



## **Bilaga till rapport**

Hormonbehandling vid könsdysfori - barn och unga/ Hormone treatment of children and adolescents with gender dysphoria, rapport 342 (2022)

### **Bilaga 3. Inkluderade studier**

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**Table 1.** Effects on mental health by puberty suppression in adolescents

<b>Author, Year (ref)</b> Title	<b>De Vries et al 2014 (1)</b> <i>Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment</i>
Country Study design	The Netherlands Longitudinal cohort study, before-after 2008-2012
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at assessment pre-treatment: Range 11.1–17.0 years 13.6 years (SD 1.9) At start of puberty suppression: Range 11.5–18.5 14.8 years (SD 1.8) At start of cross-sex hormones: Range 13.9–19.0 years 16.7 years (SD 1.1)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	196 referred 111 prescribed puberty suppression 15 non-participating 1 death after vaginoplasty  55 individuals evaluated: 22 transwomen 33 transmen 40 complete data 15 missing data
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT) Gender reassignment surgery: vaginoplasty, mastectomy, hysterectomy, ovariectomy, (phalloplasty)
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRH duration: Not specified CSHT duration: Not specified Age at Follow-up: at assessment Post-Treatment Mean 20.7 years (SD 1.0) Range 19.5–22.8
<b>OUTCOMES –</b> Reported outcomes	Gender Dysphoria Utrecht Gender Dysphoria Scale (UGDS) Global functioning Children’s Global Assessment Scale (CGAS) Depressive symptoms: The Beck Depression Inventory (BDI) Anger Spielberger’s Trait Anger (TPI) Anxiety: Spielberger’s Trait Anxiety (STAI) Body Image Scale (BIS) Child Behavior Checklist (CBCL)
<b>RESULTS</b> Extracted outcomes	<b>Before start / During puberty suppression / After gender reassignment (mean (SD))</b>  <u>Gender dysphoria (UGDS)</u> Total 53.51 (8.29) / 54.39 (7.70) / 15.81 (2.78) MtF 47.07 (11.05) / 48.95 (10.80) / 17.27 (2.57) FtM 56.74 (3.74) / 57.11 (3.40) / 15.08 (2.64) <u>Global functioning (CGAS)</u> Total 71.13 (10.46) / 74.81 (9.86) / 79.94 (11.56) MtF 74.33 (7.53) / 78.20 (9.56) / 82.40 (8.28) FtM 67.65 (11.87) / 70.65 (9.89) / 76.29 (14.48) <u>Depression (BDI)</u> Total 7.89 (7.52) / 4.10 (6.17) / 5.44 (8.40) MtF 4.73 (4.20) / 2.25 (3.54) / 3.38 (4.40) FtM 10.09 (8.34) / 5.05 (7.08) / 6.95 (9.83) <u>Anxiety (STAI)</u> Total 39.57 (10.53) / 37.52 (9.87) / 37.61 (10.39) MtF 31.87 (7.42) / 31.71 (8.36) / 35.83 (10.22) FtM 44.41 (9.06) / 41.59 (9.03) / 39.20 (10.53) <u>Anger (TPI)</u> Total 17.55 (5.72) / 17.22 (5.61) / 16.01 (5.28) MtF 14.17 (3.01) / 14.00 (3.36) / 5.58 (3.92) FtM 19.55 (5.96) / 19.25 (5.69) / 16.56 (6.06)

<b>Author, Year (ref)</b>	<b>Costa et al 2015 (2)</b>
Title	<i>Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria.</i>
Country	The UK
Study design	Longitudinal cohort study, before-after, 2010-2014
<b>POPULATION (ages)</b>	Age at baseline: Range 12-17 years Age at start Range 12-17 years Age in cohort 15.6 years (SD 1.7) natal male 15.4 years (SD 1.2) natal female Tanner stage
	Age at start of GnRH: Range 13-17 years 16.6 years (SD 1.22) natal male 16.4 years (SD 1.3) natal female
<b>POPULATION (n)</b>	436 referred [1: 1.7 natal male/natal female ratio]
n patients	235 did not complete diagnostic procedure
natal male (M-t-F)	201 completed diagnostic procedure [1: 1.6 natal male/natal female ratio]
natal female (F-t-M)	121 eligible for puberty suppression 80 not eligible for puberty suppression after 6 months psychological support*
	101 GnRH treated "Immediate eligible": 35 GnRH treated evaluated at end of study 100 GnRH untreated "Delayed eligible": 36 GnRH untreated evaluated at end of study
<b>INTERVENTION (type)</b>	GnRH: Drug, dose and treatment frequency not indicated.
Puberty suppression (GnRH)	Start after 6 months of psychological assessment and support (mean 0.75 + 0.6 years), referred as "diagnostic procedure".
Cross-sex hormone treatment (CSHT)	Psychotherapeutic interventions: "Individual or family or group therapy, carried out on a regular basis (at least one a month)"
<b>INTERVENTION (time)</b>	GnRH duration:
Treatment duration	12 months
Follow-up time,	Psychological support:
Follow-up age	18 months total Follow-up times: 6 months, 12 months, 18 months
<b>OUTCOMES –</b>	UGDS
Reported outcomes	Children's Global Assessment Scale (CGAS) [high score=better psychosocial functioning]
<b>RESULTS</b>	<b>Psychosocial functioning:</b>
Extracted outcomes	<u>Children's Global Assessment Scale score:</u> All GD adolescents, during diagnostic procedure (n=201): 57.7 (SD 12.3) at enrolment 60.7 (SD 12.5) 6 months after psychological support only  GnRH treated group: (n= 101 at baseline) 60.9 (SD 12.2) after 6 months psychological support only (n= 61) 67.4 (SD 13.9) at 18 months psychological support + GnRH (7-18 months) (n= 35)  Delayed group: (n= 100 at baseline) 60.3 after 6 months psychological support only 62.5 after 18 months (n= 36)

<b>Author, Year (ref)</b>	<b>Becker-Hebly et al 2020 (3)</b>
Title	<i>Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions</i>
Country	Germany
Study design	Retrospective cohort study, before-after 2013-2018
<b>POPULATION (ages)</b>	Age at baseline (intake): Minimum 11 years
Age at start	Minimum 11 years
Age in cohort	Mean 15.5 years (SD 1.2)
Tanner stage	Range 11.2 - 18.0 years
	Age at Follow-up: Mean 17.4 years (SD 1.7)
	Range 11.95 - 21.0 years
<b>POPULATION (n)</b>	434 adolescents
n patients	164 dropouts at baseline
natal male (M-t-F)	129 dropouts during follow-up
natal female (F-t-M)	
	75 evaluated: 64 birth assigned female 11 birth assigned male 21 no hormone 11 GnRH 32 GnRH + CSHT 11 CSHT + surgery (type not specified) Excluded severe psychiatric problems (psychosis, suicidality)
<b>INTERVENTION (type)</b>	GnRH: Drug, dose and treatment frequency not indicated.
Puberty suppression (GnRH)	CSHT: Drug, dose and treatment frequency not indicated.
Cross-sex hormone treatment (CSHT)	Groups: No hormone treatment (no GnRH, no CSHT) GnRH GnRH + CSHT CSHT + surgery (surgery type not specified, "mainly mastectomy") Psychotherapy (79%)
<b>INTERVENTION (time)</b>	Duration of GnRH or CSHT: not specified.
Treatment duration	
Follow-up time,	Possible range 7-49 months, "time since first referral"
Follow-up age	GnRH: minimum 7 months CSHT: up to 40 or 47 months Follow-up time: Mean 21.4 (SD 12.2) months  Range 6 months - 4 years
<b>OUTCOMES -</b>	<b>Psychological functioning:</b>
Reported outcomes	Children's Global Assessment Scale (CGAS, clinician-rated) HR QoL (mental and physical dimensions): assessed by Kidscreen-27 (>18 years) SF-8 (<18 years) Youth Self Report (YSR, ages 11-18y) Adult version (ASR, >18y)

<b>RESULTS</b> Extracted outcomes	<p><b>Psychosocial functioning:</b></p> <p><u>CGAS Global functioning</u> Baseline/ Follow-up (mean (SD))</p> <p>No medical treatment (diagnostics or psychosocial interventions) 68.10 (11.23) / 70.00 (12.25)</p> <p>Puberty suppression (GnRH) 67.27 (11.91) / 81.82 (7.51)</p> <p>GA hormones (GnRH and GAH) 73.13 (10.91) / 85.63 (9.14)</p> <p>GA surgery (at least one operation and GAH) 66.36 (14.33) / 83.64 (8.09)</p> <p><u>Health-related quality of life</u> (mean <math>\pm</math> SD)</p> <p>Baseline T Mental dimension/T Physical dimension</p> <p>No medical treatment (diagnostics or psychosocial interventions) 34.86 (6.27) / 37.51 (8.27)</p> <p>Puberty suppression (GnRH) 39.04 (9.25) / 43.43 (8.61)</p> <p>GA hormones (GAH and GnRH) 36.16 (6.78) / 39.12 (7.10)</p> <p>GA surgery (at least one operation and GAH) 37.88 (6.53) / 39.88 (8.49)</p> <p>Follow-up T Mental dimension/T Physical dimension</p> <p>No medical treatment (diagnostics or psychosocial interventions) 36.37 (7.71) / 42.51 (10.40)</p> <p>Puberty suppression (GnRH) 43.17 (10.20) / 49.57 (11.64)</p> <p>GA hormones (GAH and GnRH) 42.07 (10.74) / 49.36 (9.81)</p> <p>GA surgery (at least one operation and GAH) 43.44 (9.57) / 53.87 (6.15)</p>
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<b>Author, Year (ref)</b> Title Country Study design	<b>Cantu et al 2020 (4)</b> <i>Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic</i> USA Retrospective cohort study chart review, before-after, 2017 - 2019
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at start: Min 11 years Max 18 years  Age in cohort: Mean 15.1 years (SD 1.8)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	80 15 female affirmed 58 male affirmed 7 nonbinary  In Follow-up cohort: 13 hormone blockers 25 hormone treatment (HT) 4 hormone blockers + HT 38 no treatment
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	Previous intervention: Drug, dose and treatment frequency not indicated.  Hormone blockers only Hormone treatment (HT) only (feminizing; masculinizing) Both hormone blockers and HT Neither hormone blockers nor HT  Of 28 youth: 6 feminizing hormones 22 masculinizing hormones
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Duration of GnRH or CSHT: Not specified.  Time between initial visit and follow-up appointment: Mean 4.7 months Range < 1 - 11 months
<b>OUTCOMES –</b> Reported outcomes	Depression: assessed with PHQ-9 (Patient Health Questionnaire-9) Anxiety: assessed with GAD-7 (Generalized Anxiety Disorder-7)
<b>RESULTS</b> Extracted outcomes	<b>Psychosocial functioning:</b>  <u>Acute distress (not defined)</u> Baseline/follow-up Mean (SD)  PHQ-9 HT initiated (n=28) 9.8 (7.1)/ 10.3 (7.3) No HT (n=51) 11.1 (6.3)/ 10.1 (5.9)  GAD-7 HT initiated (n=27) 8.4 (6.4)/ 8.5 (5.5) No HT (n=50) 9.6 (5.9)/ 9.1 (5.8)  <u>Suicidality</u> “Of the 27 (34%) youth who endorsed suicidality at intake, 22 (81%) continued to endorse suicidality at their follow-up visit, and only 4 (4%) no longer endorsed suicidality at follow-up”.

<b>Author, Year (ref)</b>	<b>Carmichael et al 2021 (5)</b>
Title	<i>Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK</i>
Country	The UK
Study design	Prospective cohort, 2011 -2015
<b>POPULATION (ages)</b>	Age at consent (median, IQR): 13.6 years (12.8 - 14.6)
Age at start	13.6 years (12.8 - 14.6)
Age in cohort	Range 12.0 - 15.3 years
Tanner stage	At end of pathway (median, IQR): 16.1 years (16.0 - 16.4)
<b>POPULATION (n)</b>	44 recruited:
n patients	25 birth registered males
natal male (M-t-F)	19 birth-registered females
natal female (F-t-M)	Tanner stage: (n (%), birth registered males, birth registered females):
	Stage 2: 0, 0
	Stage 3: 17 (68%), 2 (10%)
	Stage 4: 5 (20%), 11 (58%)
	Stage 5: 3 (12%), 6 (32%)
	1 discontinued GnRH
<b>INTERVENTION (type)</b>	GnRHa: triptorelin
Puberty suppression (GnRH)	Psychosocial assessment and support:
Cross-sex hormone treatment (CSHT)	Before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6 years). Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. Local psychological services provided support for co-occurring difficulties as required.
	No interview conducted before young people started GnRHa
<b>INTERVENTION (time)</b>	Follow-up time:
Treatment duration	12 months follow-up (n=44), 24 months (n=24), 36 months (n=14)
Follow-up time,	Median time in study: 31 months (IQR 20 to 42, range 12 to 59 months).
Follow-up age	Age at end of pathway (IQR): 16.1 years (16.0, 16.4)
<b>OUTCOMES -</b>	Child Behaviour Checklist (CBCL) (parent report)
Reported outcomes	Youth Self Report (YSR)
	Kidscreen-52 questionnaire
	Body Image Scale (BIS) is
	Utrecht Gender Dysphoria Scale (UGDS)
	Children's Global Assessment Scale (CGAS)
	Semi-structured qualitative interviews.
	Participant experience and satisfaction with GnRHa
	No interview conducted before young people started GnRHa

<p><b>RESULTS –</b> Extracted outcomes</p>	<p><b>CBCL Parent report, Total problems t-score: mean (95% CI):</b> Baseline; 12 months, change; 24 months, change; 36 months, change 61.6 (58.4, 64.7); 61.8 (58.4, 65.1), 0.3 (-2.0, 2.6); 60.2 (54.6, 65.8), -1.0 (-4.0, 2.1); 61.1 (52.3, 69.9), -1.3 (-6.6, 4.0)</p> <p><b>CBCL Parent report, Self-harm: median (IQR):</b> Baseline; 12 months; 24 months; 36 months 0 (0,1) ; 0 (0,1) ; 0 (0,1) ; 0 (0,1) ; 0 (0,1)</p> <p><b>YSR Self-report, Total problems t-score: mean (95% CI):</b> Baseline; 12 months, change; 24 months, change 57.9 (55.0, 60.8); 58.4 (54.6, 62.2), 0.8 (-3.1, 4.8); 56.5 (50.6, 62.5), 1.5 (-3.4, 6.3)</p> <p><b>YSR Self-report, Self-harm: median (IQR):</b> Baseline; 12 months; 24 months 0 (0,1) ; 0 (0,2) ; 0 (0,0)</p> <p><b>Kidscreen-52, HRQOL, Parent report, Psychological wellbeing, t-score, mean (95% CI)</b> Baseline; 12 months; 24 months 43.0 (39.6, 46.4); 41.1 (37.0, 45.2); 51 (45.8, 56.2)</p> <p><b>Kidscreen-52, HRQOL, Self-report, Psychological wellbeing, t-score, mean (95% CI)</b> Baseline; 12 months; 24 months 39.8 (36.7, 42.8) ; 39.0 (35.4, 42.6) ; 42.4 (36.9, 48)</p> <p><b>Body image scale, Overall score: mean (95% CI)</b> Baseline; 12 months; 24 months; 36 months 3.1 (2.8, 3.3) ; 3.2 (3.0, 3.4) ; 3.0 (2.7, 3.2) ; 3.1 (2.4, 3.7)</p> <p><b>Utrecht Gender dysphoria score: median (IQR)</b> Baseline; 12 months; 24 months 4.8 (4.6, 5.0) ; 4.7 (4.6, 5.0) ; 4.7 (4.3, 5.0)</p> <p><b>CGAS global score, mean (95% CI)</b> Baseline; 12 months; 24 months; 36 months 62.9 (59.6, 66.2) ; 64.1 (59.9, 68.3) ; 65.7 (59.6, 71.8) ; 66.0 (58.1, 73.9)</p> <p>No changes from baseline to 12 or 24 months in CBCL or YSR total t-scores or for CBCL or YSR self-harm indices, nor for CBCL total t-score or self-harm index at 36 months. Most participants reported positive or a mixture of positive and negative life changes on GnRH<sub>a</sub>.</p>
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<b>Author, Year (ref)</b> Title	<b>Hisle-Gorman et al 2021 (6)</b> <i>Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment</i>																
Country	USA																
Study design	Retrospective cohort study (military healthcare data), 2010–2018																
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at Study Initiation: years (median (IQR)) 10 years (8–13) transgender 9 years (4–14) siblings Age of First Affirming Medication (CSHT), years (median (IQR)) 18.2 years (16.6–19.8) Age at Study Completion, years (median (IQR)) 18 years (16–21) transgender 17 years (11–21) siblings																
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	3754 transgender 1193 (31.8%) male at birth 2561 (68.2%) female at birth  963 transgender adolescents receiving hormone treatment (before-after data) 6603 cisgender siblings																
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	<u>Hormone treatment (n=963)</u> Puberty Suppressant n=96 (7.2%) Masculinizing Hormone n=591 (61.4%) Feminizing Hormone n=276 (28.7%) Psychotropic medication n=857 (89%)																
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Full study period: 8.5 years in total follow-up time Hormone treatment: Years followed (median (IQR)) 7.1 years (5.6–7.9) before HT 1.5 years (0.7–2.7) after HT																
<b>RESULTS</b> Reported outcomes																	
<b>RESULTS</b> Extracted outcomes	<p><u>Mental health over full 8-year study period*:</u> <i>TGD adolescents compared to siblings were more likely to have a mental health diagnosis, be prescribed more psychotropic medications and use more mental healthcare services:</i> Mental health diagnosis (n (%)): 3352 (89.3%) transgender vs 3308 (50.1%) siblings; adjusted OR 5.45 (4.77–6.24) On psychotropics (n (%)): 2820 (75.1%) transgender vs 2425 (37.7%) siblings Psychotropic medication days: All mental health meds (medications days per year): 111.4 transgender vs 42.5 siblings; adjusted IRR 2.57 (2.36–2.80)</p> <p><u>Mental health diagnoses at some point during the 8-year study period:</u> Transgender vs Siblings (n (%); adjusted odds of mental health diagnosis* aOR (95% CI)) <i>*after adjustment for age at study initiation, assigned sex at birth, parent rank, and number of outpatient visits per year, odds of having any mental health diagnosis:</i></p> <table> <tr> <td>All Mental Health</td> <td>3352 (89.3%) vs 3308 (50.1%); aOR 5.45 (4.77–6.24)</td> </tr> <tr> <td>Mood</td> <td>2413 (64.3%) vs 1182 (18.9%); aOR 6.12 (5.51–6.8)</td> </tr> <tr> <td>Anxiety</td> <td>1908 (50.8%) vs 1216 (18.4%); aOR 3.30 (2.98–3.65)</td> </tr> <tr> <td>ADHD</td> <td>1119 (29.8%) vs 1229 (18.6%); aOR 1.77 (1.59–1.97)</td> </tr> <tr> <td>Adjustment</td> <td>1687 (44.9%) vs 1191 (18.0%); aOR 1.09 (1.80–3.41)</td> </tr> <tr> <td>Psychotic</td> <td>363 (9.7%) vs 104 (1.6%); aOR 5.38 (4.20–6.88)</td> </tr> <tr> <td>Personality disorders</td> <td>86 (2.3%) vs 43 (0.7%); aOR 2.54 (1.71–3.78)</td> </tr> <tr> <td>Suicide</td> <td>683 (18.2%) vs 162 (2.5%); aOR 7.45 (6.11–9.08)</td> </tr> </table> <p>(suicidal ideation/attempted suicide/self-harm)</p> <p><u>Psychotropic medication*:</u></p>	All Mental Health	3352 (89.3%) vs 3308 (50.1%); aOR 5.45 (4.77–6.24)	Mood	2413 (64.3%) vs 1182 (18.9%); aOR 6.12 (5.51–6.8)	Anxiety	1908 (50.8%) vs 1216 (18.4%); aOR 3.30 (2.98–3.65)	ADHD	1119 (29.8%) vs 1229 (18.6%); aOR 1.77 (1.59–1.97)	Adjustment	1687 (44.9%) vs 1191 (18.0%); aOR 1.09 (1.80–3.41)	Psychotic	363 (9.7%) vs 104 (1.6%); aOR 5.38 (4.20–6.88)	Personality disorders	86 (2.3%) vs 43 (0.7%); aOR 2.54 (1.71–3.78)	Suicide	683 (18.2%) vs 162 (2.5%); aOR 7.45 (6.11–9.08)
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*\*including antidepressants (wellbutrin, SSRI, SNRI, other antidepressant) benzodiazepines, sleep medications, anti-psychotics, lithium*

Transgender vs Siblings (medication days per year):  
 All mental health medications:  
 1114 days vs 425 days; adjusted IRR 2.57 (2.36-2.80)

After hormone treatment:  
 (n=963 individuals-initiated puberty suppression or CSHT, median age 18.2 years):  
 Crude rate of medication days (number of days, Before - After hormone treatment))  
 All Mental Health Medications: (days)  
 119.7 before vs 211.5 after; aIRR 1.67 (1.46-1.91)

Psychotropic medication use:  
 increased from mean 120 days per year to mean 212 days per year  
 following gender affirming pharmaceutical care.

Medication days by type of medication:  
(number of medication days: Before vs After hormone treatment):

Wellbutrin	6.3 before vs 16.2 after; aIRR 2.51 (2.71-3.69)
SSRI	44.8 before vs 73.9 after; aIRR 1.72 (1.47-2.00)
SNRI	4.7 before vs 14.0 after; aIRR 2.59 (1.52-4.38)
other antidepressant	9.2 before vs 18.9 after; aIRR 1.61 (1.18-2.21)
sleep medications	6.4 before vs 16.2 after; aIRR 2.23 (1.61-3.10)
benzodiazepines	3.0 before vs 12.7 after; aIRR 3.01 (1.95-4.65)
anti-psychotics	15.9 before vs 30.1 after; aIRR 1.77 (1.34-2.35)
lithium	1.3 before vs 2.3 after; aIRR 1.11 (0.48-2.59)
stimulants	26.4 before vs 25.1 after; aIRR 0.96 (0.72-1.26)
migraine medications	1.5 before vs 2.2 after; aIRR 0.76 (0.37-1.53)

<b>Author, Year (ref)</b> Title	<b>Staphorsius et al 2015 (7)</b> <i>Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria</i>
Country Study design	The Netherlands Functional MRI study, Cross-sectional, up to 2014
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at start: Minimum 12 years, Tanner B2, Tanner G2-G3 Age at GnRH start: Not indicated Age in cohort: (mean $\pm$ SD) Age at scan: 15.1 years $\pm$ 2.4 M-t-F 15.8 years $\pm$ 1.9 F-t-M Control group age: 14.9 years $\pm$ 1.5 (boys) 14.4 years $\pm$ 1.8 (girls)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	41 adolescents 22 F-t-M (natal females): (12 using GnRH, "suppressed FM") (10 untreated, "untreated FM") 18 M-to-F (natal males): (8 using GnRH, "suppressed FM") (10 untreated, "untreated FM") Control group* (siblings, friends): 24 girls (F) 21 boys (M) 10 not investigated due to brain scan problems
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH: triptorelin (Decapeptyl-CR®) 3,75 mg/4w, s.c. or i.m Study intervention: MRI scan (3.0 T) axial T2*-weighted whole-brain volumes sensitive to BOLD contrast, sagittal T1-weighted Tasks in MRI: 1 executive function task: event-related parametric version of the Tower-of-London (ToL) task 3 cognitive tasks: verbal fluency task, mental rotation task, face recognition task
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Puberty suppression duration (mean $\pm$ SD): 1.6 $\pm$ 1.0 years: 1.8 years $\pm$ 0.8 MtF 1.4 years $\pm$ 1.1 FtM
<b>OUTCOMES -</b> Reported outcomes	<u>Executive function:</u> Tower-of-London (ToL) performance scores: reaction times, accuracy Region-of-interest (ROI) analyses: left DLPFC (dorsolateral prefrontal cortex), bilateral RLPFC (rostromedial prefrontal cortex), precuneus <u>Psychological functioning:</u> Child Behaviour Checklist (CBCL) <u>IQ:</u> Wechsler Intelligence Scales (WISC-III®, Wechsler, 1991; WAIS-III®, Wechsler, 1997)
<b>RESULTS</b> Extracted outcomes	<u>Executive function: Functional task (ToL):</u> <u>Accuracy (%)</u> mean $\pm$ SD 88.5 $\pm$ 6.8 boys (M) ; 87.2 $\pm$ 11.9 girls (F) 79.1 $\pm$ 10.3 M-t-F (total) 73.9 $\pm$ 9.1 suppressed ; 83.4 $\pm$ 9.5 untreated 87.1 $\pm$ 10.0 F-t-M (total) 85.7 $\pm$ 10.5 suppressed ; 88.8 $\pm$ 9.7 untreated <u>Reaction time (sec)</u> mean $\pm$ SD 9.6 $\pm$ 2.5 boys (M) ; 9.0 $\pm$ 1.8 girls (F) 10.4 $\pm$ 3.5 M-t-F (total) 10.9 $\pm$ 4.1 suppressed ; 9.9 $\pm$ 3.1 untreated 10.0 $\pm$ 2.6 F-t-M (total) 9.9 $\pm$ 3.1 suppressed ; 10.0 $\pm$ 2.0 untreated  <u>Psychological functioning: CBCL scores,</u> mean $\pm$ SD 48.4 $\pm$ 10.5 boys (M) ; 48.4 $\pm$ 10.3 girls (F) 57.8 $\pm$ 9.2 M-t-F (total) 57.4 $\pm$ 9.8 suppressed ; 58.2 $\pm$ 9.3 untreated 60.4 $\pm$ 10.2 F-t-M (total) 57.5 $\pm$ 9.4 suppressed ; 63.9 $\pm$ 10.5 untreated

**Table 2.** Effects on bone health by puberty suppression in adolescents

<b>Author, Year (ref)</b>	<b>Joseph et al 2019 (8)</b>
Title	<i>The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort</i>
Country	UK
Study design	Retrospective review of national cohort, before-after, 2011–2016
<b>POPULATION (ages)</b>	Age at GnRH start: Range 12–14 years
Age at start	
Age in cohort	
Tanner stage	Age in First year cohort: Age at treatment start: (mean (SD)) 13.2 (1.4) trans girls 12.6 (1.0) trans boys Age at 1 year scan: 14.4 (1.5) trans girls 13.8 (1.1) trans boys  Age in Longitudinal cohort Age at treatment start: 13.0 (1.1) trans girls 12.9 (3.0) trans boys Age at 2 years scan: 15.8 (1.3) trans girls 15.6 (3.5) trans boys
<b>POPULATION (n)</b>	First year cohort: 70 31 trans girls 39 trans boys  Longitudinal cohort: 31 10 trans girls 21 trans boys
<b>POPULATION (n)</b>	
n patients	
natal male (M-t-F)	
natal female (F-t-M)	
<b>INTERVENTION (type)</b>	GnRH
Puberty suppression (GnRH)	<u>Study intervention:</u> DXA - dual energy X-ray absorptiometry
Cross-sex hormone treatment (CSHT)	Z-scores [calculated from Crabtree et al. from ALPHABET study using UK norms for Caucasian subjects]. Hip BMAD Z-scores not calculated (no reference ranges available)
<b>INTERVENTION (time)</b>	GnRH duration: 1 year (1st year cohort) 2.8 years (longitudinal cohort)
Treatment duration	
Follow-up time, Follow-up age	Follow-up time: 1–2.8 years
<b>OUTCOMES -</b>	<u>Bone health:</u>
Reported outcomes	Hip (femoral neck) and lumbar spine (L1-L4): BMD - bone mineral density BMAD - bone mineral apparent density Z-score compared to natal sex (birth sex, age) Hip BMD g/cm <sup>2</sup> Hip BMD Z score Spine BMD g/cm <sup>2</sup> Spine BMD Z score Spine BMAD g/cm <sup>3</sup> Spine BMAD Z score

RESULTS – Extracted outcomes	Characteristics, mean (SD)
	<p><b>Baseline / 1 year</b></p> <p><u>Trans girls (n=31/31)</u></p> <p>Age, year 13.2 (1.4) / 14.4 (1.5)            Height, cm 161.0 (8.0) / 163.7 (8.1)            Weight, kg 64.7 (17.1) / 70.3 (21.2)            BMI, kg/m<sup>2</sup> 24.8 (5.3) / 26.1 (6.9)            Hip BMD, kg/m<sup>2</sup> 0.894 (0.118) / 0.905 (0.104)            Hip Z-score 0.157 (0.905) / -0.340 (0.816)            Spine BMD, kg/m<sup>2</sup> 0.860 (0.154) / 0.859 (0.129)            Spine BMD Z-score -0.016 (1.106) / -0.461 (1.121)            Spine BMAD, g/cm<sup>3</sup> 0.235 (0.030) / 0.233 (0.029)            Spine BMAD Z-score 0.859 (0.154) / -0.228 (1.027)</p> <p><u>Trans boys (n=39/39)</u></p> <p>Age, years 12.6 (1.0) / 13.8 (1.1)            Height, cm 158.4 (9.5) / 163.3 (8.7)            Weight, kg 51.0 (13.7) / 56.2 (13.4)            BMI, kg/m<sup>2</sup> 20.1 (4.1) / 21.4 (5.4)            Hip BMD, kg/m<sup>2</sup> 0.772 (0.137) / 0.785 (0.120)            Hip Z-score -0.863 (1.215) / -1.440 (1.075)            Spine BMD, kg/m<sup>2</sup> 0.694 (0.149) / 0.718 (0.124)            Spine Z-score -0.395 (1.428) / -1.276 (1.410)            Spine BMAD, g/cm<sup>3</sup> 0.196 (0.035) / 0.201 (0.033)            Spine BMAD Z-score -0.186 (1.230) / -0.541 (1.396)</p> <p><b>Baseline / 2.8 years</b></p> <p><u>Trans girls (n=10/10)</u></p> <p>Age, years 13.0 (1.1) / 15.8 (1.3)            Height, cm 160.3 (5.4) / 165.1 (5.7)            Weight, kg 66.4 (14.6) / 82.9 (30.5)            BMI, kg/m<sup>2</sup> 25.8 (5.3) / 30.5 (8.6)            Hip BMD, kg/m<sup>2</sup> 0.920 (0.116) / 0.910 (0.125)            Hip Z-score 0.45 (0.781) / -0.600 (1.059)            Spine BMD, kg/m<sup>2</sup> 0.867 (0.141) / 0.878 (0.130)            Spine BMD Z-score 0.130 (0.972) / 0.890 (1.075)            Spine BMAD, g/cm<sup>3</sup> 0.240 (0.027) / 0.240 (0.030)            Spine BMAD Z-score 0.486 (0.809) / -0.279 (0.93)</p> <p><u>Trans boys (n=21/21)</u></p> <p>Age, years 12.9 (3.0) / 15.6 (3.5)            Height, cm 159.0 (35.8) / 168.7 (37.5)            Weight, kg 49.8 (17.1) / 59.5 (19.6)            BMI, kg/m<sup>2</sup> 19.4 (5.9) / 20.9 (6.6)            Hip BMD, kg/m<sup>2</sup> 0.766 (0.215) / 0.773 (0.197)            Hip Z-score -1.075 (1.145) / -1.779 (0.816)            Spine BMD, kg/m<sup>2</sup> 0.695 (0.220) / 0.731 (0.209)            Spine BMD Z-score -0.715 (1.406) / -2.000 (1.384)            Spine BMAD, g/cm<sup>3</sup> 0.195 (0.058) / 0.198 (0.05)            Spine BMAD Z-score -0.361 (1.439) / -0.913 (1.318)</p>

<b>Author, Year (ref)</b> Title Country Study design	<b>Klink et al (9) 2015</b> <i>Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria</i> The Netherlands Retrospective longitudinal cohort study , before-after, 1998–2012
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	<b>Age at start of GnRH:</b> Range 11.4–18.3 years Transwomen: Tanner G5 Mean: 14.9 years $\pm$ 1.9 SD Transmen: Tanner B4 Mean: 15.0 years $\pm$ 2.0 SD  <b>At start of CSHT:</b> Range 15.6–19 years Transwomen: Mean: 16.6 years $\pm$ 1.4 SD Transmen: Median: 16.4 years (2.3 IQR)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	34 15 MtF 19 FtM
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	<b>GnRH:</b> Triptorelin (Decapeptyl-CR): 3.75 mg/4 weeks s.c. <b>CSHT:</b> 17-estradiol p.o. (incremental dosing), dose not indicated. Mixed testosterone esters i.m. 250 mg/ml/ 2–4 weeks (incremental dosages), dose not indicated. Surgery: gonadectomy (min age 18 years)  <b>Study intervention:</b> DXA (dual energy x-ray absorptiometry Lumbar spine (LS), Femoral region (FN)  aBMD Z-scores according to natal sex, age, and ethnicity based on the <i>National Health and Nutrition Examination Survey</i> reference in Manitoba, Canada. LS Z scores available from start of the study. FN Z scores available in 2003, 5 years after the start of the study. Volumetric BMD (bone mineral apparent density (BMAD)) of the LS and FN calculated as previously described, Z scores determined using UK reference population. Reference values of BMAD in young adulthood are not available. In females lumbar peak bone mass (PBM) expressed as BMAD is attained at age 18–20 years and in males between 18 and 23 years (8). To calculate the Z score of the LS BMAD at age 22 years, the reference of LS BMAD of 17 years was used.
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	<b>GnRH duration</b> Median: 1.3 years natal boys, Range: 0.5–3.8 years Median: 1.5 y natal girls, Range: 0.25–5.2 years <b>CSHT duration</b> Median: 5.8 years natal boys, Range: 3.0–8.0 years Median: 5.4 years natal girls, Range: 2.8–7.8 years <b>GnRH + CSHT duration:</b> Median: 3.1 years natal boys, Range: 2.1–4.5 years Median: 2.2 years natal girls, Range: 1.4–3.1 years After gonadectomy: GnRH terminated and CSHT continued. <b>FU until age 22 years</b>
<b>OUTCOMES -</b> Reported outcomes	<b>Bone health</b> Bone mineral density (BMD): Bone mineral apparent density (BMAD) Areal BMD (aBMD, g/cm <sup>2</sup> ) lumbar spine and femoral region: BMAD (g/cm <sup>3</sup> ) BMAD Z-score aBMD (g/cm <sup>2</sup> ) aBMD Z-score T-score Z-score relative natal sex

<b>RESULTS –</b> Extracted outcomes	<p><b>Start GnRH / Start CSH / Age 22 years (mean ± SD)</b></p> <p><b>Transwomen</b></p> <p>Height cm 174.6 8.9 / 179.9/ 181 ± 9.3</p> <p><i>Lumbar spine</i></p> <p>BMAD, g/cm<sup>3</sup> 0.22 ± 0.03 / 0.22 ± 0.02 / 0.23 ± 0.03          BMAD Z score -0.44 ± 1.10 / -0.90 ± 0.80 / -0.78 ± 1.03          aBMD, g/cm<sup>2</sup> 0.84 ± 0.13 / 0.84 ± 0.11 / 0.93 ± 0.10          aBMD Z score -0.77 ± 0.89 / -1.01 ± 0.98 / -1.36 ± 0.83          T-score at 22 years: -1.5 ± 1.10</p> <p><i>Femoral neck</i></p> <p>BMAD, g/cm<sup>3</sup> 0.28 ± 0.04 / 0.26 ± 0.04 / 0.28 ± 0.05          BMAD Z score -0.93 ± 1.22 / -1.57 ± 1.74 / --          aBMD, g/cm<sup>2</sup> 0.88 ± 0.1 / 0.87 ± 0.08 / 0.94 ± 0.11          aBMD Z score -0.66 ± 0.77 / -0.95 ± 0.63 / -0.69 ± 0.74          T-score at 22 years: -0.75 ± 0.78</p> <p><b>Transmen</b></p> <p>Height cm 165.2 ± 9.1 / 168.4 ± 8.3 / 170.6 ± 7.9</p> <p><i>Lumbar spine</i></p> <p>BMAD, g/cm<sup>3</sup> 0.25 ± 0.03 / 0.24 ± 0.02 / 0.25 ± 0.28          BMAD Z score 0.28 ± 0.90 / -0.50 ± 0.81 / -0.033 ± 0.95          aBMD, g/cm<sup>2</sup> 0.95 ± 0.12 / 0.91 ± 0.10 / 0.99 ± 0.13          aBMD Z score 0.17 ± 1.18 / -0.72 ± 0.99 / -0.33 ± 1.12          T-score at 22 years: -0.43 ± 1.2</p> <p><i>Femoral neck</i></p> <p>BMAD, g/cm<sup>3</sup> 0.32 ± 0.04 / 0.31 ± 0.04 / 0.33 ± 0.05          BMAD Z score 0.01 ± 0.70 / -0.28 ± 0.74 / --          aBMD, g/cm<sup>2</sup> 0.92 ± 0.10 / 0.88 ± 0.09 / 0.95 ± 0.10          aBMD Z score 0.36 ± 0.88 / -0.35 ± 0.79 / -0.35 ± 0.74          T-score at 22 years: 0.005 ± 0.87</p>
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<b>Author, Year (ref)</b> Title Country Study design	<b>Vlot, et al 2017 (10)</b> <i>Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents</i> The Netherlands Retrospective, cohort study, before after 2001-2011
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	<b>Age at start of GnRH:</b> Min Tanner B2 or G2  <b>Age in cohort:</b> <i>Transmen:</i> Median: 15.1 years Range: 11.7–18.6 years Tanner B2-B5 <i>Transwomen:</i> Median: 13.5 years Range: 11.5–18.3 years Tanner G2-G5  <b>Age at start of CSHT (min age 16 years):</b> <i>Transmen:</i> Median: 16.3 years Range: 15.9–19.5 years <i>Transwomen:</i> Median: 16.0 years Range: 14.0–18.9 years
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	<i>In Table 1:</i> 70 42 female-to-male (transmen) 28 male-to-female (transwomen)  <i>In abstract:</i> 56 34 female-to-male (transmen) 22 male-to-female (transwomen)
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	<b>GnRH:</b> Triptorelin (Decapeptyl-CR <sup>®</sup> ) 3.75 mg s.c. /4 weeks <b>CSHT:</b> Testosterone esters (Sustanon) i.m.: 25 mg/m <sup>2</sup> /2 weeks, 6-month increment until 250 mg/4 w 17-β estradiol: 5 µg/kg/day, 6-months increments until 2 mg/day  <b>Study intervention:</b> DXA- dual energy X-ray absorptiometry BMAD Z-scores calculated for sex assigned at birth using UK reference population, due to the lack of consensus with regard to the use of either sex assigned at birth or desired sex reference values in transgender adolescents. The lack of validated reference values of bone age needed to calculate the BMAD, and Z-scores limits the use of bone age and therefore the chronological calendar age of the transgender adolescents was used. Reference values of L- M- and S-values of 17-year-old biological males and females were used to calculate the BMAD for patients older than 17 years, due to the lack of reference values of adolescents exceeding the age of 17 years.  Two groups: Young group: bone age <15 years in transwomen or <14 years in transmen Old group: bone age ≥15 years in transwomen or ≥14 years in transmen
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	<b>GnRH</b> Approximately 1 year in transmen Approximately 2–3 years in transwomen <b>CSHT</b> Up to 24 months.
<b>OUTCOMES -</b> Reported outcomes	<b>Bone mineral turnover markers:</b> N-terminal propertied of type I collagen (PINP) Osteocalcin (OC) Carboxy terminal cross linked telopeptide of type I collagen (ICTP) Bone mineral apparent density (BMAD) of lumbar spine (LS) and femoral neck (FM) Z-scores



<b>RESULTS –</b> Extracted outcomes	<p><b>At start GnRH / at start CHST / at 24 months</b></p> <p>Height, cm, median (range)  <i>Transmen:</i> 164.2 (149.6–180.1) / 165.8 (152.6–181.2) / 168.6 (155.6–183)  <i>Transwomen:</i> 166.9 (153.9–185.7) / 176.3 (165.1–186.4) / 180.7 (167.4–195.0)</p> <p><b>Transmen, “young”</b>          P1NP median/range: 783 (516–1090) / 324 (194–402) / 186 (163–334)          OC median/range: 5 (2.2–11.7) / 6.8 (1.8–7.7) / 4.9 (4.2–7.8)          ICTP median/range: 24 (17–29.9) / 11 (7.8–12) / 12 (11–14)</p> <p>BMAD HIP: 0.31 (0.26–0.36) / 0.30 (0.22–0.35) / 0.33 (0.23–0.37)          BMAD HIP Z-score: -0.01 (-1.30–0.91) / -0.37 (-2.28–0.47) / -0.37 (-2.03–0.85)          BMAD LS: 0.23 (0.20–0.29) / 0.23 (0.19–0.28) / 0.25 (0.22–0.28)          BMAD LS Z-score: -0.05 (-0.78–2.94) / -0.84 (-2.2–0.87) / -0.15 (-1.38–0.94)</p> <p><b>Transmen, “old”</b>          P1NP median/range: 110 (38–471) / 127 (61–321) / 101 (44–181)          OC median/range: 2.4 (0.4–4.6) / 3.9 (0.4–8.6) / 2.9 (0.8–5)          ICTP median/range: 7 (5.2–15) / 6.9 (4.6–14) / 8.2 (4.1–16)</p> <p>BMAD HIP: 0.33 (0.25–0.39) / 0.30 (0.23–0.41) / 0.32 (0.23–0.41)          BMAD HIP Z-score: 0.27 (-1.39–1.32) / -0.27 (-1.91–1.29) / 0.02 (-2.1–1.35)          BMAD LS: 0.26 (0.21–0.29) / 0.24 (0.20–0.28) / 0.25 (0.21–0.30)          BMAD LS Z-score: 0.27 (-1.6–1.8) / -0.29 (-2.28–0.90) / -0.06 (-1.76–1.61)</p> <p><b>Transwomen, “young”</b>          P1NP median/range: 935 (617–1348) / 363 (185–643) / 204 (137–314)          OC median/range: 4.8 (2.6–21.9) / 6.4 (0.7–12.8) / 5.4 (3.9–12.5)          ICTP median/range: 23 (15–34) / 13 (8.7–21) / 10 (8.5–13)</p> <p>BMAD HIP: 0.29 (0.20–0.33) / 0.27 (0.20–0.33) / 0.27 (0.20–0.36)          BMAD HIP Z-score: -0.71 (-3.35–0.37) / -1.32 (-3.39–0.21) / -1.3 (-3.51–0.92)          BMAD LS: 0.21 (0.17–0.25) / 0.20 (0.18–0.24) / 0.22 (0.19–0.27)          BMAD LS Z-score: -0.2 (-1.82–1.18) / -1.52 (-2.36–0.42) / -1.10 (-2.44–0.69)</p> <p><b>Transwomen, “old”</b>          P1NP median/range: 191 (96–792) / 140 (111–467) / 119 (55–296)          OC median/range: 2.29 (0.8–11) / 2.2 (0.5–6.1) / 3.3 (1.8–6.8)          ICTP median/range: 12 (6.9–21) / 7.4 (6.9–13) / 6.8 (4.8–15)</p> <p>BMAD HIP: 0.30 (0.26–0.36) / 0.30 (0.26–0.34) / 0.29 (0.24–0.38)          BMAD HIP Z-score: -0.44 (1.37–0.93) / -0.36 (-1.5–0.46) / -0.56 (-2.17–1.29)          BMAD LS: 0.22 (0.18–0.25) / 0.22 (0.19–0.24) / 0.23 (0.21–0.26)          BMAD LS Z-score: -1.18 (-1.78–1.09) / -1.15 (-2.21–0.08) / -0.66 (-1.66–0.54)</p>
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<b>Author, Year (ref)</b> Title Country Study design	<b>Schagen et al 2020 (11)</b> <i>Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones</i> The Netherlands Prospective observational study, 1998 - 2009
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	At the start of GnRHa: Early pubertal group: Tanner stage 2 or 3 Late pubertal group: Tanner stage 4 or 5  At start of GnRH: (mean $\pm$ SD) 14.1 $\pm$ 1.7 trans girls 14.5 $\pm$ 2.0 trans boys  At start of CSHT: 16.2 $\pm$ 1.2 trans girls 16.9 $\pm$ 1.1 trans boys
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	<b>GnRHa group:</b> 121 51 trans girls 70 trans boys Pubertal group: Early (Tanner 2-3) / Late (Tanner 4-5) 15 / 36 trans girls 14 / 56 trans boys  <b>GnRHa + CSHT group:</b> 78 36 trans girls 42 trans boys Pubertal group: Early (Tanner 2-3) / Late (Tanner 4-5) 10 / 26 trans girls 5 / 37 trans boys
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRHa i.m. 3.75 mg/ 4 weeks (Triptorelin) CSHT: Oestrogens oral Testosterone i.m. (Sustanon) In subjects > 16 years at the start of puberty suppression: CSHT started at half the adult dose and increased to the adult dose after 6 months. (2 mg 17beta-estradiol/day, 125 mg testosterone-esters/ 2 weeks considered an adult dose).  Study intervention: Dual-energy x-ray absorptiometry (DXA) Calculate z-scores based on age and sex using <i>National Health and Nutrition Examination Surveys (NHANES)</i> references values; reference population of the birth-assigned sex was used. BMAD (g/cm <sup>3</sup> ) calculated as described by Ward [Ward et al. 2007 <i>UK reference data for the Hologic QDR Discovery dual-energy x ray absorptiometry scanner in healthy children and young adults aged 6-17 years</i> . Arch Dis Child. 92(1): 53-59). BMAD Z-scores calculated using LMS data from an English reference population [Ward et al. 2007].
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Duration of GnRH: (years) 1.9 $\pm$ 1.03 mean 2.0 $\pm$ 0.94 transgirls 1.8 $\pm$ 1.11 transboys Early pubertal groups were on GnRHa for a significantly longer time (2.5 years in transgirls (n = 7) and 4.0 years in transboys (n = 3)) when compared with both late-pubertal groups (1.5 years in transgirls and 1.7 years in transboys)  Duration of CSHT: 3 years (not further detailed)
<b>OUTCOMES -</b> Reported outcomes	Bone mineral apparent density (BMAD) BMAD Z-scores (age- and sex-specific) Serum bone markers: P1NP, P3NP, osteocalcin, 1CTP Areal BMD (aBMD, g/cm <sup>2</sup> ) lumbar spine, nondominant hip, whole body; Bone mineral content of the whole body (BMC-WB, g)

<b>RESULTS –</b> Extracted outcomes	<p><b>aBMD 2 Years of GnRHa Treatment, Baseline / 24 months</b></p> <p><b>Transgirls</b>          Early Pubertal (n=15)          aBMD_hip g/cm<sup>2</sup> 0.81 (0.03) / 0.86 (0.03)          Z-score -0.49 (0.24) / -0.93 (0.21)          Late-Pubertal (n=36)          aBMD_hip g/cm<sup>2</sup> 0.87 (0.02) / 0.89 (0.02)          Z-score -0.43 (0.16) / -1.01 (0.15)</p> <p><b>Transboys</b>          Early-pubertal (n=14)          aBMD_hip g/cm<sup>2</sup> 0.79 (0.03) / 0.83 (0.03)          Z-score 0.09 (0.26) / -0.50 (0.24)</p> <p><b>Transboys</b>          Late-pubertal (n=56)          aBMD_hip g/cm<sup>2</sup> 0.93 (0.01) / 0.89 (0.02)          Z-score 0.46 (0.13) / -0.56 (0.13)</p> <p><b>aBMD GnRHa + 3 Years of Gender-Affirming Hormone Treatment, Baseline / 36 months</b></p> <p><b>Transgirls</b>          Early-Pubertal: (n=10)          aBMD_hip g/cm<sup>2</sup> 0.87 (0.03) / 1.02 (0.04)          Z-score -0.99 (0.23) / -0.09 (0.28)</p> <p><b>Transgirls</b>          Late-Pubertal: (n=26)          aBMD_hip g/cm<sup>2</sup> 0.88 (0.02) / 0.96 (0.02)          Z-score -0.86 (0.14) / -0.70 (0.18)</p> <p><b>Transboys</b>          Early-pubertal: (n=5)          aBMD_hip g/cm<sup>2</sup> 0.83 (0.04) / 1.02 (0.06)          Z-score -0.82 (0.33) / 0.59 (0.43)</p> <p><b>Transboys</b>          Late-pubertal: (n=37)          aBMD_hip g/cm<sup>2</sup> 0.88 (0.02) / 0.96 (0.02)          Z-score -0.50 (0.12) / 0.12 (0.16)</p>
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<b>Author, Year (ref)</b> Title Country Study design	<b>Stoffers et al 2019 (12)</b> <i>Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria</i> The Netherlands Retrospective, cohort study before-after, 2010-2018
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	<b>At start of GnRH:</b> Median: 16.5 years Range: 11.8–18.0 years  <b>At start of testosterone:</b> Median: 17.2 years Range: 14.9–18.4 years
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	62 trans males (FtM) 17 evaluated 0 discontinued testosterone "Excluded psychological, medical, or social problems that might interfere with treatment"
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH (Decapeptyl-CR®): 3.75 mg /4 weeks s.c. for at least 6 months Testosterone (Sustanon®); start at 250 mg i.m. Age 15–16 years: increased every 6 months using 25 mg/m <sup>2</sup> /2 weeks, 50 mg/m <sup>2</sup> /2 weeks, and 75 mg/m <sup>2</sup> /2 weeks, leading up to a standard adult dose of 125 mg every 2 weeks. ≥16 years: start 75 mg/m <sup>2</sup> /2 weeks for 6 months, thereafter 125mg/m <sup>2</sup> /2 weeks  Study intervention: Dual energy x-ray absorptiometry. Lumbar spine (LS) and hip (n=17) BMD Z-scores calculated using female reference data from <i>Bone Mineral Density in Childhood Study (USA)</i> for those >16 years of age, reference data from the <i>Third National Health and Nutrition Examination Survey</i> for the neck area of the hip and Hologic adult reference data for the LS were used. Bone mineral apparent density (BMAD) calculated and Z- scores determined for lumbar spine and left femoral neck as described by Ward et al. (UK). Reference values provided for up to 17 years, reference values for 17-year-olds used for those >17 y.
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	<b>GnRH duration</b> Median: 8 months Range: 3–39 months (3.25 years) <b>Testosterone duration</b> Min: 6 months Mean: 12 months Range: 5–33 months (2.75 years)
<b>OUTCOMES -</b> Reported outcomes	Virilization (acne, hair growth, voice deepening, absence of menses) height, weight, BMI, BP, hematcrit, cholesterol, ALP, triglycerides, Hb Hormone levels: FSH, LH, DHAES, FT4, testosterone, estradiol, TSH, prolactin, androstenedione, sex-hormone binding globulin (SHBP) Bone mineral density (BMD) lumbar spine, femoral neck BMD Z-scores
<b>RESULTS –</b> Extracted outcomes	<b>Bone health:</b> <b>At start GnRH (n=62) / at start testosterone (n=62) / at 24 months (n=15)</b> Blood pressure, mm Hg (median (IQR)) Systolic 124 (115-129) / 118 (114-126) / 126 (117-129) Diastolic 68 (65-73) / 72 (66-77) / 74 (63-76) Height (cm (mean ± SD)) 167.1 ± 6.9 / 168.2 ± 6.2 / 167.8 ± 5.3  BMD, g/cm <sup>2</sup> (mean ± SD) Lumbar spine 0.96 ± 0.11 / 0.90 ± 0.11/ 0.95 ± 0.11 Left hip 0.84 ± 0.11 / 0.76±0.09/ 0.86 ± 0.09 Right hip 0.84 ± 0.11 / 0.77 ±0.08/ 0.85 ± 0.11  BMD Z-score (mean ± SD) Lumbar spine: 0.02 ± 1.00 / -0.81 ± 1.02/ -0.74 ± 1.1 Left hip -0.19 ± 1.04 / -1.07 ± 0.85/ -0.20 ± 0.70 Right hip -0.16 ± 1.00/ -0.97 ± 0.79/ -0.31 ± 0.84

<b>Author, Year (ref)</b> Title	<b>Navabi et al 2021 (13)</b> <i>Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria</i>
Country Study design	Canada Retrospective review of medical records 2006 - 2017
<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age in cohort: (years $\pm$ SD) 15.2 ( $\pm$ 1.8) transgender males 15.4 ( $\pm$ 2.0) transgender females  90.7 % Tanner 4–5 transgender males 80.3 % Tanner 4–5 transgender females
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	198 youth 172 included 119 transgender males (female at birth) 51 transgender females (male at birth) 2 nonbinary  Pre-Post GnRH analysis: 116 individuals: 80 transgender males 36 transgender females
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRHa: leuprolide acetate i.m. start at 7.5 mg/4 weeks (3 doses), followed by 11.25 mg/ 12 w. calcium carbonate 500 mg twice daily (advised for youth with poor calcium intake) vitamin D 1000 to 2000 IU daily (advised for all youth)  Dual-energy radiograph absorptiometry
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	FU times: 6, 12 and 18 months  Pre-GnRHa DXA: at $-51.4 \pm 41.3$ days (range -158 to +28 days) relative to GnRHa initiation. Post-GnRHa DXA: at $355.2 \pm 96.7$ days (range 188–676 days) after GnRHa initiation (median 352.5 (294.5, 385.8) Mean time interval between pre- and post-DXA scans: $406.7 \pm 98.3$ days (range 210–720 days).
<b>OUTCOMES -</b> Reported outcomes	aBMD areal bone mineral density aBMD z scores Lumbar spine (LS) (L2–L4) left total hip (LTH) aBMD z scores Vitamin D status
<b>RESULTS –</b> Extracted outcomes	At baseline: Transgender females had lower z scores at lumbar spine aBMD, LS BMAD, left total hip aBMD, and bone mineral content (BMC) than transgender males. 55.2 % of transgender youth had vitamin D deficiency or insufficiency.  <b>Post-pre-GnRH mean difference (95% CI)</b> Transgender males: Lumbar spine aBMD z score -0.74 (-0.85 to -0.63) BMAD z score -0.59 (-0.74 to -0.45) Left total hip aBMD z score -0.33 (-0.40 to -0.26) Total body less head aBMD z score -0.34 (-0.43 to -0.25)  Transgender females: Lumbar spine aBMD z score -0.33 (-0.46 to -0.19) BMAD z score -0.37 (-0.61 to -0.14) Left total hip aBMD z score -0.46 (-0.60 to -0.31) Total body less head aBMD z score -0.34 (-0.48 to -0.21)
<b>Author, Year (ref)</b> Title  Country Study design	<b>van der Loos et al 2021 (14)</b> <i>Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty</i>  The Netherlands Retrospective cohort, 2011-2018

<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at start of GnRH: (min Tanner B2, Tanner G2–G3): 11-17 years Age at start of CSHT: 15 – 17 years  At start of GnRH: early, mid or late puberty groups: Tanner stage: early: B2; mid: B3; late: B4 and B5 Testicular volume: early: ≤9 mL; mid: 10–19 mL; late: ≥20 mL
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	322 included 106 transwomen (early: n=32; mid: n=30; late: n=44) 216 transmen (early: n=8; mid: n= 22; late: n=186) 115 gonadectomy
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRHa: triptorelin s.c. 3.75 mg / 4 weeks, or 11.25 mg /12 weeks CSHT (GAH- gender affirming hormone treatment): 17-beta-estradiol oral, start at 5 µg/kg, increased up to 2 to 4 mg/day. Testosterone ester mixture i.m. 25 mg/m2, increased up to 250 mg / 3 to 4 weeks. Surgery: Gonadectomy at earliest age 18 years (if performed, GnRH was stopped afterwards) Study intervention: DXA: narrow neck hip structure analysis (HSA)
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRH duration (min 6 months): range 1-4 years CSHT duration: range 2-6 years DXA after ≥2years of CSHT
<b>OUTCOMES -</b> Reported outcomes	Subperiosteal width Endocortical diameter BMI, Height, Hormone levels
<b>RESULTS –</b> Extracted outcomes	<b>Subperiosteal Width and Endocortical Diameter</b> , Change in Centimeters, mean (95% CI) Δ between start of GnRHa and start of GAH / Δ between the start of GnRHa and after ≥2 years of GAH / Δ between the start of GAH and after ≥2 years of GAH / <u>Trans women</u> Early puberty Subperiosteal width 0.38 (0.16; 0.60) / 0.44 (0.23; 0.65) / 0.06 (–0.15; 0.27) Endocortical diameter 0.39 (0.16; 0.61) / 0.38 (0.17; 0.60) / –0.00 (–0.21; 0.21) Mid puberty Subperiosteal width 0.33 (0.15; 0.50) / 0.57 (0.39; 0.75) / 0.25 (0.11; 0.38) Endocortical diameter 0.34 (0.17; 0.51) / 0.55 (0.37; 0.72) / 0.21 (0.08; 0.34) Late puberty Subperiosteal width 0.06 (–0.08; 0.20) / 0.27 (0.16; 0.39) / 0.21 (0.09; 0.34) Endocortical diameter 0.08 (–0.06; 0.22) / 0.27 (0.15; 0.40) / 0.19 (0.06; 0.33) <u>Trans men</u> Early puberty Subperiosteal width 0.63 (0.58; 0.68) / 0.79 (0.72; 0.85) / 0.15 (0.12; 0.19) Endocortical diameter 0.62 (0.57; 0.67) / 0.73 (0.67; 0.79) / 0.11 (0.08; 0.14) Mid puberty Subperiosteal width 0.10 (–0.09; 0.29) / 0.31 (0.11; 0.50) / 0.21 (0.03; 0.38) Endocortical diameter 0.09 (–0; 11; 0.30) / 0.27 (0.06; 0.48) / 0.18 (–0.01; 0.36) Late puberty Subperiosteal width 0.07 (–0.03; 0.18) / 0.15 (0.04; 0.26) / 0.07 (–0.04; 0.18) Endocortical diameter 0.10 (–0.01; 0.21) / 0.17 (0.05; 0.28) / 0.07 (–0.04; 0.17)  “development of hip bone geometry in transgender adolescents resembled that of the experienced gender if the GnRHa treatment was initiated during early puberty and was followed by a start of GAH. Only participants starting during early puberty showed more resemblance to the reference curves of their experienced gender. Participants starting GnRHa and GAH treatments during mid or late puberty continued within the curve of their gender assigned at birth”
<b>Author, Year (ref)</b> Title Country Study design	<b>Lee et al 2020 (15)</b> <i>Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study</i> USA Cross-sectional analysis of prospective, observational, longitudinal cohort, multicenter

<b>POPULATION (ages)</b> Age at start Age in cohort Tanner stage	Age at start of GnRH: 11.0 ± 1.4 years designated females at birth (DFAB) 12.1 ± 1.3 years designated males at birth (DMAB)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	63 transgender youth 30 designated females at birth (DFAB) 33 designated males at birth (DMAB) Tanner stages 2-3: 40 (63.5%) Tanner 2 23 (36.5%) Tanner 3
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH (not further specified)  Study intervention: DXA (before or 2 months after start of GnRH): DXA scans: total body less head (TBLH) lumbar spine total hip femoral neck Quantitative computed tomography (QCT): cortical and trabecular vBMD: midshaft femur L1-L3 vertebral bodies.
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRH duration before DXA: 0-2 months
<b>OUTCOMES -</b> Reported outcomes	Areal and volumetric BMD Z-scores dietary calcium serum 25-hydroxy-vitamin D physical activity (assessed with Physical Activity Questionnaire for Older Children (PAQ-C))
<b>RESULTS –</b> Extracted outcomes	Bone health: Areal and volumetric BMD Z-scores.  BMD assessed before initiation of GnRH: 90% (57/63) of participants  Low aBMD or vBMD Z-score, defined as < -2: in 30% (95% CI 15.6-48.7) of DMAB (10/33) in 13% (95% CI 3.8-30.7) of DFAB (4/30)  At least 1 BMD Z-score was < -2 in: 30% of DMAB 13% of DFAB  Designated males at birth (DMAB): BMD Z-scores below-average compared with male reference standards.  Designated females at birth (DFAB): BMD Z-scores below-average when compared with female reference standards except at hip sites.  Physical Activity Questionnaire for Older Children: low score in youth with low BMD than youth with normal BMD.  Dietary calcium intake: suboptimal in all youth. Vitamin D: no significant deficiencies.

**Table 3** Effects on anthropometric measures and metabolism by puberty suppression in adolescents

<b>Author, Year (ref)</b>	<b>Schagen et al 2016 (16)</b>
Title	<i>Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents</i>
Country	The Netherlands
Study design	Prospective cohort study, before-after, 1998 – 2009
<b>POPULATION (ages)</b>	Age at start: M-t-F: Range 11.6–17.9 years Median 13.6 years Tanner G2–G5 F-t-M: Range 11.1–18.6 years Median 14.2 years Tanner B2-B5
<b>POPULATION (n)</b>	116
n patients	49 M-t-F
natal male (M-t-F)	67 F-t-M
natal female (F-t-M)	77 analyzed: 36 M-t-F 41 F-t-M 0 discontinued GnRH treatment
<b>INTERVENTION (type)</b>	GnRH: Triptorelin (Decapeptyl-CR) 3.75 mg i.m. at 0, 2, and 4 weeks, followed by every 4 weeks.
Puberty suppression (GnRH)	Study intervention:
Cross-sex hormone treatment (CSHT)	Dual energy x-ray absorptiometry (DEXA)
<b>INTERVENTION (time)</b>	GnRH duration:
Treatment duration	3 to 12 months
Follow-up time, Follow-up age	(depended on when the individual reached the age at which CSHT could be added)
<b>OUTCOMES -</b>	Physical examination
All reported outcomes	Tanner stage (breast development, testicular volume) Height and weight, height SD score Body mass index (BMI), BMI SD score Body composition: (fat mass, fat %, lean body mass %) Hormone levels: LH, FSH, testosterone, estradiol Liver enzymes: alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase Creatinine
<b>RESULTS</b>	<b>At start GnRH / at 1 y GnRH (mean (SD))</b>
Extracted outcomes	<u>M-t-F (n=36):</u> Height (cm) 167.8 (7.5) / 172.3 (6.5) Weight (kg) 57.4 (11.1) / 63.3 (11.9) BMI (kg/m <sup>2</sup> ) 20.3 (3.0) / 21.2 (3.2) Lean body mass (%) 74.6 (6.4) / 70.9 (7.3) Alkaline phosphatase (U/L) 303 (109) / 216 (79) Creatinine (mmol/L) 70 (12) / 66 (13) <u>F-t-M (n=41):</u> Height (cm) 161.4 (8.4) / 163.5 (7.9) Weight (kg) 55.1 (14.7) / 59.5 (14.4) BMI (kg/m <sup>2</sup> ) 21.0 (4.5) / 22.1 (4.6) Lean body mass (%) 71.5 (6.7) / 67.7 (6.7) Alkaline phosphatase (U/L) 215 (101) / 168 (58) Creatinine (mmol/L) 73 (8) / 68 (13)



<b>Author, Year (ref)</b> Title	<b>Klaver et al. 2018 (17)</b> <i>Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents</i>
Country Study design	The Netherlands Retrospective cohort study of medical records, before-after, 1998–2014
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of GnRH: Min age: 12 years Min Tanner B2 (girls) Min Tanner G3 (boys) 14.5 ± 1.8 years transwomen 15.3 ± 2.0 years transmen  Age at start of CSHT: Min age 16 years 16.4 ± 1.1 years transwomen 16.9 ± 0.9 years transmen
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	192 71 transwomen (MtF) (birth-assigned boys) 121 transmen (FtM) (birth-assigned girls)
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH: 3.75 mg for 4 weeks until gonadectomy Cross-sex hormonal treatment (CSHT): 17 $\beta$ -estradiol oral (5 mg/kg/day, increased by 5 mg/kg/day every 6 months until 2 mg/day) mixed testosterone esters i.m. (25 mg/m <sup>2</sup> / 2 weeks, increased by 25 mg/m <sup>2</sup> every 6 months until 250 mg/m <sup>2</sup> /3-to 4 weeks) Surgery: Gonadectomy  Study intervention: Whole-body dual-energy x-ray absorptiometry
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRH duration: until gonadectomy, at earliest age 18  Follow-up time: <i>GnRH monotherapy:</i> 2.1 years (1.0–2.8) transwomen (M-t-F) 1.0 years (0.5–2.9) transmen (F-t-M) <i>GnRH + CSHT:</i> 3.1 years (2.5–3.6) transwomen (M-t-F) 2.4 years (2.0–3.1) transmen (F-t-M) <i>CSHT monotherapy:</i> 2.8 years (1.6–3.4) transwomen (M-t-F) 3.0 years (1.9–3.4) transmen (F-t-M)  Follow-up age: 22 years
<b>OUTCOMES -</b> All reported outcomes	Body weight, BMI Waist circumference (cm), Hip circumference Change in waist-hip ratio (WHR) total body fat (TBF), android (%), gynoid (%) total lean body mass (LBM)
<b>RESULTS</b> Extracted outcomes	<b>At start of GnRH (<math>\pm</math>4months) / at start of CSHT (<math>\pm</math>4months) / at age 22 (<math>\pm</math>1.5 years)</b>  <u>Transwomen (MtF):</u> Body weight (kg) 58 (56–61) / 66 (63–69) / 76 (71–82) BMI (kg/m <sup>2</sup> ) 20.2 (19.4–20.9) / 21.3 (20.5–22.0) / 23.2 (21.6–24.8) WHR 0.81 (0.79–0.82) / 0.79 (0.78–0.80) / 0.77 (0.75–0.79) LBM (%) 75 (74–77) / 69 (68–71) / 66 (64–68)  <u>Transmen (FtM):</u> Body weight (kg) 58 (56–61) / 63 (60–65) / 69 (66–71) BMI (kg/m <sup>2</sup> ) 21.6 (20.9–22.3) / 22.5 (21.7–23.2) / 23.9 (23.0–24.7) WHR 0.77 (0.76–0.78) / 0.76 (0.75–0.77) / 0.80 (0.78–0.82) LBM (%) 70 (69–71) / 67 (66–68) / 73 (72–74)

<b>Author, Year (ref)</b> Title	<b>Klaver et al. 2020 (18)</b> <i>Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents</i>
Country Study design	The Netherlands Retrospective cohort study, before after, 1998–2015
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	At min age 12 years Tanner B2 (girls) Tanner G3 (boys)  Age at start of GnRHa (mean (SD)): 14.6 years (1.8) transwomen 15.2 years (2.0) transmen Age at start of CSHT: (mean (SD)): 16.4 years (1.1) transwomen 16.9 years (0.9) transmen
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	192 71 transwomen (M-t-F) 121 transmen (F-t-M)
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH: 3.75 mg/4 weeks s.c. Cross sex hormonal treatment (CSHT): (from age 16 years): 17-b estradiol (E2) oral (5 µg/kg/day, increased every 6 months until 2 mg/day) mixed testosterone esters i.m. (25 mg/m <sup>2</sup> /2 weeks, increased every 6 months until 250 mg/3–4 weeks.  When GnRHs were started after age 16: Cross-sex hormones added: after 3 to 6 months: start dose 1 mg E2 daily or 75 mg of testosterone esters i.m weekly after 6 months: 2 mg E2 daily or 250 mg of testosterone esters /3–4 weeks
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRHa monotherapy duration (median (IQR)): 2.1 (1.0–2.7) transwomen 1.0 (0.5–2.9) transmen GnRHa + CSHT duration (median (IQR)): 3.1 (2.5–3.6) transwomen 2.3 (1.8–2.8) transmen CSHT monotherapy duration (median (IQR)): 2.2 (1.1–3.1) transwomen 2.9 (1.7–3.4) transmen  Follow-up age: 22 years: Range 20.5–23.5 years
<b>OUTCOMES -</b> All reported outcomes	Changes in body mass index (BMI) systolic blood pressure (SBP) diastolic blood pressure (DBP) glucose homeostatic model assessment for insulin resistance (HOMA-IR) lipid values prevalence of obesity dyslipidaemia

RESULTS Extracted outcomes	At start of GnRH / at 22 years/ change during GnRH / change between start of CSHT and age 22 (mean (95% CI))
	<u>Transwomen (n=71):</u>
	BMI 20.2 (19.4 to 20.9) / 23.2 (21.6 to 24.8) / +1.1 (0.7 to 1.5) / +1.9 (0.6 to 3.2)
	SBP (mmHg) 120 (116 to 123) / 117 (113 to 122) / +1 (-3 to 5) / -3 (-8 to 2)
	DBP (mmHg) 65 (63 to 67) / 75 (72 to 78) / +4 (1 to 7) / +6 (3 to 10)
	Glucose (mmol/L) 5.0 (4.8 to 5.2) / 5.0 (4.8 to 5.1) / -0.1 (-0.3 to 0.1) / +0.1 (-0.1 to 0.2)
	Insulin (mU/L) 9.5 (6.7 to 12.2) / 13.0 (8.4 to 17.6) / +0.8 (-2.5 to 4.1) / +2.7 (-1.7 to 7.1)
	HOMA-IR 2.3 (1.2 to 3.4) / 2.9 (1.9 to 3.9) / 0.0 (-1.2 to 1.2) / +0.7 (-0.2 to 1.5)
	Total cholesterol (mmol/L) 3.7 (3.5 to 3.9) / 4.1 (3.8 to 4.4) / 0.3 (0.2 to 0.5) / 0.1 (20.2 to 0.4)
	HDL cholesterol (mmol/L) 1.4 (1.3 to 1.5) / 1.6 (1.4 to 1.7) / +0.2 (0.1 to 0.3) / 0.0 (-0.1 to 0.2)
	LDL cholesterol mmol/L 1.9 (1.7 to 2.1) / 2.0 (1.8 to 2.3) / +0.2 (0.0 to 0.3) / 0.0 (-0.3 to 0.2)
	Triglycerides (mmol/L) 0.8 (0.7 to 0.9) / 1.1 (0.9 to 1.4) / +0.1 (-0.1 to 0.2) / +0.2 (0.0 to 0.5)
	<u>Transmen (n=121):</u>
	BMI 21.6 (20.9 to 22.3) / 23.9 (23.0 to 24.7) / +0.9 (0.5 to 1.3) / +1.4 (0.8 to 2.0)
	SBP (mmHg) 120 (118 to 122) / 126 (122 to 130) / +2 (-1 to 4) / +5 (1 to 9)
	DBP (mmHg) 67 (66 to 69) / 74 (72 to 77) / +1 (-1 to 3) / +6 (4 to 9)
	Glucose (mmol/L) 4.8 (4.7 to 4.9) / 4.8 (4.7 to 5.0) / +0.1 (-0.1 to 0.2) / 0.0 (-0.2 to 0.2)
	Insulin (mU/L) 9.5 (8.0 to 11.0) / 8.6 (6.9 to 10.2) / +1.2 (-0.6 to 3.0) / -2.1 (-3.9 to -0.3)
	HOMA-IR 2.1 (1.6 to 2.5) / 1.8 (1.4 to 2.2) / +0.3 (-0.2 to 0.8) / -0.5 (-1.0 to -0.1)
	Total cholesterol (mmol/L) 3.9 (3.7 to 4.0) / 4.6 (4.3 to 4.8) / +0.3 (0.2 to 0.4) / +0.4 (0.2 to 0.6)
	HDL cholesterol (mmol/L) 1.5 (1.4 to 1.5) / 1.3 (1.2 to 1.3) / +0.1 (0.1 to 0.2) / -0.3 (-0.4 to -0.2)
	LDL cholesterol (mmol/L) 2.1 (1.9 to 2.2) / 2.6 (2.4 to 2.8) / +0.2 (0.1 to 0.3) / +0.4 (0.2 to 0.6)
	Triglycerides (mmol/L) 0.8 (0.7 to 0.8) / 1.3 (1.1 to 1.5) / 0.0 (0.0 to 0.1) / +0.5 (0.3 to 0.7)
	<b>Obesity prevalence (at age 22):</b>
	BMI ≥30 in both sexes
	9.9% in transwomen (M-t-F)
	6.6% in transmen (F-f-M)
	2.2% in ciswomen (females)
	3.0% in cismen (males)

<b>Author, Year (ref)</b>	<b>Perl et al 2020 (19)</b>
Title	<i>Blood Pressure Dynamics After Pubertal Suppression with Gonadotropin-Releasing Hormone Analogs Followed by Testosterone Treatment in Transgender Male Adolescents: A Pilot Study</i>
Country	Israel
Study design	Retrospective pilot study, 2013 - 2018
<b>POPULATION (ages)</b>	Age at start of GnRH: 14.4 ± 1.0 years
Age at Tx start	14.4 ± 1.0 years
Age in cohort	Tanner stage 4/5
Tanner stage	Age at start of testosterone: 15.1 ± 0.9
<b>POPULATION (n)</b>	48 transgender male adolescents
n patients	15 included
natal male (M-t-F)	15 GnRH
natal female (F-t-M)	subsequently were 9 treated with testosterone
<b>INTERVENTION (type)</b>	Previous intervention:
Puberty suppression (GnRH)	GnRHa D-Trp-6-LHRH depot (3.75mg/4 weeks intramuscular injection)
Cross-sex hormone treatment (CSHT)	CSHT: (patients who reached ≥14 years of age) testosterone enanthate intramuscular injection (250 mg/mL), starting dose of 50–100 mg /4 weeks.  Medical nutrition counseling, not further specified. Psychosocial support , not further specified
<b>INTERVENTION (time)</b>	GnRHa duration:
Treatment duration	3 ± 1 months.
Follow-up time,	Testosterone duration:
Follow-up age	4 ± 2 months
<b>OUTCOMES -</b>	BMI
All reported outcomes	BP (procedure for measurement not given) luteinizing hormone (LH) follicle-stimulating hormone (FSH) estradiol testosterone
<b>RESULTS</b>	Anthropometric
Extracted outcomes	(before GnRH; after GnRH; before testosterone; after testosterone) mean – SD  BMI (kg/m2), mean ± SD 21.3 ± 4.7 ; 22.0 ± 4.8 ; 23.3 ± 5.6 ; 24.2 ± 4.6 BMI-SDS did not increase significantly during GnRHa therapy.  Diastolic BP percentiles: mean ± SD 56% ± 26 ; 74% ± 9.0 ; 74% ± 9.0 ; 56% ± 17 DBP percentiles increased significantly after GnRHa treatment and remained significant after adjusting for the change in BMI-SDS. DBP percentile decreased after adding testosterone. BP levels did not meet criteria for hypertension.  Systolic BP percentiles: mean ± SD 71% – 19 ; 76% – 14 ; 76% – 14 ; 72% – 21 BP levels within the normal range and did not meet criteria for pediatric hypertension.

<b>Author, Year (ref)</b> Title Country Study design	<b>Schulmeister et al. 2021 (20)</b> <i>Growth in Transgender / Gender-Diverse Youth in the First Year of Treatment with Gonadotropin-Releasing Hormone Agonists</i> USA Multisite prospective observational study, 2016 - 2018
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at GnRHa start (mean (range)): 11.5 years (9.0-14.5) total 11.9 years (10.2-14.5) male at birth 11.1 years (9.0-13.9) female at birth  Comparison group: 11.0 ± 2.8 years, Tanner I  Tanner stage at GnRHa start (n (%)): Tanner II 34 (62%) total; 21 (81%) male at birth; 13 (45%), female at birth Tanner III 16 (29%) total; 3 (12%) male at birth; 13 (45%) female at birth Tanner IV 5 (9%) total; 2 (8%) male at birth; 3 (10%) female at birth
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	92 enrolled 55 in cohort 26 male at birth 29 female at birth Comparison group: 226 participants: 118 males 108 female Prepubertal, presumed cisgender youth not receiving hormonal intervention from the <i>Bone Mineral Density in Childhood Study (BMDCS)</i> (Age-based reference ranges for annual height velocity in US children. Kelly, Winer, Kalkwarf, Oberfield, Lappe, Gilsanz, Zemel; J Clin Endocrinol Metab 2014 Jun; 99(6): 2104-12).  Exclusions: Serious psychiatric symptoms.
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH: Drug, dose and frequency not reported.  Full description of study protocol published in [Olson-Kennedy J, Chan YM, Garofalo R, et al. Impact of early medical treatment for transgender youth: Protocol for the longitudinal, observational trans youth care study. J Med Internet Res 2019; 21: e14434]
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Duration: GnRHa: min 10 months max 14 months.  FU time: Prior to beginning GnRHa (baseline), 6- and 12-month follow-up visits.
<b>OUTCOMES -</b> All reported outcomes	HV (height velocity) BMI FSH (follicle-stimulating hormone) LH (luteinizing hormone) estradiol testosterone

<p><b>RESULTS</b></p> <p>Extracted outcomes</p>	<p>Height velocity (HV) in the first year of GnRHa use:  5.1 (3.7-5.6) cm/year (median (IQR)).  Later Tanner stage at GnRHa initiation was associated with lower HV:  5.3 (4.4-5.6) cm/year for Tanner stage II  4.4 (3.3-6.0) cm/year for Tanner stage III  1.6 (1.5-2.9) cm/year for Tanner stage IV</p> <p>Height velocity by Tanner stage at baseline ((cm/year) median (IQR))  (total; designated male at birth; designated female at birth)  Tanner stage II 5.3 (4.4-5.6) total; 5.6 (4.7-5.7) male at birth; 5.0 (4.2-5.4) female at birth  Tanner stage III 4.4 (3.3-6.0) total; 4.2 (2.3-6.4) male at birth; 4.4 (4.0-5.5) female at birth  Tanner stage IV 1.6 (1.5-2.9) total; 1.5 (1.4-1.6) male at birth; 2.9 (1.5-3.5) female at birth</p> <p>BMI z-score (mean (SD))  (total; designated male at birth; designated female at birth)  Baseline visit 0.46 (0.89) total; 0.56 (0.84) male at birth; 0.38 (0.94) female at birth  12-month visit 0.66 (0.97) total; 0.68 (1.00) male at birth; 0.63 (0.95) female at birth</p> <p>When controlled for age, there was not a significant difference in mean height velocity between transgender youth and prepubertal youth (comparison group);</p>
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<b>Author, Year (ref)</b> Title Country Study design	<b>Nokoff et al 2020 (21)</b> <i>Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth</i> USA Cross-sectional study, controlled, 2016-2019
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of GnRH (mean $\pm$ SD): 12.1 $\pm$ 1.9 years transgender males 12.8 $\pm$ 1.3 years transgender females Age in cohort (mean $\pm$ SD): 13.8 $\pm$ 1.7 years (range 10.1–16.0) transgender males 13.7 $\pm$ 1.2 years (range 12.6–16.1) transgender females  Comparator groups: 10.6–16.2 years cisgender females 12.5–15.5 years cisgender males
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	17 youth 9 transgender males on GnRH 8 transgender females on GnRH  Comparator groups: 31 youth 14 cisgender females 17 cisgender males  Exclusions: Significant medical or psychiatric comorbidities (incl. diabetes or antipsychotic treatment)
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	GnRH: Drug, dose and frequency not reported.
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	GnRH duration (mean $\pm$ SD): 20.9 $\pm$ 19.8 months transgender males (range 17.5-70.4 months) 11.3 $\pm$ 7 months transgender females (range 4.7-24.2 months)
<b>OUTCOMES -</b> All reported outcomes	insulin sensitivity and body composition insulin sensitivity (1/ (fasting insulin), homeostatic model of insulin resistance [HOMA-IR]), glycemia (hemoglobin A1C (HbA1c), fasting glucose), BMI, body mass index BP, blood pressure AST, aspartate aminotransferase ALT, alanine aminotransferase HDL, high-density lipoprotein LDL, low-density lipoprotein SHBG, sex hormone-binding globulin LH, luteinizing hormone FSH, follicle stimulating hormone estradiol testosterone
<b>RESULTS</b> Extracted outcomes	Transgender males vs cisgender females: 1/fasting insulin (0,067 $\pm$ 0,02 vs 0,103 $\pm$ 0,049 mL/ $\mu$ U) HOMA-IR (3,7 $\pm$ 1,7 vs 2,3 $\pm$ 1,1) fasting glucose (89 $\pm$ 4 vs 79 $\pm$ 13 mg/dL) HbA1c (5.4 $\pm$ 0.2 vs. 5.2 $\pm$ 0.2%) percent body fat (36 $\pm$ 7 vs 32 $\pm$ 5%)  Transgender females vs cisgender males: 1/fasting insulin (0,076 $\pm$ 0,029 vs 0,135 $\pm$ 0,049 mL/ $\mu$ U) HOMA-IR (3,5 $\pm$ 1,4 vs 2,2 $\pm$ 1,3) HbA1c (5.4 $\pm$ 0.1% vs 5.1 $\pm$ 0.2%) percent body fat (31 $\pm$ 9 vs 24 $\pm$ 10%) lower percent lean mass (66 $\pm$ 8 vs 74 $\pm$ 10%)

**Table 4** Effects of cross-sex hormonal treatment started before age of 18 years without previous puberty suppression

<b>Author, Year (ref)</b> Title	<b>Tack et al 2016 (22)</b> <i>Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis.</i>
Country	Belgium
Study design	Retrospective cohort study, 2010–2015
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of lynestrenol: Min Tanner B4 (post menarche) 15 years and 10 months (mean)  Age at start of testosterone: 17 years and 5 months (mean)
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	45 initials 43 in cohort (F-t-M)  Of 45 subjects: 25 testosterone added later 11 psychiatric comorbidities (unspecified) 1 suicide during follow-up 1 did not consent use of data
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	Hormone treatment: Androgenic progestin: lynestrenol (L) (Orgametril®) monotherapy: dose not reported Testosterone esters (Sustanon®): added from age 16: start at 50 mg (16 years) or 100 mg (17–19 years)/ 2 weeks (injection); incremental increases (+25 mg) up to 125 mg/2 weeks, up to 18 months. Vitamin D and calcium supplements  Psychiatric intervention: During treatment, patients seen every 3 months by the team child psychologist. In the absence of psychiatric comorbidity, evaluated twice by the team child psychiatrist during this phase; once before initiation of lynestrenol and once more at start of lynesterol + testosterone.
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Treatment duration: (min 6 months, up to 18 months) Mean 12.6 months Lynestrenol (L) Mean 11.4 months Lynestrenol (L) + testosterone esters (T):
<b>OUTCOMES -</b> All reported outcomes	Anthropometry Safety parameters, side effects Biochemical analysis: complete blood count, electrolytes, liver, and renal function, fasting glucose, insulin, lipid metabolism Hormone levels: Thyroid stimulating hormone (TSH), free thyroxin (ft4), luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol (E2), total and free testosterone (T and free T), sex hormone-binding globulin (SHBG), anti-Müllerian hormone (AMH)
<b>RESULTS</b> Extracted outcomes	<b>At start of lynestrenol / at 12 months of L / at start of testosterone / at 12 months of T</b>  Mean height    164.6 / -- / -- / 167.6 / -- Weight         61.48 / 61.03 / 58.65 / 65.10 BMI             22.58 / 22.39 / 20.69 / 23.26 Triglycerides (mmol/L)    0.838 / 0.661 / 0.651 / 1.394 Total cholesterol (mmol/l) 4.153 / 4.237 / 4.212 / 4.450 HDL (mmol/l)         1.481 / 1.017 / 1.098 / 1.085  Side effects: Metrorrhagia: in L+T long term Acne:            in L no increase, in L+T significant increase Headaches:    in L Hot flushes:    in L Fatigue:        in L+T



<b>Author, Year (ref)</b> Title	<b>Jarin et al 2017 (23)</b> <i>Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria</i>
Country	USA
Study design	Retrospective, cohort study, 2008-2014
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age in cohort: Range: 13 – 25 years Affirmed male: mean 16 years range 13 - 22 Affirmed female: mean 18 years range 14 - 25
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	161 adolescents: 72 affirmed males (FtM) 44 affirmed females (MtF) 7 affirmed males on GnRH before treatment 2 affirmed females on GnRH before treatment 2 affirmed males reported hormone use outside medical practice (street hormones) 5 affirmed females reported exogenous street hormone use.  Comorbidities: 35 depression 11 anxiety 8 ADHD 10 HIV
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	CSHT: Testosterone (s.c.): 25 mg/ week, weekly doses of 25, 50, or 100 mg at subsequent visits. Oestrogen ( ± testosterone blocker spironolactone): orally at 1, 2, 3, 4, 6, and 8 mg daily; or intramuscularly at 20, 40, or 80 mg monthly; or trans dermally at 0.025, 0.05, 0.100, or 0.200 mg weekly
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Follow-up time: Up to 35 months. Follow-up groups: 1 to 3 months after initiation 4 to 6 months after initiation 6 months and beyond
<b>OUTCOMES - All reported outcomes</b>	Body mass index (BMI) Systolic blood pressure (SBP), Diastolic blood pressure (DBP) Hematokrit, Haemoglobin Total testosterone Estradiol Total cholesterol, Low density lipoprotein (LDL), High density lipoprotein (HDL), Triglycerides (TG) TG : HDL ratio Creatinine Prolactin Aspartate aminotransferase, (AST), Alanine aminotransferase (ALT) HbA1c
<b>RESULTS</b> Extracted outcomes	<u>Affirmed male (FtM):</u> BMI: increased at 6 months (from 26.0 to 27.3) DBP: reduced at 6 months (from 71 to 67 mm Hg) Hematokrit: increased at 6 months (from 39.4% to 44.5%) 2 subjects had supraphysiologic hematokrit levels (>50%) after 3 months of treatment, 1 subject maintained elevated hematokrit levels after 6 and 9 months (51.0% and 52.7%) Haemoglobin: increased at 6 months. Cholesterol: nonsignificant increase at 6 months (nonsignificant), plateau after 3 months. (6 subjects had cholesterol levels >200 mg/dL). LDL: nonsignificant increase at 6 months, plateau after 3 months. HDL: level decreased at 6 months (from of 50.2 to 45.0 mg/dL).  <u>Affirmed female (MtF):</u> No significant changes in any other parameter tested were found. No statistically significant difference in measured metabolic parameters among the various methods of oestrogen administration (patch, oral, or intramuscular).

<b>Author, Year (ref)</b> Title	<b>Mullins et al 2021 (24)</b> <i>Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy.</i>
Country	USA
Study design	Retrospective chart review, 2013 - 2019
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of CSHT: range 13 - 24 years 17 years (IQR 15–19) total cohort 18 years (IQR 15.5–20) estrogen 17 years (IQR 15–19) testosterone
<b>POPULATION (n)</b> n patients natal male (M-t-F) natal female (F-t-M)	611 participants 428 female at birth 183 male at birth
<b>INTERVENTION (type)</b> Puberty suppression (GnRH) Cross-sex hormone treatment (CSHT)	Estrogen: 4.0 mg (2.0–6.0mg): oral (90.7%), transdermal (5.5%), intramuscular (3.8%) Testosterone: 70.0 mg (60.0–80.0) s.c (72.7%), i.m. (24.4%), gel (2.8%), transdermal (0.7%) Previous hormones used (%): Norethindrone contraceptive pill (24.2%) Depo-medroxyprogesterone acetate (18.5%) Combined oral contraceptive pill (5.7%) Norethindrone acetate (2.5%) LNG-IUS (2.5%) Etonogestrel implant (0.3%)
<b>INTERVENTION (time)</b> Treatment duration Follow-up time, Follow-up age	Treatment duration, days (median, IQR): 554 days (283.0–1037.5) estrogen 577 days (283.0–923.0) testosterone
<b>OUTCOMES -</b> All reported outcomes	Incidence of arterial or venous thrombosis during GAHT Prevalence of thrombosis risk factors, risk factors for thrombosis (migraine with aura, elevated BMI, tobacco use, medical diagnoses associated with increased risk of thrombosis, family history of thrombosis (arterial or venous) and laboratory measures of risk factors for thrombosis) testosterone and estradiol levels complete blood counts coagulation testing result thrombophilia evaluation arterial or venous thrombosis therapeutic anticoagulation treatment prophylactic anticoagulation treatment concurrent with CSHT duration of anticoagulation treatment
<b>RESULTS</b> Extracted outcomes	<u>Hematologic Evaluation and Incidence of Thrombosis</u> 17 (2.8%) referred to haematology Thrombophilia evaluation: 4 (23.5%) elevated factor VIII (>150%) 10 (2.0%) erythrocytosis (>17.7 g/dL) 1 (6.3%) activated protein C resistance ratio (<0.78) 5 (31.3%) PAI-1 (<16.3 IU/mL) 2 (11.8%) Factor V Leiden heterozygous 2 (12.5%) prothrombin G20210A heterozygous 3 (21.4%) MTHFR 677 homozygous 5 (35.7%) PAI-1 4G homozygous 2 (20.0%) elevated homocysteine (>10.7 µmol/L) Thromboprophylaxis before GAHT: 5 (0.8%) Overall cohort 2 (0.3%) History of thrombosis before GAHT 3 (0.5%) No history of thrombosis before GAHT 0 Thrombosis on GAHT Multiple thrombotic risk factors were noted among the cohort, including obesity, tobacco use, and personal and family history of thrombosis.  BMI median IQR: 26.0 (22.1–32.0) 40 (6.5%) BMI <18.5 212 (34.7%) BMI 18.5–25 148 (24.2%) BMI 25–30 211 (34.5%) BMI >30

**Table 5.** Studies investigating discontinuation of treatment and regret in adolescents with gender dysphoria

Author, Year Country	Inclusion period	Population	Treatment	Follow-up method	Follow-up time	Regret
Pullen Sansfaçon et al 2019 (25) Canada	November 2017 – August 2018	35 trans and gender diverse young people aged 9 to 17 years	Puberty blockers, hormone therapy, surgery	Semi-structured interviews	Follow-up-time not reported	0/35
Segev-Becker et al 2020 (26) Israel	March 2013 – January 2019	106 (10 prepubertal) consecutive children and adolescents with gender dysphoria, aged <18 years	77 (80%) pubertal patients began GnRH. 61 of these (83%) started gender affirming treatment	Chart review	Median 1.2 years (range, 0 to 5.1 years)	2/96 (pubertal at start) 16/77 (21%) on GnRH did not start gender affirming treatment
Cohen-Kettenis et al 1997 (27) The Netherlands	Time period not given	22 patients (15 FtM, 7 MtF) Mean age at pretest: 17.5 years (range 15-20) Mean age at follow-up: 22.0 years (range 19-27) Post-treatment sample: 14 FtM, 5 MtF	Surgically reassigned (various procedures)	Questionnaires and interview	1 year or more	0/19
Olson-Kennedy et al 2018 (28) USA	June – December 2016	68 FtM undergoing chest surgery Mean age 18.9 (SD 2.5) (range 14–25)	Chest surgery	Chest dysphoria score,	1–5 years after surgery	1/68
Smith et al 2001 (29) The Netherlands	Not given Follow-up interviews from March 1995 until July 1999	Prospective 20 treated adolescent transsexuals Mean age at pretest 16.6 years (range 15–19) Mean age at follow-up 21.0 years (range 19–23)	Surgical reassignment Not specified	Semi-structured interview	1–4 years post-surgery	0/20
Mehringer et al 2021 (30) USA	Not given	30 transmasculine 13 to 21 years mean age 17.5 (14-21)  14 had undergone chest surgery. Mean age 16.4 years	Chest surgery/ dysphoria	Interview transcripts coded employing modified grounded theory	19 (6–48) months after surgery	0/14 All post-surgery youth reported near or total resolution of chest dysphoria, lack of regret, improved quality of life and functioning
Nieder et al 2021 (31) Germany	Sept 2013 – June 2017	75  11-21 years	Varying, hormones, various surgery	Clinical follow-up	2 years	0/75
Carmichael et al 2021 (5) The UK	April 2011 – April 2014	44 25 trans women 19 trans male 11-15 years	GnRH	Clinical follow-up	Median 31 months	No data on regret 1/44 did not start gender affirming treatment
Littman 2021 (32) USA	Dec 2016 – April 2017	100 detransitioners, mean age at detransition 26 years Mean age at transition 22 years	Varying gender affirming treatments	Open survey over Internet		

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