria, body image, global functioning, depression, anxiety, emotional problems behavioural problems; Objective wellbeing: social and educational/ professional functioning; Subjective wellbeing: quality of life, satisfaction with life happiness

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Dhejne et al 2011 [61] Sweden	At study entry **Female at birth** Range: 20–62 years Mean: 33.3 (SD 8.7) **Male at birth** Range: 21–69 years Mean: 36.3 (SD 10.1)	Population-based matched cohort study, 1973–2003 n=324 sex-reassigned persons n=191 MtF n=133 FtM **Follow-up** Mean: 10.4 years (risk of being hospitalized for any psychiatric disorder); Mean: 11.4 years (all-cause mortality) Linkage of Swedish national registers used: Hospital Discharge Register Total Population Register Medical Birth Register Cause of Death Register Crime Register	To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons.	**Mortality** All-cause mortality Death by definite/uncertain suicide Death by cardiovascular disease Death by tumour **Psychiatric morbidity** Any psychiatric disorder (gender identity disorders excluded) Alcohol/drug misuse and dependence Definite/uncertain suicide attempt Accidents Crime
Dhejne et al 2016 [53] Sweden	>18 years	Systematic Review n=38 included studies Included study designs: 27cross-sectional studies 11 longitudinal studies	To systematically review the prevalence of psychiatric disorders and psychopathology among trans people, and the psychiatric outcome following gender-confirming medical interventions (GCMI), either cross-sex hormone treatment (CHT) and/or gender-confirming genital surgery (GCGS)	Prevalence rates of psychiatric disorders and/or psychopathology Psychiatric outcome of post gender-confirming medical interventions

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Gómez-Gil et al 2012 [54] Spain	**Range** 15–61 years **Mean** 29.87 (SD 9.15)	Questionnaires n=187 transsexual patients n=120 hormonal treatment n=84 MtF n=36 FtM n=67 no hormonal treatment n=29 MtF n=38 FtM	To evaluate the presence of symptoms of current social distress, anxiety and depression in transsexuals. **Previous intervention** Hormonal treatment w/o SRS **Duration** **Hormone Treatment** MtF patients: mean 11.0 years (SD: 9.9), range 1–46 years FtM patients: mean 4.7 years (SD 5.2), range 1–22 years	Social anxiety: assessed with Social Anxiety and Distress Scale (SADS) Depression and anxiety: assessed with Hospital Anxiety and Depression Scale (HADS)
Jellestad et al 2018 [62] Switzerland	**Range** 18–75 years **Mean** Transfeminine: 51.51 (SD 17.06) Transmasculine: 35.95 (SD 12.79)	Retrospective Cross-sectional cohort study N=143 individuals n=77 transfeminine n=41 transmasculine n=25 nonbinary gender	Examine associations between GAI and quality of life in transitioned trans individuals. **Previous intervention** Hormonal treatment w/o SRS Duration: Hormone Treatment: 0 to >20 years	Quality of Life: assessed with Short Form Health Survey questionnaire (SF-36) Depressive Symptoms: Allgemeine Depressionsskala (ADS-K), a validated German short form adaptation of the Centre for Epidemiologic Studies Depressions Scale (CES-D)
Keo-Meier et al 2015 [55] USA www.sbu.se/307	**Mean** 26.6 years **Range** 16–51 years transgender men **Range** 18–50 years non-transgender male **Range** 18–54 years non-transgender female	Prospective Controlled Study n=48 transgender men **Matched controls** n=53 non-transgender male n=62 non-transgender female **Follow-up** 3 months after testosterone initiation	Investigate the short-term effects of testosterone treatment on psychological functioning in transgender men. Intervention: Testosterone treatment:	Psychological functioning: assessed with Minnesota Multiphasic Personality Inventory (MMPI–2) The MMPI–2 is the most commonly utilized assessment of psychopathology Personality profiles and 10 clinical scales: "Hypochondriasis, Depression, Hysteria, Psychopathic- Deviate, Masculinity- Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania, and Social Introversion"

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Lindqvist et al 2017 [63] Sweden	**Range** 19–76 years **Mean** 36 years	Prospective cohort study 2003–2015 n=190 patients undergoing male-to-female GRS **Follow-up** 1, 3 and 5 years post-operatively	Examine the quality of life of transgender women undergoing gender reassignment surgery (GRS).	Quality of Life: Swedish version of the Short Form-36 Health Survey (SF-36)
Millet et al 2017 [56] United Kingdom	**Range** 7–65 years	Systematic Review 25 articles included (17 cross-sectional studies, 8 longitudinal studies) **Follow-up** At different stages of transition	To collect and critically appraise the information from the available studies describing prevalence rates of anxiety disorders and symptoms.	Anxiety disorder: Generalized Anxiety Disorder Panic disorder, Social phobia, Specific phobia, Agoraphobia, Obsessive Compulsive Disorder Measurement tools: Structured clinical interview for DSM (SCID-I) Short interview (MINI-Plus) Symptom Checklist Revised (SCL-90-R) Brief Symptom Inventory (BSI) Hospital Anxiety and Depression Scale (HADS) Speilberger State and Trait Anxiety Inventory (STAI)
Murad et al 2010 [57] USA www.sbu.se/307	**Mean** 38 years MF 31 years FM	Systematic Review 28 included studies whereof 20 cross-sectional and 8 longitudinal n=1 833 participants n=1 093 MtF n= 801 FtM **Follow-up** Mean 6 years	Prognosis of individuals with gender identity disorder receiving hormonal therapy as a part of sex reassignment in terms of quality of life and other self-reported psychosocial outcomes. **Previous intervention** Hormonal therapy (self-reported) Sex reassignment surgery	Resolution of Gender dysphoria Psychiatric comorbidity (depression, anxiety, suicide, suicidal thoughts) Sexual function Quality of life (employment, social situation)

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Owen-Smith et al 2018 [58] USA	**At time of survey** **Range** 18–55+ years +	Cohort study, Survey 2015–2017. n=697 subjects n=347 FtM n=350 MtF n=234 Hormone treatment without any surgery n=404 surgery (any)	Examine the degree to which individuals' body-gender congruence, body image satisfaction, depression and anxiety differed by gender confirmation treatments (GCT) groups in cohorts of transmasculine and transfeminine individuals. **Previous intervention** Hormone therapy, "top" surgery, "bottom" surgery	Body-gender congruence Body image satisfaction Depression Anxiety
Özata Yildizhan et al 2018 [69] Turkey	**Mean** 32.60 ± 7.16 years GRT group **Mean** 27.04 ± 7.56 years NR group	Interviews n= 20 gender reassigned transsexuals n=50 new referrals Follow-up: 1–22 years post- surgery.	Family and social relationships (social adaptation) and the quality of life in people with gender dysphoria with and without history of sex reassignment surgery.	Mental Health Disorders: Major Depression, Anxiety Disorders, Alcohol/Substance Abuse, Any Psychiatric Diagnosis, Suicide Attempts. Assessments made with: Structured Clinical Interview for DSM-IV TR Axis I Disorders (SCID-I), Family Assessment Device (FAD), Multidimensional Scale for Perceived Social Support (MSPSS), World Health Organization Quality of Life Scale (WHOQOL- BREF)
Rowniak et al 2019 [59] USA	>15 years	Systematic Review up to 2017 7 included studies n=552 individuals Includes evidence grading using GRADE. Critically appraised JBI critical appraisal tools	**Review question** What are the effects of cross-sex hormone treatment on the quality of life, depression and anxiety of transgender persons? **Periods intervention** Oestrogen or testosterone	Quality of life: assessed with SF-36, SQUALA, WHOQOL-100; Depression: assessed with BDI, SDS, SCL-90, SCL-90-R, MMPI, MMPI-2; Anxiety: assessed with: SAS, SCL-90, SCL-90-R.

Author Year Ref Country	Age	Study design n Follow-up	Aims/ Research question(s) Intervention/Exposure	Outcome measures
Ruppin and Pfafflin 2015 [64] Germany	**Mean** 47.0 years (SD 10.42) **MtF** 52.9 years (SD 10.82) **FtM** 41.2 years (SD 5.78)	Interviews & Questionnaires n=71 participants with legal name change n=35 MtF n=36 FtM **Follow-up** 10–24 years **Mean** 13.8 years (SD2.78) Inclusion criteria: the legal recognition of participants' gender change via a legal name change had to date back at least 10 years	Long-term follow-up of former patients with gender identity disorder whose aim it was to re-examine these patients from a psychosocial perspective after as long a period of time as possible after their name change and legal transition into their desired gender role	Positive and desired changes, wellbeing and social integration. Psychological problems: assessed with the Symptom Checklist (SCL-90-R Interpersonal difficulties: assessed with the Inventory of Interpersonal Problems (IIP) Gender role stereotypes: measured using the Bem Sex Role Inventory (BSRI) Personality: assessed with Freiburg Personality Inventory (FPI-R)
Simonsen et al 2016 [65] Denmark	**At referral** **Mean** 30.3 years MtF 27.0 years FtM **At initiating cross-sex hormones** **Mean** 32.0 years MtF 29.8 years FtM **At permission for SRS:** **Mean** 37.1 years MtF 32.6 years FtM	Retrospective register study 1978–2010 n =104 sex reassigned individuals n=56 MtF n=48 FtM **Follow-up** up to 16 years after SRS: **Register** Danish Psychiatric Central Research Register, Cause of Death Register	To investigate psychiatric morbidity before and after sex reassignment surgery among Danish individuals To investigate mortality among Danish individuals who underwent sex reassignment surgery during the period of 1978–2010.	Mortality Psychiatric morbidity: Depression Anxiety Abuse Personality disorder Neurotica personalis Psychosis Any psychiatric diagnosis

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)** **Intervention/Exposure**	**Outcome measures**
Tomita et al 2019 [60] USA	**Mean** 33.3 years	Survey 2013 n=868 participants n=363 trans feminine n=505 trans masculine Data collected as part of the Trans Health Survey, a national U.S. web-based health survey	Examine relationships between hormone therapy, chest surgery, and genital surgery—and the mental health outcomes of suicidality, depression, social anxiety, generalized anxiety, PTSD, alcohol use, and drug use. **Previous intervention** Hormone therapy w/o surgery	Depression Social anxiety Generalized anxiety Post traumatic stress disorder Suicidality Alcohol abuse Drug abuse
Weinforth et al 2019 [66] Germany	**Range** 18–76 years **Mean** 39.9 years	Systematic Review 13 articles included (11 quantitative, 2 mixed quantitative/ qualitative studies) N=1 101 transwomen **Follow-up** 3 months – 30 years	Overview of the currently available data on quality of life after male-to-female sex reassignment surgery.	Postoperative quality of life Life satisfaction Emotional wellbeing Sexuality Urinary incontinence
Wernick et al 2019 [67] USA www.sbu.se/307	**Range of means** 17–51 years	Systematic Review 33 articles included (16 pre- postoperative studies 17 cross-sectional studies)	Understand the impact of gender-affirming surgeries on the psychological well-being of individuals with gender dysphoria. **Previous interventions** Breast augmentation, mastectomy, chest reconstruction, surgical voice feminization, craniofacial reconstructive surgery, vaginoplasty, or phalloplasty.	Gender Dysphoria, Quality of life: Satisfaction with Life Scale (SWLS), and the World Health Organization Quality of Life Assessment (WHOQOL-100); Body image/satisfaction: Body Image Scale (BIS) and the BREAST-Q General psychological functioning: Rosenberg Self-Esteem Scale (RSES), Hospital Anxiety and Depression Scale (HADS), and the Symptom Checklist-90 (SCL-90). Depression Anxiety Psychosocial outcomes

Table 4 Articles on effects on cognition and brain function by puberty suppressive and gender affirming hormonal treatment.

Author **Year** **Country**	**Age**	**Study design** **n** **FU**	**Aims/ Research question(s)** **Intervention**	**Outcome measures**
Nguyen et al 2019 [72] USA		Systematic review		
Schneider et al 2017 [71] Brazil	**Mean** 28.75 ± 6.53 years	Before- and -after study 2009–2015 n=32 male-to-female who underwent surgery and hormonal treatment **Follow-up** At least 6 months post-SRS (mean 279.28 ± 190.34 days after SRS	To measure preoperative and postoperative serum BDNF levels in transsexual individuals as a biomarker of alleviation of stress related to gender incongruence after SRS. **Previous intervention** Hormone treatment Penile inversion vaginoplasty	BDNF serum levels Time elapsed between the pre-SRS and post-SRS blood collections
Staphorsius et al 2015 [70] The Netherlands	**Range** 14–16 years	MRI n=41 adolescents n=22 female-to-males: (n=12 using GnRHa) (n=10 untreated FM) n=18 male-to-females: (n=8 using GnRHa) (n=10 untreated MF) n=45 age-matched controls n=24 girls (F) n=21 boys (M)	Determine whether the performance on the Tower of London task (ToL), a commonly used (executive functiontask, was altered in adolescents with GD when treated with GnRHa. Determine whether untreated adolescents with GD showed sex-atypical brain activation during Tower of London performance. **Intervention** triptorelin (Decapeptyl-CR®) every 4 weeks, s.c. or i.m Treatment duration: mean 1.6 ± SD 1.0 years	Tower of London performance scores (reaction times, accuracy) Region-of-interest (ROI) analyses (left DLPFC, bilateral RLPFC, praecuneus) CBCL: Child Behaviour Checklist IQ (measured with Wechsler Intelligence Scales)

GD = Gender dysphoria; GnRHa = Gonadotropin releasing hormone analogue; SRS = Sex reassignment surgery

Table 5 Articles on cancer development, cardiac disease and bone health after puberty suppression and gender affirming hormone treatment.

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Tumours				
De Blok et al 2019 [75] The Netherlands	**Range** 31–57 years **Median** 47 years **At start of hormone treatment** Range: 21–38 years Median: 28 years	Retrospective, nationwide cohort study n=3 489 n=2 260 male at birth n=1 229 female at birth **Duration of treatment** **Transwomen** Median 18 years Range 7–37 years **Transmen** Median 15 years Range 2–17 years	Incidence and characteristics of breast cancer in transgender people. **Intervention** Gender affirming hormone treatment.	Breast cancer: Incidence and characteristics (histology, hormone receptor status)
Joint et al 2018 [73] United Kingdom	Not reported	Systematic Review 43 articles included (33 case reports, 5 cohort, 3 case-control, 2 cross-sectional)	Assess breast and reproductive cancer prevalence. Elucidate any associations between gender-affirming hormones and risk of these cancers.	Breast/reproductive cancer: : In transgender women: breast cancer, neovaginal cancer, testicular cancer, prostate cancer. In transgender men: breast cancer, ovarian cancer, uterine/cervical cancer, vaginal cancer.
McFarlane et al 2018 [74] Australia	**At commencement of hormone treatment** 23–49 years	Systematic Review 43 studies included (7 cohort studies, 2 cross-sectional 34 case reports) **Follow-up** 2 months – 41 years	Determine whether tumour risk in transgender individuals differs from the general population. **Duration of hormone treatment** Range 2 months – 41 years	Sex hormone-dependent tumours, all organs : Breast, Prostate, Other (lung, gastric, leukaemia, glioblastoma, meningioma, colon, haematological, GI tract, brain, melanoma, lymphoma)

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Nota et al 2018 [76] The Netherlands	**At start of cross-sex hormone treatment** **Median** Transwomen 31 years Transmen 23 years	Retrospective chart study 1972–2015 n=3 928 n=2 555 transwomen n=1 373 transmen **Follow-up** **Transwomen** Median 6.22 years Range 0.01–54.77 **Transmen** Median 4.16 years Range 0.02–41.66	Compare the incidence of common benign brain tumours in transgender individuals receiving cross-sex hormone treatment, with those reported in general Dutch or European populations. Previous interventions: In transgirls (<18 years): cyproterone acetate or triptorelin. In transboys (<18 years): lynestrenol or triptorelin, From age 16: cross-sex hormonal treatment combined with oestrogens (mostly oestradiol valerate, ethinylestradiol, or oestradiol hemihydrate) in transgirls and testosterone (mostly testosterone esters) in transboys. Adults: In transwomen: oestrogens (ethinylestradiol, conjugated oestrogens, oestradiol patches, oestradiol implants, oestradiol injections, oestradiol valerate, oestradiol gel) anti-androgens (cyproterone acetate , spironolactone) or orchiectomy. In transmen: testosterone gel, intramuscular testosterone esters, oral or intramuscular testosterone undecanoate, lynesterol	Benign brain tumours: meningiomas, pituitary adenomas (non-secretive and secretive), and vestibular schwannomas

Author Year Ref Country	Age	Study design n Follow-up	Aims/ Research question(s)	Outcome measures
Cardiovascular				
Maraka et al 2017 [77] USA	**MtF:** Range of means: 19.3–43.7 years **FtM** Range of means: 21.7–37.5 years	Systematic Review up to 2015 29 included studies whereof 28 cohort studies and one randomized trial n=4 731 transgender patients n=3 231 MtF n=1 500 FtM **Follow-up** 3 months – 41 years	To evaluating the effect of sex steroid use on lipids, myocardial infarction, stroke, venous thromboembolism, and mortality in transgender individuals. Intervention: MtF: oestrogens, cyproterone acetate, GnRHa agonists (goserelin, triptorelin), spironolactone, anastrozole. FtM: testosterone	Serum lipids (TG, LDL-C, HDL-C, total cholesterol) Death Stroke Myocardial infarction Venous thromboembolism
van Velzen et al 2019 [78] The Netherlands	**Mean** 32.3 years (SD ±12.6) transwomen **Mean** 26.4 years (SD ±9.1) transmen	Prospective observational sub study 2010–2017 n=558 participants n=242 transwomen n=188 transmen from **Follow-up** up to 12 months	The effects of 1 year of treatment with oral or transdermal administration of oestrogen (plus cyproterone) and transdermal or IM application of testosterone on serum lipid levels and blood pressure were assessed in transgender persons. **Intervention** oestrogen, testosterone	Blood pressure, Serum lipids Total cholesterol High density lipoprotein Low density lipoprotein Triglycerides Haematocrit Creatinine
Dutra et al 2019 [80]		Review		Cardiovascular disease

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Getahun et al 2018 [79] USA	Age at index date: 18 to >55 years	Electronic medical record-based cohort study, enrolled 2006–2014 n=2 842 transwomen n=2 118 transmen **Matched to** n=48 686 cisgender men n=48 775 cisgender women **Follow-up** **Transwomen** mean 4.0 years **Transmen** mean 3.6 years	To examine the incidence of acute cardiovascular events in a cohort of transgender persons.	Acute cardiovascular events: Venous thromboembolism Ischemic stroke Myocardial infarction events
Goldstein et al 2019 [81] USA	Not reported	Systematic review 1989 and 2018 13 studies	To examine the degree to which routes of administration, patient comorbidities, and type of hormone utilized affect the safety of oestrogen therapy. **Previous intervention** ethinyl oestradiol, cyproterone acetate (CPA), conjugated oestrogens, 17β-oestradiol gel, oestradiol valerate, premarin, finasteride, spironolactone, progesterone	Venous thromboembolism

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Khan et al 2019 [82] USA	**Range** 21–44 years	Systematic review 12 articles included n=2 518 patients **Follow-up** Duration of monitoring for thrombotic events: range: 1–10 years	To conduct a systematic review and meta-analysis to provide an estimate of the risk of venous thrombotic events associated with oestrogen therapy in transgender women based on all available evidence.	Venous thromboembolism, incidence rate Medications Risk of thrombotic events
Wierckx et al 2013 [51] Belgium	**At the time of study** **Mean** Transwomen: 43.7 ± 12.6 years Transmen: 37.5 ± 11.0 years	Cross-sectional study, questionnaires 1986–2012 n=214 transwomen n=138 transmen age- and gender-matched control population. **Follow-up/treatment duration** **Transwomen** mean 7.7 years (3 months–35 years) **Transmen** mean 9.4 years (3 months–49 years)	Short- and long-term cardiovascular- and cancer-related morbidities during cross-sex hormone therapy. Previous intervention: Cross-sex hormone therapy: Transwomen: transdermal oestradiol, 17b-estradiol gel, oestradiol patch, oral oestrogens, oestradiol valerate, estriol, ethinyl oestradiol, ethinyl oestradiol oral contraceptive, orchiectomy. Transmen: intramuscular testosterone, testosterone esters (testosterone decanoate, testosterone isocaproate, testosterone phenylpropionate, testosterone propionate, testosterone undecanoate, transdermal testosterone, oral testosterone undecanoate, hysterectomy, ovariectomy	Cardiovascular disease: Physical health Adverse events

Author Year Ref Country	Age	Study design n Follow-up	Aims/ Research question(s)	Outcome measures
Bone health				
Fighera et al 2019 [86] Brazil	**Range** 21–47 years	**Systematic Review** 19 included studies whereof 6 cross-sectional and 14 before and after studies n=1 299 n=487 transmen n=812 transwomen **Duration of cross-sex hormone treatment / exposure** Transmen: 12 months – 18 years Transwomen: 12 months – 16 years	Effects of cross-sex hormone treatment on bone mineral density (BMD) in transgender men and women. Intervention: cross-sex hormone treatment Transmen: Testosterone esters, testosterone undecanoate, transdermal testosterone, Testosterone isobutyrate, testosterone propionate Transwomen: Oestradiol valerate, mestranol, norethisterone, ethinyloestradiol, levonorgestrel, cyproterone, conjugated equine oestrogen, ethinyloestradiol, cyproterone acetate, levonorgestrel, depot oestrogens (oestradiol valerate or mestranol 1 norethisterone), transdermal oestradiol, oral oestradiol valerate, transdermal 17b-estradiol, spironolactone	Bone health: Bone mineral density assessed by DXA)Clinical factors affecting bone mass Physical activity, serum vitamin D levels, calcium intake, use of calcium and vitamin D supplements, duration of cross-sex hormone treatment, previous gender-affirming surgery, duration of follow-up, bone mineral density, T- score and Z-score for bone mineral density at various sites cross-sex hormone treatment duration
Joseph et al 2019 [83] United Kingdom www.sbu.se/307	**Range** 12–14 years	Retrospective review of national cohort 2011–2016 n=70 in cohort over the first treatment year n=31 transgirls n=39 transboys n=31 longitudinal analysis where patients had scans over a 2-year treatment period n=10 transgirls n=21 transboys	Examine changes in BMD and bone mineral apparent density (BMAD) whilst on GnRHa therapy. **Intervention** Yearly dual energy X-ray absorptiometry (DXA) scans.	Bone health: bone mineral density bone mineral apparent density hip and lumbar spine

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Klink et al 2015 [84] The Netherlands	Mean age at start of GnRHa:15 years **At follow-up** 22 years	Longitudinal observational study n=34 subjects n=15 transwomen n=19 transmen **Follow-up** Gonadectomy between 1998–2012	Assess bone mineral density development during GnRHa therapy and at age 22 years in young adults with GD who started sex reassignment during adolescence. **Intervention** GnRHa monotherapy followed by CSH with discontinuation of GnRHa after gonadectomy. Treatment duration: GnRHa: 1.3–1.5 years CSH: 5.8–5.4 years	Bone mineral density
Singh-Ospina et al. 2017 [85] USA	**Range** 15–43 years	Systematic Review 1996–2015 13 articles included n=639 individuals n=392 MtF n=247 FtM **Follow-up** 12–63 months	Evaluate bone health in transgender individuals receiving sex steroids. **Previous intervention** MTF individuals: oral, transdermal, or intramuscular oestrogens, some regimens included cyproterone acetate, GnRH agonists (goserelin, triptorelin), spironolactone, or anastrozole. FTM individuals: intramuscular transdermal or oral testosterone	Bone health: lumbar spine, femoral neck, or total hip bone mineral density fractures
van Kesteren et al 1998 [90] The Netherlands www.sbu.se/307	**MtF:** Range: 16–38 years Mean: 25.4 years **FtM:** Range: 16–39 years Mean: 25.0 years	Observational n=39 n=20 MtF n=19 FtM **Follow-up** after 1 year and after 28–63 months	Whether long term cross-sex hormone treatment affects the human skeleton. **Intervention** Cross-sex hormones: anti-androgens, oestrogen, androgens, gonadectomy	Bone health: Bone mineral density Bone turnover markers (osteocalcin, alkaline phosphatase, fasting urinary calcium/creatinine, hydroxyproline/creatinine)

Author Year Ref Country	Age	Study design n Follow-up	Aims/ Research question(s)	Outcome measures
Wiepjes et al 2019 [87] The Netherlands	**Transwomen** <50 years (mean 38 ± 9 years) ≥50 years (mean 60 ± 8 years) **Transmen** (mean 40 ± 14 years)	Nationwide cohort study, review of medical records. 2013 and 2015 n=1089 transwomen <50 years n=934 transwomen ≥50 years n=1 036 transmen Linked to a random population-based sample of 5 age-matched reference men and 5 age-matched reference women per person. **Follow-up** **Transwomen** using HT: median 8 years (<50 years) median 19 years (>50 years) **Transmen** using HT: median 9 years	To compare fracture incidence in transgender people using long-term hormone treatment with an age-matched reference population. Previous Intervention: HT treatment: Transwomen: anti-androgens (cyproterone acetate), orchiectomy, oestrogens (17-beta oestradiol, oral valerate, and oestradiol gel, ethinyl oestradiol, conjugated oestrogens) Transmen: testosterone gel, testosterone undecanoate, intramuscular testosterone esters Surgery: after >1 year of HT treatment and age > 18 years: vaginoplasty, orchiectomy, hysterectomy, oophorectomy.	Bone health: Bone mineral density measurements with DXA Fracture incidence Hormone blood levels (oestradiol, testosterone, LH)
Wiepjes et al 2019 [88] The Netherlands www.sbu.se/307	**Transwomen** Median: 35 years **Transmen** Median: 25 years	Retrospective chart review,1998 and 2016. n=711 transwomen n=543 transmen **Follow-up** DXA scans after 2, 5, and/or 10 years of HT	Investigate the change in BMD during the first 10 years of HT, to determine whether HT is safe and if assessing BMD during HT is necessary. Previous intervention: HT treatment: Transwomen: oestrogens, gonadectomy, anti-androgens. Transmen: testosterone. Surgery: after at least 1 to 1.5 years of HT	Bone health: BMD measurements with (DXA) Hormone blood levels (oestradiol, testosterone, LH)

Author **Year** **Ref** **Country**	**Age**	**Study design** **n** **Follow-up**	**Aims/ Research question(s)**	**Outcome measures**
Wiepjes et al 2019 [89] The Netherlands	**Age time of DEXA** 20–29 years 30–39 years 40–59 years	Retrospective chart review 2011–2016 n=535 transwomen n=473 transmen **Follow-up** After 5, 15, or 25 years of HT	And TBS in adult transgender people at different time points, up to 25 years, of HT **Previous intervention** HT treatment: Transwomen: oestrogens, gonadectomy, anti-androgens. Transmen: testosterone. DXA scans: at start of hormone treatment and every 5 years	Bone health: Hip structure analysis: measured by subperiosteal width, endocortical diameter, average cortical thickness, section modulus. Trabecular bone score: calculated based on lumbar spine DXA images.

Table 6 Articles on management of children and adolescents with gender dysphoria published from 2013 and onwards.

Psychosocial support

Author **Year** **Ref** **Country**	**Age** **(years)**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Alanko et al 2019 [91] Finland	**Range** 15–25 years **Mean** 20.0 (SD=2.5)	Survey, web questionnaire April–June 2013 n=1 613 n=370 transgender n=1 243 cisgender (=no gender conflict)	How the quality of relationships to parents, friends and partners affects the mental well-being. **Intervention** Web questionnaire investigating health and living conditions of sexual and gender minority youth.	Demographics Relationship quality Mental well-being: measured by Short Warwick–Edinburgh Mental Well-being Scale
Bebes et al 2015 [92] Israel	**Range** 14–21 years **Mean** 16.71 (SD 1.84)	Survey Recruited via Israeli adolescent LGBT internet sites n=234 lesbian, gay, bisexual and transgendered Israeli adolescents. N=8 identified themselves as female to male transgendered or ‘‘other’’	Associations between perceived parental acceptance, perceived parental psychological control and self-reported psychological symptoms.	Perceived parental acceptance and psychological control: measured with the Child Report of Parenting Behaviour Inventory (CRPBI) Psychological Symptoms: measured with the Brief Symptoms Inventory (BSI) Socio-Demographics
Costa et al 2015 [93] United Kingdom	**Mean** 15.5 years ± 1.4 years **At start of GnRHa** Range: 13–17 Mean: 16.5 years	Longitudinal 2010–2014 n=201 Natal male/natal female ratio: 1: 1.4 **Follow-up** 18 months	Global functioning after psychological support and puberty suppression GnRHa psychotherapeutic interventions	Gender Dysphoria: measured by Utrecht Gender Dysphoria Scale (UGDS) Psychosocial functioning: measured by Children’s Global Assessment Scale (CCAS)
de Vries et al 2016 [94] Holland and Canada	13–18 years	Retrospective, Amsterdam: 1996–2008 Toronto: 1980–2010 n=316 n=139 Amsterdam clinic n=177 Toronto clinic	To examine behavioural and emotional problems in children and adolescents with gender dysphoria in a comparative analysis between two clinics in Toronto, Ontario, Canada and Amsterdam, the Netherlands.	Child Behaviour Checklist (CBCL) Youth Self-Report (YSR) Demographic characteristics

Author **Year** **Ref** **Country**	**Age** **(years)**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Johns et al 2018 [95]	11–26 years	Systematic Review 1999–2014 21 studies	To supplement the growing evidence on health risks encountered by transgender/ GV youth, we identified factors theorized to be protective for these youth across all four levels of Bronfenbrenner's socioecological model (individual, relationship, community, societal)	Protective factors to a health or behavioural outcome.
Levitan et al 2019 [96] Germany	11–18 years **Mean** 15.5 years (SD 1.33)	Cross-sectional, Questionnaire-based, single-subject study design. Sept 2013–June 2017 n=180 n=146 birth-assigned females n=34 birth-assigned males	Impact of poor peer relations and general family functioning on the development of psychological problems	Poor Peer Relations (PPR) General Family Functioning (GFF) Psychological functioning: The Youth Self-Report (YSR) Sociodemographics Clinical features
Simons et al 2013 [97] USA	12–24 years **Mean** 19.06 years (SD 2.88)	Survey February 2011 and April 2012 n=66 transgender youth n=32 birth-assigned male (asserted female) n=34 birth-assigned female (asserted male)	Relationships among parental support, quality of life, and depression	Parental support: assessed using the family subscale of the Multidimensional Scale of Perceived Social Support (help, advice, and confidante support), Quality of life: Satisfaction, Burden Depression: Beck Depression Inventory II

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Thorne et al 2019 [98] United Kingdom	16–25 years **Mean** 20.16 years (SD 2.69)	Questionnaire, part of a longitudinal study investigating the outcome of gender affirming medical treatment. June 2015–June 2017 N=388 young people n=331 (85.3 %) binary n=57 (14.7 %) non-binary **Follow-up** 2-years	This study aimed to compare levels of mental health symptomatology (anxiety, depression, and non-suicidal self-injury behaviour) and social support of treatment seeking non-binary transgender young individuals with those self-identified as binary transgender young individuals.	Anxiety and depression (Hospital Anxiety and Depression Scale, HADS) Self-esteem (The Rosenberg Self-Esteem Scale, RSE) Non-suicidal self-injury (Non-Suicidal Self-Injury (NSSI): Treatment Related (SIQ-TR) Social support (Multidimensional Scale of Perceived Social Support, MSPSS)
Weinhardt et al 2019 [99] USA	13–21 years **Mean** 17.35 years (SD 2.04)	Mixed-methods study (quantitative and qualitative data) survey at a Pride event in a Midwest US city n=154 transgender and gender nonbinary youth 92 % female at birth; 27 % identified as transmasculine, 38 % genderqueer, 24 % more than one gender.	To describe the relationship between social support, resilience, and well-being among transgender youth. Quantitative procedures were conducted with the Gender Identity and Health Youth Survey (GIHYS)	Living as one's affirmed gender, Social support: measured by the Multidimensional Scale of Perceived Social Support (MSPSS), Affirmed gender: a single item from the GMSR measure, Mental health: two questions about experiences of depression and anxiety, Meaning in life: Meaning in Life Questionnaire (MLQ), Quality of life: assessed by the Youth Quality of Life scale (YQoL 2.0), Resilience: two subscales of the Gender Minority Stress and Resilience Measure: community connectedness and pride; Demographic characteristics

Author **Year** **Ref** **Country**	**Age** **(years)**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Wilson et al 2016 [100] USA	16–24 years	Cross-sectional, August 2012–Dec 2013 n=216 transgender females	We assessed differences in mental health outcomes based on exposure to discrimination among transgender female youth in the San Francisco Bay Area	Mental health outcomes: Psychological distress: measured with Brief Symptom Inventory (BSI-18), Trauma symptoms: assessed by the primary care posttraumatic stress disorder screen items from the brief New York Posttraumatic Stress Disorder Risk Score Resiliency Promoting Protective Factors: Connor Davidson Resilience Scale (CD-RS) Social support: adapted measure developed based on the 12-item Multidimensional Scale of Perceived Social Support (MSPSS) Support from transgender peers: we used our transgender community connectedness measure Socio-demographic Factors
Yadegarfard et al 2014 [101] Thailand	**Range** 15–25 years **Mean** 20 years	Survey questionnaire n=260 male respondents n=129 transgender n=131 non-transgender	This study examined the influence of family rejection, social isolation, and loneliness on negative health outcomes among Thai male-to-female transgender adolescents.	Family rejection Social support Loneliness Depression Protective factors Suicidal thoughts and attempts Sexual risk behaviour

Psychotherapy and other psychological treatments

Author Year Ref Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Costa et al 2015 [93] United Kingdom	**Mean** 15.5 years ±1.4 years **At start of GnRHa** Range: 13–17 Mean: 16.5 years	Longitudinal 2010–2014 n=201 Natal male/ natal female ratio: 1: 1.4 **Follow-up** 18 months	Global functioning after psychological support and puberty suppression GnRHa psychotherapeutic interventions	Gender Dysphoria: measured by Utrecht Gender Dysphoria Scale (UGDS) Psychosocial functioning: measured by Children's Global Assessment Scale (CCAS)
Grossman et al 2016 [102] USA	**Mean** 18 years (SD 1.74)	Survey Longitudinal study of a community sample n=129 transgender and gender nonconforming (TGNC) youth: Female-to-male (FTM) Male-to-female (MTF) Female-to-different-gender (FTDG) Male-to-different gender (MTDG)	**Intervention** Interpersonal psychological theory of suicide (IPTS) was used to examine suicidal thoughts and behaviours	Suicide attempts Suicidal ideation: assessed with INQ, Interpersonal Needs Questionnaire (INQ) Painful and Provocative Events (PPES) Acquired Capability Suicide Scale (ACSS) Self-Harm Behaviour Questionnaire (SHBQ) Demographic Characteristics
Turban et al 2019 [103] USA	Not reported	Survey Cross-sectional non-probability sample n=27 716 **Follow-up** lifetime exposure	To examine exposure to Psychological Attempts to Change a person's Gender Identity from transgender to cisgender (PACGI)	Lifetime exposure to PACGI Exposure to PACGI 2010-2015 Total number of transgender people in the United States exposed to PACGI

Puberty suppression

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Chew et al 2018 [104]	**At start of treatment** Range of means: 13–16 years	Systematic Review up to 2017 13 included studies	To review evidence for the physical, psychosocial, and cognitive effects of GnRHa, gender-affirming hormones, antiandrogens, and progestins on transgender adolescents. Intervention: GnRHa, Anti-androgens (progesterones, spironolactone), Testosterones, Oestrogens	Physical effects (blocking of puberty progression, anthropometric measurements, development of sexual characteristics, bone health, blood pressure, cholesterol) Cognitive effects (visuospatial ability, memory, executive functioning) Psychosocial effects (gender dysphoria, self-perception, body image, mood, anxiety, depression, bullying) Side effects
Costa et al 2015 [93] United Kingdom	**Mean** 15.5 years ±1.4 years **At start of GnRHa** Range: 13–17 Mean: 16.5 years	Longitudinal 2010–2014 n=201 Natal male/natal female Ratio: 1:1.4 **Follow-up** 18 months	Global functioning after psychological support and puberty suppression GnRHa psychotherapeutic interventions	Gender Dysphoria: measured by Utrecht Gender Dysphoria Scale (UGDS) Psychosocial functioning: measured by Children's Global Assessment Scale (CCAS)
de Vries et al. 2014 [52] The Netherlands	**Range** 13.6–20.7 years **Before the start of puberty suppression** Mean: 13.6 years; When cross-sex hormones were introduced: Mean: 16.7 years **>1 year after gender reassignment surgery** Mean: 20.7 years	Follow-up study. Individuals receiving puberty suppression during adolescence 2004–2011. N=55 n=22 natal males, n=33 natal females **Follow-up** >1 year after gender reassignment surgery	Longer-term longitudinal evaluation of puberty suppression by means of GnRHa	Psychological functioning: Gender dysphoria, body image, global functioning, depression, anxiety, emotional and behavioural problems; Objective wellbeing: social and educational/professional functioning; Subjective wellbeing: quality of life, satisfaction with life and happiness

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Joseph et al 2019 (83] United Kingdom	12–14 years	Retrospective review of national cohort (2011–2016) N=70 (n=70) cohort over the first treatment year (31 transgirls, 39 transboys). (n=31) longitudinal analysis where patients had scans over a 2-year treatment period (10 transgirls, 21 transboys).	Examine changes in bone mineral density and bone mineral apparent density whilst on GnRHa therapy. Intervention: Yearly DXA scans.	Bone health: bone mineral density (BMD) bone mineral apparent density (BMAD) hip and lumbar spine
Klaver et al 2018 [105] The Netherlands	**Age at start of GnRHa** Transwomen: 14.5 ± 1.8 years Transmen: 15.3 ± 2.0 years **Age at start of CHT** Transwomen: 16.4 ± 1.1 years Transmen: 16.9 ± 0.9 years	Retrospective study of medical records 1998–2014 n=71 transwomen (birth-assigned boys) n=121 transmen (birth-assigned girls) **Follow-up** Until age 22	To examine the change in body shape and composition from the start of treatment with GnRHa. Intervention: GnRHa: at a min age of 12 years Cross-sex hormonal treatment: from 16 years (oral 17b-estradiol or mixed testosterone esters) Duration of GnRHa monotherapy: Transwomen: 2.1 years (1.0–2.8) Transmen: 1.0 years (0.5–2.9) Duration of GnRHa + CHT: Transwomen:3.1 years (2.5–3.6) Transmen: 2.4 years (2.0–3.1) Duration of CHT monotherapy: Transwomen: 2.8 years (1.6–3.4) Transmen: 3.0 years (1.9–3.4)	Anthropometric and whole-body dual-energy x-ray absorptiometry data waist-hip ratio (WHR) total body fat (TBF) total lean body mass (LBM)
Kreukels et al 2011 [106]		Review		

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Klink et al 2015 [84] The Netherlands	**At start of GnRHa** 15 years **At follow-up** 22 years	Longitudinal observational study N=34 subjects n=15 transwomen n=19 transmen **Follow-up** Gonadectomy between 1998–2012	Assess bone mineral density development during GnRHa therapy and at age 22 years in young adults with gender dysphoria who started sex reassignment during adolescence. **Intervention** GnRHa monotherapy followed by cross-sex hormonal with discontinuation of GnRHa after gonadectomy. Duration: GnRHa: 1.3–1.5 years CSH: 5.8–5.4 years	Bone mineral density
Lynch et al 2015 [107] USA	Under 19 years	Retrospective chart review October 1995–March 2013. N=16 n=7 MtF n=6 FtM	Determine the efficacy and safety of medroxyprogesterone) for puberty sex hormone suppression	Age of onset of gender identity disorder symptoms comorbid diagnoses
Mahfouda et al 2017 [108]		Review		
Martinerie et al 2018 [109]		Review		

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Neyman et al 2019 [110] USA	**Range** 12–18.4 years **Mean** 16 years ± 1.77 **Median age when starting bicalutamide** 16.63 years	Retrospective review between 2013 and 2018 n=23 transwomen adolescents	Bicalutamide 50 mg daily as a second-line puberty blocker Monotherapy or with concurrent oestrogen treatment	Change in breast Tanner stage during treatment Age Timing of oestrogen initiation laboratory studies: liver function, sex steroids
Schagen et al 2016 [111] The Netherlands	**MtF (male-to-female)** Range 11.6–17.9 years Median: 13.6 years **FtM (female-to-male)** Range: 11.1–18.6 years Median: 14.2 years	Prospective observational 1998–2009 n=49 transwomen n=67 transmen **Follow-up** 12 months	To evaluate the efficacy and safety of GnRHa treatment to suppress puberty in gender dysphoric adolescents. Gonadotropin-releasing hormone agonists (GnRHa): triptorelin intramuscular injections 3.75 mg triptorelin . Duration of treatment with GnRHa alone depended on when the individual reached the age at which cross-sex hormone therapy could be added.	Physical examination: Tanner stage: breast development, testicular volume, genital development; height, weight, body mass index Blood samples: luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, oestradiol; Liver enzymes and renal function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, g-glutamyl transferase, creatinine Body composition: evaluated using dual energy x-ray absorptiometry: lean body mass, fat percentage

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Schagen et al 2018 [112] The Netherlands	**Age at GnRHa start** Transgirls: Range: 11.6–17.9 years Mean: 14.0 years ± 1.6 Transboys: Range: 11.5–18.6 Mean: 14.3 ± 2.0 **Age at GAH start** Transgirls: Range: 13.9–18.9 Mean: 16.3 ± 1.2 Transboys: Range: 13.6–19.5 Mean: 16.8 ± 1.1	Prospective study. 1998–2009 n=127 n=73 transgirls n=54 transboys **Follow-up** 4 years	Effects of gonadotropin-releasing hormone analogues (GnRHa) treatment and gender-affirming hormone (GAH) treatment on adrenal androgen levels 2 years of GnRHa treatment only, 2 years of GnRHa combined with gender-affirming hormone treatment (oestradiol or testosterone) Treatment: intramuscular injections of the GnRHa triptorelin. Duration of treatment with GnRHa alone depended on when the individual reached the age at which gender-affirming hormone therapy could be added (approximately 16 years). Gender-affirming hormone treatment: daily oral doses of 17-beta oestradiol, intramuscular injections testosterone esters	Adrenal androgen levels: dehydroepiandrosterone-sulfate (DHEAS) Androstenedione
Staphorsius et al 2015 [70] The Netherlands	**MtF (male-to-female)** Mean: 15.1 ± 2.4 **FtM (female-to-male)** Mean: 15.8 ± 1.9	Unreported design, preclinical. N=41 n=22 FtM [n=12 of which were using GnRHa (suppressed FtM) and n=10 who were not (untreated FtM)) n=18 MtF [n=8 were using GnRHa (suppressed MtF) and 10 were not (untreated MtF))	To examine the effects of puberty suppression on executive functioning **Intervention** Tower-of-London test Magnetic resonance imaging of the brain	Executive functioning: performance on the Tower of London task, a commonly used EF task Region-of-interest analyses

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Stoffers et al 2019 [113] The Netherlands	**At start of GnRHa** Range: 11.8–18.0 years Median: 16.5 years **At start of testosterone** Range: 14.9–18.4 years Median: 17.2 years	Retrospective study, 2010–2018 N=62 FtM **Follow-up** median 12 months after testosterone treatment	This study aimed to investigate the efficacy and safety of testosterone treatment in transgender adolescents. **Intervention** GnRHa treatment and subsequent testosterone Duration of GnRHa: median 8 months (range 3-39 moths) Duration of testosterone: median 12 months (range 5–33 months)	Virilization (voice deepening, hair growth) Anthropometry (height, weight) Laboratory parameters (high density lipoprotein, cholesterol, sex hormone binding globulin, haematocrit, haemoglobin, prolactin, androstenedione, dehydroepiandrosterone sulphate, lipids, HbA1c, vitamin D) Bone mineral density
Tack et al 2018 [114] Belgium	**At the start of progestin** Mean: 16.2 ± 1.05 years in transboys Mean 16.3 ± 1.21 years in transgirls	Cohort study, who used progestins 2011–2017 n=44 transboys n=21 transgirls **Follow-up** Lynestrenol: 11.6 months (range 4–40) Cyproterone acetate: 10.6 months (range 5–31)	To study prospectively the evolution of body composition and bone mass in late-pubertal trans adolescents using the proandrogenic or antiandrogenic progestins lynestrenol (L) and cyproterone acetate (CA), respectively. **Intervention** lynestrenol (L) or cyproterone acetate (CA) Assessment before the start of progestin and before addition of cross-sex hormones.	Anthropometry (body weight, waist circumference) Grip strength, Body composition (bone mass, size, and density): using dual-energy X-ray absorptiometry Bone mineral density and bone geometry: using peripheral quantitative computed tomography Serum analyses (sex hormone–binding globulin (SHBG), total testosterone, free testosterone, total oestradiol, total testosterone/oestradiol ratio, follicle-stimulating hormone, luteinizing hormone, serum 25-OH vitamin D, parathyroid hormone (PTH), serum C-terminal telopeptide (s-CTX), and procollagen type I Nterminal propeptide (PINP))

Author **Year** **Country**	**Age** **(years)**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Turban et al 2018 [35]		Review		
Vlot et al 2017 [115] The Netherlands	**Transmen** Range: 11.7–21.9 years **Transwomen** Range: 11.5–20.9 years	Preclinical n=34 FtM (transmen) n=22 MtF (transwomen) **Follow-up** 24 months	Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) **Intervention** Treatment with GnRHa triptorelin and CSHT added in incremental doses from the age of 16 years. Transmen received testosterone esters and transwomen received 17-β estradiol.	Bone turnover markers (BTM): measured with: P1NP, osteocalcin, ICTP Bone mineral density: densitometry with DXA-scan of the lumbar spine and femoral neck of the non-dominant hip Body weight and height Stages of pubertal development: assessed according to Tanner

Gender affirming hormone treatment

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
de Vries et al 2014 [52] The Netherlands	Range 13.6–20.7 years **Before the start of puberty suppression** Mean: 13.6 years; **When cross-sex hormones were introduced** Mean: 16.7 years; >1 year after gender reassignment surgery: Mean: 20.7 years	Follow-up study. Individuals receiving puberty suppression during adolescence 2004–2011. n=55 n=22 natal males, n=33 natal females **Follow-up** >1 year after gender reassignment surgery	Longer-term longitudinal evaluation of puberty suppression by means of gonadotropin-releasing hormone analogues	Psychological functioning: gender dysphoria, body image, global functioning, depression, anxiety, emotional and behavioural problems; Objective wellbeing: social and educational/professional functioning; Subjective wellbeing: quality of life, satisfaction with life and happiness
Hahn et al 2016 [116] Austria	**Mean** 27.3 years (SD 6.4) (mean age controls 24.6 SD 5.2 years)	Brain imaging study, imaging before and after n=32 n=18 MtF n=16 healthy controls **Follow-up** at least 4 weeks	Assess the influence of continuous high-dose testosterone application on language processing in adult female-to-male transsexuals **Intervention** Testosterone (lynestrenol, desogestrel)	Morphometry analysis (grey matter volume) in Broca's and Wernicke's areas Structural connectivity Functional connectivity
Sequeira et al 2019 [117] USA	13–19 years	A retrospective chart review before and during testosterone use n=46 patients **Follow-up** 6 and 12 months after initiation.	The effect of testosterone on body mass index, z-score in transmasculine adolescents at 6 and 12 months after initiation.	Body mass index (BMI) z-score

Gender affirming surgery

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
de Vries et al. 2014 [52] The Netherlands	**Range** 13.6–20.7 years **Before the start of puberty suppression** Mean: 13.6 years; **When cross-sex hormones were introduced** Mean: 16.7 years; >1 year after gender reassignment surgery: Mean: 20.7 years	Follow-up study. Individuals receiving puberty suppression during adolescence 2004–2011. n=55 n=22 natal males, n=33 natal females **Follow-up** >1 year after gender reassignment surgery	Longer-term longitudinal evaluation of puberty suppression by means of gonadotropin-releasing hormone analogues	Psychological functioning: gender dysphoria, body image, global functioning, depression, anxiety, emotional and behavioural problems; Objective wellbeing: social and educational/professional functioning; Subjective wellbeing: quality of life, satisfaction with life and happiness
Marinkovic and Newfield 2017 [118] USA	**Age at initial visit** Range 4.7–20.9 years Mean: 15.2 years **Age at chest reconstruction** Range: 13.4–19.7 years (3 subjects <16 years) Mean: 17.2 years	Retrospective observational study Jan 2011–Dec 2017 n=167 chest reconstruction n= 55 transfemales n= 108 transmales n= 4 nonbinary	Chest reconstructive surgeries (female to male) in transgender youth, experience from one paediatric centre. **Type of procedure** Double incision, keyhole, Locations of surgery: San Diego, CA; San Francisco CA; Thousand Oaks, CA, Tijuana Mexico, Philadelphia PA, Annapolis MD.	Surgical complications: keloid, fluid collection, hematoma Satisfactions rate Initial visit age Onset of GD Testosterone start age Surgery age Medications at time of surgery: GnRHa, testosterone Other medical conditions: anxiety, Asperger's, ADHD, depression, bipolar, Hashimoto's thyroiditis, obesity, acne Additional medications: antidepressants, mood stabilizers, vitamins/minerals, acne creams

Author **Year** **Country**	**Age** **(years)**	**Study design** **n**	**Aims/ Research question(s)**	**Outcome measures**
Olson-Kennedy et al 2018 [119] USA	**Range** 13–25 years **Mean** 19 years (SD 2.5) postsurgical participants **Mean** 17 years (SD 2.5) nonsurgical participants	Survey data June 2016–Dec 2016 N=136 female at birth n=68 postsurgical participants n=68 nonsurgical participants **Follow-up** 1–5 years post-surgery	To examine the amount of chest dysphoria in transmasculine youth who had had chest reconstruction surgery compared with those who had not undergone this surgery.	Testosterone use Chest dysphoria composite score Desire for chest surgery Complications after surgery: hematoma, loss of nipple sensation, loss of sensation of other areas of the chest, keloid (excessive) scarring Regret
Cohen-Kettenis et al 1997 [120] The Netherlands	**At pre-test** Mean: 17.5 years Range: 15–20 years **At follow-up** Range: 19–27 years Mean: 22.0 years	Follow-up study. Interviews by independent psychologist. n=22 after sex reassignment surgery (SRS) n=15 FtM n=7 MtF **Follow-up** >1 year post surgery	To investigate postoperative functioning of the first 22 consecutive adolescent transsexual patients who underwent sex reassignment surgery.	Psychological, social, and sexual functioning: Gender Dysphoria: Utrecht Gender Dysphoria Scale Body Image Scale Personality Inventory: Dutch version of Minnesota Multiphasic Personality Inventory; Dutch Personality Questionnaire, Treatment Evaluation/satisfaction Social Reactions Questionnaire

Author Year Country	Age (years)	Study design n	Aims/ Research question(s)	Outcome measures
Smith et al 2001 [121] The Netherlands	**Treated* group** At pre-test: Range: 15–19 years Mean: 16.6 years **At Follow-up** Range: 19–23 years Mean: 21 years **Non-treated group** At pre-test: Range: 13.7–20.2 years Mean: 17.3 years **At Follow-up** Range: 15.7–26.2 years Mean: 21.6 years	Prospective follow-up study. March 1995–July 1999. n=20 treated adolescent transsexuals n=21 nontreated n=6 delayed-treatment adolescents *treated: indicates hormone treatment and sex reassignment surgery (SRS) **Follow-up** 1–4 years after surgery for treated patients 1–7 years after application for sex reassignment for nontreated patients	Prospective follow-up study with treated adolescent transsexuals to evaluate early sex reassignment, and with nontreated and 6 delayed-treatment adolescents to evaluate the decisions not to allow them to start sex reassignment at all or at an early age	Psychological, social, and sexual functioning. Intelligence: measured by Wechler scales (WISC-R) and WAIS Gender Dysphoria: measured by Utrecht Gender Dysphoria Scale Body Dissatisfaction: measured by Body Image Scale (BIS) Physical Appearance: measured by Appraisal of Appearance Inventory Psychological functioning: measured by Dutch Short MMPI (NVM) and the Dutch version of the Symptom Checklist 90 (SCL-90) Quality of Life: measured by the Affect Balance Scale Treatment Satisfaction Social and Sexual Functioning Satisfaction With Surgery Public Confrontation Questionnaire
Smith et al 2002 [122] The Netherlands	**Age at follow-up** Range: 18–27 years Mean: 22.5 years (SD 2.09)	Follow-up study N=19 adolescents n=6 MtF n=13 FtM **Follow-up** Mean: 58.5 months (SD 14.5) Range: 40.5–87.2 months	Assess postoperative psychological functioning in transsexuals who applied for sex reassignment in adolescence. **Intervention** Rorschach protocols before and after sex reassignment.	Postoperative psychological functioning: assessed by the Rorschach Comprehensive System

Table 7 Planned or ongoing systematic reviews registered in the PROSPERO data-base.

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Aimee Morrison 2017	The Effects of Gender-Affirming Hormone Therapy on Fertility and Pregnancy: A Systematic Review.	Yale School of Medicine, USA	Any age	What is the effect of gender-affirming hormone therapy on fertility and pregnancy in the transgender population?	Receipt of long-term gender-affirming hormone therapy, including cross-hormones, puberty blockers, hormone antagonists.	Rates of fertility preservation and pregnancy, including both clinical pregnancy and live births.
Annie Wang 2018	Reporting outcomes and outcome measures in female-to-male microsurgical phalloplasty surgery: a systematic review.	University of British Columbia, Canada	Not indicated	What are the outcomes and outcome measures used to evaluate postoperative results for microsurgical phalloplasty surgery of female-to-male transgender patients?	Microsurgical phalloplasty	All published outcomes
Annie Wang 2018	Reporting outcomes and outcome measures in male-to-female transgender chest surgery: a systematic review.	University of British Columbia, Canada	Not indicated	What are the outcomes and outcome measures used to evaluate postoperative results for gender-reaffirming chest construction surgical procedures of male-to-female transgender patients?	Breast and chest construction surgeries	All published outcomes
Charlotte Wong 2017	Systematic review and meta-analysis of psychiatric comorbidities in gender identity disorder.	None, Hong Kong	>18 years	Does male to female transsexual group have a higher prevalence of Axis-1 psychiatric disorders than female to male transsexual group?	Not applicable.	Prevalence of Axis 1 psychiatric disorders and Personality disorder.
Christina Elise Holm-Larsen 2018	A systematic review of cardiovascular disease in oestrogen treated transgender women.	University of Southern Denmark, Faculty of Health Sciences; Denmark	Not indicated	The aim of this study is to assess the incidence of cardiovascular disease and death in transgender women treated with oestrogen.	Oestrogen that is administered intramuscular (i.m.), orally (p.o.), or t.d.	Cardiovascular disease All types (including hypertension and VTE) Excluded hypertension Excluded VTE All-cause mortality
Dina Greene 2018	Risk of thrombosis in transgender women receiving oestrogen therapy.	University of Washington, USA	>18 years	Is there an increase in thrombotic risk when transgender people are prescribed oestrogen therapy?	Exogenous oestrogen administration with or without progesterone	To identify risk, risk factors, and incidence of thrombosis

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Felipe Ferreira 2018	Adverse effects of hormonal therapy in trans-woman undergoing transsexualization process: a systematic review.	University of Brasilia, Brazil	>18 years	What are the adverse drug reactions caused by hormonal and non-hormonal adjuvants used in the treatment of gender dysphoria in adult trans-woman?	Hormonal drug therapy and non-hormonal adjuvant used in the transsexualization process.	Adverse event to the hormonal drugs and non-hormonal adjuvants during the transsexualization process of trans-woman.
Haupt C et al. 2018	Antiandrogens or oestradiol treatments or both during hormone replacement therapy in transitioning transgender women. Cochrane Database of Systematic Reviews. 2018(10).	Cochrane Protocol	> 16 years	Efficacy and safety of hormone replacement therapy with antiandrogens or oestradiol or both in transitioning transgender women.	• Antiandrogens (cyproterone acetate or spironolactone) and oestradiol • Antiandrogens (cyproterone acetate or spironolactone) alone • Oestradiol alone	• Quality of life • Satisfaction • Adverse event
Helen Morgan 2018	A systematic review of parental influences on transgender and gender diverse children's and young people's health and wellbeing.	Murdoch University, Australia https://www.murdoch.edu.au/	0-25 years	How do parental influences impact on the health and wellbeing of trans and gender diverse children and young people?	Impact of parental influences; influence of the primary caregivers of the child/young person.	Aim: To comprehensively review relevant qualitative and quantitative empirical studies and grey literature regarding parental influences on trans and gender diverse (TGD) children's and young people's health and wellbeing.
Karine Schwarz 2016	Vocal treatment in gender dysphoria: a systematic review.	UFRGS, Brazil http://www.ufrgs.br/ufrgs/inicial	Not indicated	To identify and evaluate the effectiveness of the treatments used in the vocal treatment of individuals diagnosed with Gender Dysphoria, and the effect of treatment on pitch	Vocal and / or surgical treatment for voice.	Election of the best and most effective vocal treatment for gender dysphoria.

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Karine Schwarz 2017	Effectiveness of speech therapy in male to female transgender people.	UFRGS, Brazil http://www.ufrgs.br/ufrgs/inicial	Not indicated	What is the best speech therapy for vocal feminization in male to female transsexuals?	Interventions for vocal feminization include speech therapy with vocal techniques to increase voice frequency as well as to adapt the vocal resonance system. Surgical techniques, such as type IV thyreoplasty or laser techniques, promote an increase in the fundamental frequency of voice.	Effects of speech therapy on the fundamental frequency of voice. Effects of phono surgery on the fundamental frequency of voice. The best technique of vocal feminization.
Kate Whitaker	What are the negative and positive factors associated with the mental health and wellbeing of transgender adults?	Royal Holloway, University of London, United Kingdom	>18 years	What are the negative and positive factors associated with the mental health and wellbeing of transgender adults?	None. Any factors that are investigated as relating to the mental health or wellbeing of transgender adults.	Outcomes of studies should include specific measurement of mental health or wellbeing, using a standardised tool or specifically designed measure.
Kathryn Bell 2017	Genital reconstructive surgery in male to female transgender patients: a systematic review of primary surgical techniques, adverse events and functional outcomes from 1950 to present day.	Imperial College Healthcare NHS Trust, United Kingdom	Not indicated	What are the surgical techniques used to perform primary genital reconstructive surgery in trans-women?	Male to female primary genital reconstructive surgery	Adverse events for each surgical technique (including rectal injury, rectovaginal fistula, urethral meatal stenosis, vaginal stenosis, vaginal prolapse, clitoral necrosis, wound haematoma/ dehiscence/ infection and need for secondary surgery); functional outcomes for each surgical technique (including clitoral sensation, ability to orgasm, ability to have penetrative intercourse and satisfaction with aesthetics)

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Lou Pryer CB.	Is Cognitive Behavioural Therapy (CBT) culturally adapted for transgender and gender nonconforming (TGNC) individuals accessing therapy?	University of Bath, United Kingdom	Not indicated	To review the evidence for affirmative CBT in TGNC populations.	Cognitive Behaviour Therapy. All formats of intervention delivery (group, individual and telephone).	Evidence for affirmative CBT in TGNC populations.
Michelle Tollit 2019	Measuring gender identity and gender dysphoria in transgender and gender diverse children and adolescents: a systematic review.	Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Australia	up to 18 years	Which tools have been used to measure gender identity, gender incongruence or gender related distress (dysphoria)?	None; review of instruments/tools	Measurements of gender identity (or gender incongruence) or gender dysphoria in transgender and gender diverse children and adolescents. Measurement tools could be qualitative or quantitative. No Single item measures. What are the strengths, limitations and psychometric properties of these tools?
Pau Crego 2016	Regret and its consequences for transgender health: a systematic review.	University of California, Berkeley - School of Public Health, USA	Not indicated	How is regret understood in the literature regarding trans patients accessing gender-affirming hormonal and/or surgical treatments?	attempts to identify which patients truly need hormones and/or surgeries	Regret
Ritu Sharma 2019	Effects of gender-affirming surgeries for treatment of gender dysphoria in transgender people. www.sbu.se/307	JHU.edu, USA (John Hopkins University)	Not indicated	Breast/Chest Surgery; Genital surgery	Gender-affirming surgeries for transgender people	Anger Anxiety, Depression Gender dysphoria Mental health Overall satisfaction Patient satisfaction Physical functioning Quality of life Regret, Satisfaction - request for revision Harms – oncological risks [breast reconstruction for transmen –KQ1a)

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Ritu Sharma 2018	Effects of hormone therapy in transgender people.	John Hopkins University USA)	Not indicated		Hormone therapy drugs	Effects of hormone therapy treatment (before/after or one intervention compared to another intervention) in transgender people: Physical health outcomes (BMI, Weight, Height, metabolic outcomes, all of measure of bone mineal density and fractures) transition-related outcomes: (changes during testosterone and oestrogen administration, delay of puberty, impact on fertility, change in voice, masculinization caused by testosterone, feminization caused by oestrogen) adverse events
Ritu Sharma 2019	Interventions for speech, voice, and communication in transgender people.	John Hopkins University, USA	Not indicated		Behavioural, surgical, or endocrine interventions to change the voice as a part of sex reassignment:	Acoustic outcome, Perceptual outcomes, satisfaction and harms
Shan Siddiqui 2016	Suggested interventions for suicidal LGBT adolescents: a systematic review.	University of Texas Medical Branch, USA	10 - 19 years	What interventions can be used to address suicidality in lesbian, gay, bisexual, and transgender adolescents?	Interventions that address suicidality, sexuality, and/or mental health issues for sexual minority adolescents.	Reduced suicidal behaviours, attempted suicides, and/or suicides.

Author Year	Title	Organization	Age	Research question(s)	Intervention/ Exposure	Outcome
Stuart Macdonald 2019	Differences in the prevalence rates of depression, non-suicidal self-injury and suicidality between trans men and trans women: a systematic review.	University of Aberdeen, United Kingdom	18 - 65 years	Is depression, non-suicidal self-injury and suicidality more prevalent in trans men or trans women before psychological intervention?	Prevalence rates of depression, non-suicidal self-injury and suicidality in trans men and women.	It is anticipated that gender differences will be found on each of the three variables. Depression is hypothesised to be higher in Trans women, with NSSI and suicidality being higher in trans men.
Teresa Surace 2019	Prevalence of suicidality and non-suicidal self-injury in transgenders and people with gender dysphoria: a systematic review.	University of Catania, Italy	Not indicated	What is the prevalence of suicidality and non-suicidal self-injury in people with gender dysphoria or transgender people?	Prevalence only; No interventions or exposures	Prevalence of: (1) suicide rates (2) suicide attempts (3) suicidal ideation/thoughts (4) non suicidal self-injury If data will be available, we will divide outcome according to gender (male-to-female or female-to-male) and age.
Wai Chung Yong SUAS.	Association between transgender and osteoporosis: a systematic review and meta-analysis.	Baystate Franklin Medical Centre www.baystatehealth.org	18 years or older	Are patients after transgender associated with increased risk of osteoporosis	Transgender participants who had osteoporosis or osteopenia measured by bone mineral density as a predictor of fragility fracture.	Bone mineral density

Abbreviations
ASD = Autism spectrum disorder; DXA = Dual-energy X-ray absorptiometry; FtM = Female to male; GAS = Gender affirming surgery; GD = Gender dysphoria; GnRHa = Gonadotropin releasing hormone analogue; MtF = Male to female; PTSD = Posttraumatic stress syndrome, SD = Standard deviation, SRS = sex reassignment surgery