



### Bilaga 3 Tabellverk över inkluderade studier/ Appendix 3 Characteristics of included studies

#### Innehåll

Table 1 Effects on psychosocial factors and cognition by sex hormone suppression in adolescents.....	2
Table 2 Effects on bone health by sex hormone suppression in adolescents.....	13
Table 3 Effects on anthropometric measures and metabolism by sex hormone suppression in adolescents.....	26
Table 4 Effects of gender confirming hormonal treatment started before age of 18 years without previous puberty suppression.....	34
Table 5. Studies investigating regret and discontinuation of treatment in adolescents with gender dysphoria.....	38
References.....	39

**Table 1 Effects on psychosocial factors and cognition by sex hormone suppression in adolescents**

<b>Author</b>	De Vries et al (1)
<b>Year</b>	2014
<b>Country</b>	The Netherlands
<b>Study design</b>	Longitudinal cohort study, before-after 2008-2012
<b>POPULATION (ages)</b>	At baseline 13.6 years
<b>Age at Tx start</b>	At start of puberty suppression 14.8 years
<b>Age in cohort</b>	At start of cross-sex hormones: 16.7 years
<b>Tanner stage</b>	Age ≥ 1 year after gender reassignment surgery: 20.7 years
<b>POPULATION (n)</b>	196 consecutively referred
<b>n patients</b>	111 prescribed puberty suppression
<b>natal male (M-t-F)</b>	55 individuals evaluated (22 transwomen and 33 transmen)
<b>natal female (F-t-M)</b>	
<b>INTERVENTION (type)</b>	Puberty suppression (GnRH)
<b>Puberty suppression (GnRH)</b>	Cross-sex hormone treatment (CSHT)
<b>Cross-sex hormone treatment (CSHT)</b>	Gender reassignment surgery: Not specified
<b>INTERVENTION (time)</b>	GnRH duration: Not specified
<b>Hormone treatment duration</b>	CSHT duration: Not specified
<b>FU time, FU age</b>	
<b>OUTCOMES - All reported outcomes</b>	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)
<b>RESULTS</b>	Before start/ During puberty suppression/ After gender reassignment (mean (SD))
<b>Extracted outcomes</b>	Gender dysphoria (UGDS) 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)  Global functioning (CGAS) 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)  Depression (BDI) 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) Anger (TPI)

	<p>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)</p> <p>Anxiety (STAI)  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)</p>
--	--

<b>Author</b>	<b>Costa et al 2015 (2)</b>
<b>Year</b>	The UK
<b>Country</b>	
<b>Study design</b>	Longitudinal cohort study, before-after 2010-2014
<b>POPULATION (ages)</b>	Age at baseline: Range 12-17 years
<b>Age at Tx start</b>	
<b>Age in cohort</b>	15.6 years (SD 1.7) natal male 15.4 years (SD 1.2) natal female
<b>Tanner stage</b>	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
<b>n patients</b>	201 completed diagnostic procedure
<b>natal male (M-t-F)</b>	1: 1.6 natal male/natal female ratio
<b>natal female (F-t-M)</b>	"Immediate eligible": 101 GnRH treated 35 evaluated at end of study "Delayed eligible": 100 GnRH untreated 36 evaluated at end of study
<b>INTERVENTION (type)</b>	GnRH: Drug, dose and treatment frequency not indicated. Start after 6 months of psychological assessment and support (mean 0.75 + 0.6 years), referred as "diagnostic procedure".
<b>Puberty suppression (GnRH)</b>	Psychotherapeutic interventions: "Individual or family or group therapy, carried out on a regular basis (at least one a month)"
<b>Cross-sex hormone treatment (CSHT)</b>	
<b>INTERVENTION (time)</b>	GnRH duration: 12 months
<b>Hormone treatment duration</b>	Psychological support: 18 months total
<b>FU time, FU age</b>	FU time: 6 months, 12 months, 18 months
<b>OUTCOMES - All reported outcomes</b>	Psychosocial functioning: Children's Global Assessment Scale (CGAS), (high score=better psychosocial functioning).

<b>RESULTS</b> <b>Extracted outcomes</b>	<p><b>Psychosocial functioning:</b> Children's Global Assessment Scale score:</p> <p>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</p> <p>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)</p> <p>Delayed group: (n= 100 at baseline) 60.3 after 6 months psychological support only 62.5 after 18 months (n= 36)</p>
---	---

<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	<p><b>Becker-Hebly et al (3)</b> <b>2020</b></p> <p>Germany Retrospective cohort study, before-after</p>
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	<p>Age at baseline (intake): Minimum 11 years Mean 15.5 years (SD 1.2) Range 11.2 - 18.0 years</p> <p>Age at Follow-up: Mean 17.4 years (SD 1.7) Range 11.95 - 21.0 years</p>
<b>POPULATION (n)</b> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	<p>434 adolescents 164 dropouts at baseline 129 dropouts during follow-up</p> <p>75 evaluated 64 natal female 11 natal male</p> <p>21 no hormone 11 GnRH 32 GnRH + CSHT 11 CSHT + surgery (type not specified)</p> <p>Excluded severe psychiatric problems (psychosis, suicidality)</p>
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<p>Previous intervention: Drug, dose and treatment frequency not indicated.</p> <p>No hormone treatment (no GnRH, no CSHT) GnRH GnRH + CSHT CSHT + surgery (surgery type not specified, "mainly mastectomy")</p> <p>Psychotherapy (79%)</p>

<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	Duration of GnRH or CSHT: not specified. Possible range 7-49 months, "time since first referral"  GnRH: minimum 7 months CSHT: up to 40 or 47 months  FU time: Mean 214 (SD 12.2) months Range 6 months - 4 years
<b>OUTCOMES - All reported outcomes</b>	<b>Psychological functioning:</b> Children's Global Assessment Scale (CGAS, clinician-rated) (higher scores (> 80) indicating good global functioning)  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> <b>Extracted outcomes</b>	<b>Psychosocial functioning</b>  <b>CGAS Global functioning</b> Baseline/ Follow-up (mean (SD))  No medical treatment (diagnostics or psychosocial interventions) 68.10 (11.23)/ 70.00 (12.25)  Puberty suppression (GnRH) 67.27 (11.91)/ 81.82 (7.51)  GA hormones (GnRH and GAH) 73.13 (10.91)/ 85.63 (9.14)  GA surgery (at least one operation and GAH) 66.36 (14.33)/ 83.64 (8.09)  <b>Health-related quality of life mean ± SD</b> Baseline T Mental dimension/T Physical dimension  No medical treatment (diagnostics of psychosocial interventions) 34.86 (6.27)/ 37.51 (8.27)  Puberty suppression (GnRH) 39.04 (9.25)/ 43.43 (8.61)  GA hormones (GAH and GnRH) 36.16 (6.78)/ 39.12 (7.10)  GA surgery (at least one operation and GAH) 37.88 (6.53)/ 39.88 (8.49)  Follow-up T Mental dimension/T Physical dimension  No medical treatment (diagnostics or psychosocial interventions) 36.37 (7.71)/ 42.51 (10.40)  Puberty suppression (GnRH) 43.17 (10.20)/ 49.57 (11.64)

	GA hormones (GAH and GnRH) 42.07 (10.74)/ 49.36 (9.81)
	GA surgery (at least one operation and GAH) 43.44 (9.57)/ 53.87 (6.15)

<b>Author</b>	<b>Cantu et al (4)</b>
<b>Year</b>	<b>2020</b>
<b>Country</b>	USA
<b>Study design</b>	Retrospective cohort study chart review, before-after 2017 - 2019
<b>POPULATION (ages)</b>	Age at start: Min 11 years Max 18 years
<b>Age at Tx start</b>	
<b>Age in cohort</b>	Age in cohort: Mean 15.1 years (SD 1.8)
<b>Tanner stage</b>	
<b>POPULATION (n)</b>	80
<b>n patients</b>	15 female affirmed*
<b>natal male (M-t-F)</b>	58 male affirmed*
<b>natal female (F-t-M)</b>	7 nonbinary
	In Follow-up cohort: 13 hormone blockers 25 hormone treatment (HT) 4 hormone blockers + HT 38 no treatment
<b>INTERVENTION (type)</b>	Previous intervention: Drug, dose and treatment frequency not indicated.
<b>Puberty suppression (GnRH)</b>	Hormone blockers only
<b>Cross-sex hormone treatment (CSHT)</b>	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>	Duration of GnRH or CSHT: Not specified.
<b>Hormone treatment duration</b>	FU time: Time between initial visit and follow-up appointment: Mean 4.7 months Range < 1 - 11 months
<b>FU time, FU age</b>	
<b>OUTCOMES - All reported outcomes</b>	Depression: assessed with PHQ-9 (Patient Health Questionnaire-9)
	Anxiety: assessed with GAD-7 (Generalized Anxiety Disorder-7)

<b>RESULTS</b> <b>Extracted outcomes</b>	<b>Psychosocial functioning</b> Acute distress (not defined) 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)  “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</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	<b>Carmichael et al (5)</b> 2021 The UK Prospective cohort
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	12-15 years followed to end of GnRH therapy Median age at consent was 13.6 years (IQR 12.8 to 14.6, range 12.0 to 15.3). A total of 25 (57%) were birth-registered as male and 19 (43%) as female. Median age (years) at end of pathway (IQR) 16.1 (16.0, 16.4)
<b>POPULATION (n)</b> <b>n patients</b> natal male (M-t-F), natal female (F-t-M)	44 people recruited April 2011 and April 2014. 25 birth registered males and 19 females.  Tanner stage birth registered males, females, n (%) Stage 2: 0, 0 Stage 3: 17 (68), 2 (10) Stage 4: 5 (20) 11, (58) Stage 5: 3 (12), 6 (32)
<b>INTERVENTION (type)</b> Puberty suppression (GnRHa) Cross-sex hormone treatment (CSHT)	GnRHa triptorelin together with psychosocial support and therapy. Treatment period June 2011 and April 2015.  Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. In addition, local psychological services provided support for co-occurring difficulties for participants as required.
<b>INTERVENTION (time)</b> Hormone treatment HT duration FU time, FU age	44 patients had data at 12 months follow-up, 24 at 24 months and 14 at 36 months Median time in the study was 31 months (IQR 20 to 42, range 12 to 59). Participants received psychosocial assessment and support before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6).

<b>OUTCOMES - All reported outcomes</b>	<p>Child Behaviour Checklist (CBCL) (parent report)</p> <p>Youth Self Report (YSR)</p> <p>Kidscreen-52 questionnaire</p> <p>Body Image Scale (BIS) is</p> <p>Utrecht Gender Dysphoria Scale (UGDS)</p> <p>Children's Global Assessment Scale (CGAS)</p> <p>Semi-structured qualitative interviews Participant experience and satisfaction with GnRHa. Note there was no interview conducted before young people started GnRHa.</p>
<b>RESULTS – Extracted outcomes</b>	<p><b>CBCL parent report Total problems base line, 12 months, change, 24 months, change t-score mean (95% CI) 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)</b></p> <p><b>CBCL Parent report self-harm, base line, 12 months, 24 months, 36 months Median (IQR) 0(0, 1), 40 0 (0, 1) 0(0, 1), 0 (0, 1), 0 (0, 1) 0 (0, 1)</b></p> <p><b>YSR Self-report, Total problems t-score base line, 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)</b></p> <p><b>YSR Self-report self-harm base line, 12 months, 24 months Median (IQR) 0 (0, 1), 0 (0, 2), 0 (0, 0), 0 (0, 0)</b></p> <p><b>Kidscreen-52, HRQOL Psychological wellbeing t-score (95% CI at base line, 12 months, 24 months (95% CI) 43.0(39.6, 46.4), 41.1(37.0, 45.2), 51(45.8, 56.2)</b></p> <p><b>Kidscreen-52, HRQOL self-report Psychological wellbeing, t-score (95% CI at base line, 12 months, 24 months 39.8(36.7, 42.8) 39.0(35.4, 42.6), 42.4(36.9, 48)</b></p> <p><b>Body image scale Overall score base line, 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)</b></p> <p><b>Utrecht Gender dysphoria score at baseline, 12 months, 24 months Median (IQR) 41 4.8(4.6, 5.0) 40 4.7(4.6, 5.0) 18 4.7(4.3, 5.0)</b></p> <p><b>CGAS global score baseline, 12 months, 24 months, and 36 months Mean (95% CI) 42 62.9(59.6, 66.2) 35 64.1(59.9, 68.3) 18 65.7(59.6, 71.8) 12 66.0(58.1, 73.9)</b></p> <p>There were 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.</p> <p>Most participants reported positive or a mixture of positive and negative life changes on GnRHa.</p>

<b>Author</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	<b>Hisle-Gorman et al (6)</b> 2021 USA Retrospective cohort study (military healthcare data) 2010–2018
---	--



<b>POPULATION (ages)</b> Age at Tx 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) 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> <b>n patients</b> natal male (M-t-F), natal female (F-t-M)	3754 transgender adolescents 6603 cisgender siblings  1193 (31.8%) male at birth 2561 (68.2%) female at birth  963 transgender adolescents receiving hormone treatment (before-after data)
<b>INTERVENTION (type)</b> Puberty suppression (GnRHa) Cross-sex hormone treatment (CSHT)	<u>Hormone treatment (n=963 individuals)</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> Hormone treatment HT duration FU time, FU 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> <b>Extracted outcomes</b>	<u>Mental health over full 8-year study period*:</u> <i>Compared to siblings, TGD adolescents compared to siblings were more likely to have mental health diagnosis, be prescribed more psychotropic medications and more mental healthcare services:</i> Mental health diagnosis (n (%)): 3352 (89.3%) transgender vs 3308 (50.1%) siblings; aOR 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)  <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)) 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) (suicidal ideation/attempted suicide/self-harm) *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  Psychotropic medication*: Transgender vs Siblings (medication days per year): All mental health meds: 1114 days vs 425 days; adjusted IRR 2.57 (2.36-2.80) *including antidepressants (wellbutrin, SSRI, SNRI, other antidepressant)

	<p><i>benzodiazepines, sleep medications, anti-psychotics, lithium</i></p> <p><u>After hormone treatment:</u>  (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 Meds: (days)  119.7 before vs 211.5 after ; aIRR 1.67 (1.46–1.91)  <i>Psychotropic medication use increased from mean of 120 days per year to mean 212 days per year following gender affirming pharmaceutical care.</i></p> <p><u>Medication days by type of medication:</u>  (number of medication days: Before vs After hormone treatment):</p> <table> <tr> <td>Wellbutrin</td> <td>6.3 before vs 16.2 after; aIRR 2.51 (2.71–3.69)</td> </tr> <tr> <td>SSRI</td> <td>44.8 before vs 73.9 after; aIRR 1.72 (1.47–2.00)</td> </tr> <tr> <td>SNRI</td> <td>4.7 before vs 14.0 after; aIRR 2.59 (1.52–4.38)</td> </tr> <tr> <td>other antidepressant</td> <td>9.2 before vs 18.9 after; aIRR 1.61 (1.18–2.21)</td> </tr> <tr> <td>sleep medications</td> <td>6.4 before vs 16.2 after; aIRR 2.23 (1.61–3.10)</td> </tr> <tr> <td>benzodiazepines</td> <td>3.0 before vs 12.7 after; aIRR 3.01 (1.95–4.65)</td> </tr> <tr> <td>anti-psychotics</td> <td>15.9 before vs 30.1 after; aIRR 1.77 (1.34–2.35)</td> </tr> <tr> <td>lithium</td> <td>1.3 before vs 2.3 after; aIRR 1.11 (0.48–2.59)</td> </tr> <tr> <td>stimulants</td> <td>26.4 before vs 25.1 after; aIRR 0.96 (0.72–1.26)</td> </tr> <tr> <td>migraine medications</td> <td>1.5 before vs 2.2 after; aIRR 0.76 (0.37–1.53)</td> </tr> </table>	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)
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</b>	<b>Staphorsius et al (7)</b>
<b>Year</b>	<b>2015</b>
<b>Country</b>	The Netherlands
<b>Study design</b>	Functional MRI study, Cross-sectional Up to 2014
<b>POPULATION (ages)</b>	Age at start: Minimum 12 years
<b>Age at Tx start</b>	Tanner B2, Tanner G2-G3
<b>Age in cohort</b>	Age at GnRH start: Not indicated
<b>Tanner stage</b>	Age in cohort: Age at scan (mean) 15.1 years ± 2.4 M-t-F 15.8 years ± 1.9 F-t-M
	Control group age: 14.9 years ± 1.5 (boys) 14.4 years ± 1.8 (girls)
<b>POPULATION (n)</b>	41 adolescents:
<b>n patients</b>	22 F-t-M (natal females):
<b>natal male (M-t-F)</b>	(n= 12 using GnRH "suppressed FM")
<b>natal female (F-t-M)</b>	(n= 10 untreated "untreated FM")
	18 M-to-F (natal males):
	(n= 8 using GnRH "suppressed FM")
	(n= 10 untreated "untreated FM")
	Control group*: 24 girls (F) 21 boys (M) 10 not investigated due to brain scan problems

<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<p>Previous intervention: GnRH: triptorelin (Decapeptyl-CR®) 3,75 mg/4w, s.c. or i.m</p> <p>Study intervention: MRI scan (3.0 T) axial T2*-weighted whole-brain volumes sensitive to BOLD contrast, sagittal T1-weighted</p> <p>Tasks in MRI: 1 executive function task: event-related parametric version of the ToL 3 cognitive tasks: verbal fluency task, mental rotation task, face recognition task</p>
<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<p>Puberty suppression duration (mean ± SD) 1.8 years ±0.8 MtF 1.4 years ±1.1 FtM</p>
<b>OUTCOMES - All reported outcomes</b>	<p><b>Executive function:</b> 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)</p> <p><b>Psychological functioning:</b> J2 Child Behaviour Checklist (CBCL)</p> <p><b>IQ</b> Wechsler Intelligence Scales Wechsler Intelligence Scale for Children (WISC-III®, Wechsler, 1991) Wechsler Adult Intelligence Scale (WAIS-III®, Wechsler, 1997)</p>
<b>RESULTS</b> <b>Extracted outcomes</b>	<p><b>Executive function</b> Functional task (ToL):</p> <p>Accuracy (%) (mean ± SD): 88.5 ± 6.8 boys (M) 87.2 ± 11.9 girls (F)</p> <p>79.1 ± 10.3 M-t-F (total) 73.9 ± 9.1 suppressed 83.4 ± 9.5 untreated 87.1 ± 10.0 F-t-M (total) 85.7 ± 10.5 suppressed 88.8 ± 9.7 untreated</p> <p>Reaction time (sec) Mean ± SD 9.6 ± 2.5 boys (M) 9.0 ± 1.8 girls (F)</p> <p>10.4 ± 3.5 M-t-F (total) 10.9 ± 4.1 suppressed 9.9 ± 3.1 untreated 10.0 ± 2.6 F-t-M (total) 9.9 ± 3.1 suppressed 10.0 ± 2.0 untreated</p> <p>Psychological functioning: CBCL scores (mean ± SD) 48.4 ± 10.5 boys (M) 48.4 ± 10.3 girls (F) 57.8 ± 9.2 M-t-F (total)</p>

	57.4 ± 9.8 suppressed
	58.2 ± 9.3 untreated
	60.4 ± 10.2 F-t-M (total)
	57.5 ± 9.4 suppressed
	63.9 ± 10.5 untreated

**Table 2 Effects on bone health by sex hormone suppression in adolescents**

<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	<b>Joseph et al (8)</b> <b>2019</b> UK Retrospective review of national cohort, before-after 2011–2016
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	Age at GnRH start: Range 12–14 years  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> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	<b>First year cohort</b> 70 31 trans girls 39 trans boys  <b>Longitudinal cohort</b> 31 10 trans girls 21 trans boys
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Previous intervention:</b> GnRH  <b>Study intervention:</b> DXA - dual energy X-ray absorptiometry Z-scores calculated from formulae proposed by Crabtree et al. from ALPHABET study using UK norms for Caucasian subjects (8). Hip BMAD Z-scores not calculated as there were no reference ranges available.
<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<b>GnRH duration:</b> 1 year (1st year cohort) 2.8 years (longitudinal cohort)  Follow-up time: 1–2.8 years
<b>OUTCOMES - All reported outcomes</b>	<b>Bone health:</b> 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
<b>RESULTS</b> <b>Extracted</b> <b>outcomes</b>	<p><b>Characteristic, mean (SD)</b></p> <p><b>Baseline/ 1 year</b></p> <p><b>Trans girls (n=31/31)</b> 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><b>Trans boys (n=39/39)</b> Age, year 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><b>Trans girls (n=10/10)</b> Age, year 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><b>Trans boys (n=21/21)</b> Age, year 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</b> <b>Year</b> <b>Country</b> <b>Study design</b>	<b>Klink et al (9)</b> <b>2015</b> The Netherlands Retrospective longitudinal cohort study , before-after 1998–2012
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	<b>Age at start of GnRH:</b> Range 11.4–18.3 years MtF: Tanner G5 Mean: 14.9 years $\pm$ 1.9 SD FtM: 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> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	34 15 MtF 19 FtM
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Previous intervention:</b> <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. (Sustanon): 250 mg/ml/ 2–4 weeks (incremental dosages), dose not indicated.  <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). Therefore, 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> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<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 (min age 18 years): GnRH terminated and CSHT continued.  <b>FU until age 22 years</b>
<b>OUTCOMES - All reported outcomes</b>	<b>Bone health</b> Bone mineral density (BMD): Bone mineral apparent density (BMAD) Areal BMD (aBMD, g/cm <sup>2</sup> ) of 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> <b>Extracted outcomes</b>	<b>Start GnRH/ Start CSH/ Age 22 years (mean ± SD)</b>  <b>Transwomen</b> Height cm 174.6 8.9/ 179.9/ 181±9.3  <i>Lumbar spine</i> 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 <i>Femoral neck</i> 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  <b>Transmen</b> Height cm 165.2 ± 9.1/ 168.4 ± 8.3/ 170.6 ± 7.9  <i>Lumbar spine</i> 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 <i>Femoral neck</i> 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



<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	<b>Vlot, et al (10)</b> <b>2017</b> The Netherlands Retrospective, cohort study, before after 2001-2011
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	<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:</b> (min age 16 years): <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> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	<i>In Table 1:</i> 42 female-to-male (transmen) 28 male-to-female (transwomen)  <i>In abstract:</i> 34 female-to-male (transmen) 22 male-to-female (transwomen)
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Previous intervention</b> <b>GnRH</b> Triptorelin (Decapeptyl–CR <sup>®</sup> ) 3.75 mg s.c. /4 weeks <b>CSHT</b> Testosterone esters (Sustanon): start at 25 mg/m <sup>2</sup> i.m. body surface area /2 weeks, 6-month increment until 250 mg/4 weeks 17-β estradiol: start at 5 µg/kg/day, 6-months increments until maintenance dose 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 ≥15y in transwomen or ≥14 y in transmen

<b>INTERVENTION</b> <b>(time)</b> <b>Hormone</b> <b>treatment</b> <b>duration</b> <b>FU time, FU age</b>	<b>GnRH</b> Approximately 1 year in transmen Approximately 2–3 years in transwomen <b>CSHT</b> Up to 24 months.
<b>OUTCOMES -</b> <b>All reported</b> <b>outcomes</b>	<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> <b>Extracted</b> <b>outcomes</b>	<b>At start GnRH/ at start CHST/ at 24 months</b>  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)  <b>Transmen, “young”</b> <i>P1NP median/range:</i> 783 (516–1090)/ 324 (194–402)/ 186 (163–334) <i>OC median/range:</i> 5 (2.2–11.7)/ 6.8 (1.8–7.7)/ 4.9 (4.2–7.8) <i>ICTP median/range:</i> 24 (17–29.9)/ 11 (7.8–12)/ 12 (11–14)  <i>BMAD HIP:</i> 0.31 (0.26–0.36)/ 0.30 (0.22–0.35)/ 0.33 (0.23–0.37) <i>BMAD HIP Z-score:</i> -0.01 (-1.30–0.91)/ -0.37 (-2.28–0.47)/ -0.37 (-2.03–0.85) <i>BMAD LS:</i> 0.23 (0.20–0.29)/ 0.23 (0.19–0.28)/ 0.25 (0.22–0.28) <i>BMAD LS Z-score:</i> -0.05 (-0.78–2.94)/ -0.84 (-2.2–0.87)/ -0.15 (-1.38–0.94)  <b>Transmen, “old”</b> <i>P1NP median/range:</i> 110 (38–471)/ 127 (61–321)/ 101 (44–181) <i>OC median/range:</i> 2.4 (0.4–4.6)/ 3.9 (0.4–8.6)/ 2.9 (0.8–5) <i>ICTP median/range:</i> 7 (5.2–15)/ 6.9 (4.6–14)/ 8.2 (4.1–16)  <i>BMAD HIP:</i> 0.33 (0.25–0.39)/ 0.30 (0.23–0.41)/ 0.32 (0.23–0.41) <i>BMAD HIP Z-score:</i> 0.27 (-1.39–1.32)/ -0.27 (-1.91–1.29)/ 0.02 (-2.1–1.35) <i>BMAD LS:</i> 0.26 (0.21–0.29)/ 0.24 (0.20–0.28)/ 0.25 (0.21–0.30) <i>BMAD LS Z-score:</i> 0.27 (-1.6–1.8)/ -0.29 (-2.28–0.90)/ -0.06 (-1.76–1.61)  <b>Transwomen, “young”</b> <i>P1NP median/range:</i> 935 (617–1348)/ 363 (185–643)/ 204 (137–314) <i>OC median/range:</i> 4.8 (2.6–21.9)/ 6.4 (0.7–12.8)/ 5.4 (3.9–12.5) <i>ICTP median/range:</i> 23 (15–34)/ 13 (8.7–21)/ 10 (8.5–13)  <i>BMAD HIP:</i> 0.29 (0.20–0.33)/ 0.27 (0.20–0.33)/ 0.27 (0.20–0.36) <i>BMAD HIP Z-score:</i> -0.71 (-3.35–0.37)/ -1.32 (-3.39–0.21)/ -1.3 (-3.51–0.92) <i>BMAD LS:</i> 0.21 (0.17–0.25)/ 0.20 (0.18–0.24)/ 0.22 (0.19–0.27) <i>BMAD LS Z-score:</i> -0.2 (-1.82–1.18)/ -1.52 (-2.36–0.42)/ -1.10 (-2.44–0.69)  <b>Transwomen, “old”</b> <i>P1NP median/range:</i> 191 (96–792)/ 140 (111–467)/ 119 (55–296) <i>OC median/range:</i> 2.29 (0.8–11)/ 2.2 (0.5–6.1)/ 3.3 (1.8–6.8) <i>ICTP median/range:</i> 12 (6.9–21)/ 7.4 (6.9–13)/ 6.8 (4.8–15)  <i>BMAD HIP:</i> 0.30 (0.26–0.36)/ 0.30 (0.26–0.34)/ 0.29 (0.24–0.38) <b>BMAD HIP</b> <i>Z-score:</i> -0.44 (1.37–0.93)/ -0.36 (-1.5–0.46)/ -0.56 (-2.17–1.29) <i>BMAD LS:</i> 0.22 (0.18–0.25)/ 0.22 (0.19–0.24)/ 0.23 (0.21–0.26) <i>BMAD LS Z-score:</i> -1.18 (-1.78–1.09)/ -1.15 (-2.21–0.08)/ -0.66 (-1.66–0.54)

<b>Author</b>	<b>Schagen et al. (11)</b>
<b>Year</b>	<b>2020</b>
<b>Country</b>	The Netherlands
<b>Setting</b>	Prospective observational study
<b>Study design</b>	1998 - 2009
<b>POPULATION (ages)</b>	At the start of GnRH <sub>a</sub> : Early pubertal group: Tanner stage 2 or 3 Late pubertal group: Tanner stage 4 or 5
<b>Age at Tx start</b>	
<b>Age in cohort</b>	At start of GnRH: (mean ± SD 14.1 ± 1.7 trans girls 14.5 ± 2.0 trans boys
<b>Tanner stage</b>	Pubertal group: Early (Tanner 2-3)/Late (Tanner 4-5) 15/36 trans girls 14/56 trans boys
	At start of CSHT: 16.2 ± 1.2 trans girls 16.9 ± 1.1 trans boys Pubertal group: Early (Tanner 2-3)/Late (Tanner 4-5) 10/26 trans girls 5/37 trans boys
<b>POPULATION (n)</b>	GnRH <sub>a</sub> group: 121
<b>n patients</b>	51 trans girls 70 trans boys
<b>natal male (M-t-F),</b>	
<b>natal female (F-t-M)</b>	GnRH <sub>a</sub> + CSHT group: 78 36 trans girls 42 trans boys
<b>INTERVENTION (type)</b>	Previous intervention: GnRH <sub>a</sub> i.m. 3.75 mg/ 4 weeks (Triptorelin) CSHT:
<b>Puberty suppression (GnRH<sub>a</sub>)</b>	Oestrogens oral Testosterone i.m.: (testosterone propionate, -ferylpropionate, -isocaproate and -decanoate) (Sustanon)
<b>Cross-sex hormone treatment (CSHT)</b>	In subjects > 16 years at the start of pubertal 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 National Health and Nutrition Examination Surveys (NHANES) references values; reference population of the birth-assigned sex was used. BMAD (g/cm <sup>3</sup> ) calculated as described by Ward et al [Ward et al. 2007 UK reference data for the Hologic QDR Discovery dual-energy x ray absorptiometry scanner in healthy children and young adults aged 6-17 years. 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>	Duration of GnRH: (years) 1.9 ± 1.03 mean 2.0 ± 0.94 transgirls 1.8 ± 1.11 transboys
<b>Hormone treatment</b>	Early pubertal groups were on GnRH <sub>a</sub> 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)
<b>HT duration</b>	
<b>FU time, FU age</b>	Duration of CSHT: 3 years (not further detailed)

<b>OUTCOMES - All reported outcomes</b>	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, and whole body; Bone mineral content of the whole body (BMC-WB, g).
<b>RESULTS - Extracted outcomes</b>	<p>aBMD During 2 Years of GnRHa Treatment</p> <p><b>Transgirls</b></p> <p><b>Early Pubertal SE 15</b> 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)</p> <p><b>Late-Pubertal 36</b> 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></p> <p><b>Early-pubertal 14</b> 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></p> <p><b>Late-pubertal 56</b> 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 and During 3 Years of Gender-Affirming Hormone Treatment in Addition to GnRHa Treatment</b></p> <p><b>Transgirls</b></p> <p><b>Early-Pubertal</b> 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></p> <p><b>Late-Pubertal</b> 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></p> <p><b>Early-pubertal</b> 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></p> <p><b>Late-pubertal</b> 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>
<b>Author Year Country Study design</b>	<b>Stoffers et al (12)</b> <b>2019</b> The Netherlands Retrospective, cohort study before-after 2010-2018
<b>POPULATION (ages) Age at Tx start Age in cohort Tanner stage</b>	<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) n patients natal male (M-t-F)</b>	62 trans males (FtM) 17 evaluated 0 discontinued testosterone "Excluded psychological, medical, or social problems that might interfere with treatment"

natal female (F-t-M)	
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<p><b>Previous intervention:</b> GnRH (Decapeptyl-CR®): 3.75 mg /4 weeks s.c. for at least 6 months</p> <p>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</p> <p><b>Study intervention:</b> 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</i> (USA) for those &gt;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 of age, reference values for 17-year-olds were used for those aged &gt;17 years.</p>
<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<p><b>GnRH duration</b> Median: 8 months Range: 3–39 months (3.25 years)</p> <p><b>Testosterone duration</b> Min: 6 months Mean: 12 months Range: 5–33 months (2.75 years)</p>
<b>OUTCOMES - All reported outcomes</b>	<p><b>Anthropomorphic:</b> 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)</p> <p><b>Bone health</b> Bone mineral density (BMD) lumbar spine, femoral neck BMD Z-scores</p>
<b>RESULTS</b> <b>Extracted outcomes</b>	<p><b>Bone health:</b> <b>At start GnRH (n=62)/ at start testosterone (n=62)/ at 24 months (n=15)</b></p> <p>Blood pressure (mm Hg, (median (interquartile range)) Systolic 124 (115-129)/118 (114-126)/126 (117-129) Diastolic 68 (65-73)/72 (66-77)/74 (63-76)</p> <p>Height (cm (mean ± SD)) 167.1 ± 6.9/168.2 ± 6.2/167.8 ± 5.3</p> <p>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</p> <p><b>BMD Z-score (mean ± SD)</b> 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</p>

<b>Author</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	<b>Navabi et al (13)</b> 2021 Canada Retrospective review of medical records 2006 - 2017
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age in cohort: (years $\pm$ SD) 15.2 years ( $\pm$ 1.8) transgender males 15.4 years ( $\pm$ 2.0) transgender females  90.7% Tanner 4–5 transgender males 80.3% Tanner 4–5 transgender females
<b>POPULATION (n) n patients</b> 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 (GnRHa) Cross-sex hormone treatment (CSHT)	GnRHa: leuprolide acetate, starting at 7.5 mg intramuscularly /4 weeks (3 doses), followed by 11.25 mg / 12 weeks.  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> Hormone treatment HT duration FU time, FU age	FU time: 6, 12 and 18 months  Pre- and post-GnRHa DXA: Pre-GnRHa: at $-51.4 \pm 41.3$ days (range -158 to +28 days) relative to GnRHa initiation. Post-GnRHa: 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 - All reported outcomes</b>	areal bone mineral density (aBMD) aBMD z scores Lumbar spine (LS) (L2–L4) left total hip (LTH) aBMD z scores  Vitamin D status
<b>RESULTS - Extracted outcomes</b>	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.  Mean difference (95% CI) post-pre-GnRH 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

	<p>aBMD z score - 0.33 (- 0.40 to -0.26) Total body less head aBMD z score - 0.34 (- 0.43 to -0.25)</p> <p>Transgender Females</p> <p>Lumbal 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)</p>
--	---

<b>Author</b>	van der Loos et al (14)
<b>Year</b>	2021
<b>Country</b>	The Netherlands
<b>Setting</b>	Retrospective cohort
<b>Study design</b>	2011-2018
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	<p>Age at start of GnRH: min Tanner breast stage 2 min Tanner genital stage 2–3 Age data reported in early, mid or late puberty groups: Tanner stage at start of GnRH: early: B2, mid: B3, late: B4 and B5 Testicular volume at the start of GnRH: early: ≤9 mL; mid: 10–19 mL; late: ≥20 mL</p> <p>Age at start of GnRH: Range 11-17 Age at start of CSHT: 15 – 17 years</p>
<b>POPULATION (n)</b> <b>n patients</b> natal male (M-t-F), natal female (F-t-M)	<p>322 included in study 106 transwomen 216 transmen 115 gonadectomy</p>
<b>INTERVENTION (type)</b> Puberty suppression (GnRHa) Cross-sex hormone treatment (CSHT)	<p>Previous intervention: GnRHa: triptorelin s.c. 3.75 mg / 4 weeks or 11.25 mg every 12 weeks</p> <p>From age approximately 16: 17-beta-estradiol oral, starting at 5 µg/kg body weight, increased up to maintenance dose 2 to 4 mg/day. Testosterone ester mixture i.m. 25 mg/m<sup>2</sup> body surface area, increased up to maintenance 250 mg / 3 to 4 weeks Surgery: Gonadectomy at earliest age 18 years – if performed GnRH was stopped afterwards</p> <p>Study intervention: DXA: narrow neck hip structure analysis (HSA)</p>
<b>INTERVENTION (time)</b> Hormone treatment HT duration FU time, FU age	<p>GnRH duration min 6 months, range 1-3 years</p> <p>CSHT duration (with DXA after ≥2years of CSHT) range 2-6 years</p>

<b>OUTCOMES - All reported outcomes</b>	Subperiosteal width Endocortical diameter BMI, Height Hormone levels
<b>RESULTS – Extracted outcomes</b>	<p>Change in Centimeters in Subperiosteal Width and Endocortical Diameter in Trans Women and Trans Men, Derived from the Linear Mixed-Model Analyses.</p> <p>Difference in centimeters between the start of GnRH<sub>a</sub> and the start of GAH, between the start of GnRH<sub>a</sub> and after ≥2 years of GAH, between the start of GAH and after ≥2 years of GAH</p> <p>Trans women</p> <p>Early puberty</p> <p>Subperiosteal width 0.38 (0.16; 0.60) 0.44 (0.23; 0.65) 0.06 (-0.15; 0.27)</p> <p>Endocortical diameter 0.39 (0.16; 0.61) 0.38 (0.17; 0.60) -0.00 (-0.21; 0.21)</p> <p>Mid puberty</p> <p>Subperiosteal width 0.33 (0.15; 0.50) 0.57 (0.39; 0.75) 0.25 (0.11; 0.38)</p> <p>Endocortical diameter 0.34 (0.17; 0.51) 0.55 (0.37; 0.72) 0.21 (0.08; 0.34)</p> <p>Late puberty</p> <p>Subperiosteal width 0.06 (-0.08; 0.20) 0.27 (0.16; 0.39) 0.21 (0.09; 0.34)</p> <p>Endocortical diameter 0.08 (-0.06; 0.22) 0.27 (0.15; 0.40) 0.19 (0.06; 0.33)</p> <p>Trans men</p> <p>Early puberty</p> <p>Subperiosteal width 0.63 (0.58; 0.68) 0.79 (0.72; 0.85) 0.15 (0.12; 0.19)</p> <p>Endocortical diameter 0.62 (0.57; 0.67) 0.73 (0.67; 0.79) 0.11 (0.08; 0.14)</p> <p>Mid puberty</p> <p>Subperiosteal width 0.10 (-0.09; 0.29) 0.31 (0.11; 0.50) 0.21 (0.03; 0.38)</p> <p>Endocortical diameter 0.09 (-0.11; 0.30) 0.27 (0.06; 0.48) 0.18 (-0.01; 0.36)</p> <p>Late puberty</p> <p>Subperiosteal width 0.07 (-0.03; 0.18) 0.15 (0.04; 0.26) 0.07 (-0.04; 0.18)</p> <p>Endocortical diameter 0.10 (-0.01; 0.21) 0.17 (0.05; 0.28) 0.07 (-0.04; 0.17)</p> <p>“In conclusion, development of hip bone geometry in transgender adolescents resembled that of the experienced gender if the GnRH<sub>a</sub> 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 GnRH<sub>a</sub> and GAH treatments during mid or late puberty continued within the curve of their gender assigned at birth”</p>

GAH = gender-affirming hormone treatment

<b>Author</b>	<b>Lee et al (15)</b>
<b>Year</b>	<b>2020</b>
<b>Country</b>	USA
<b>Setting</b>	Cross-sectional analysis of prospective, observational, longitudinal cohort, multicenter
<b>Study design</b>	
<b>POPULATION (ages)</b>	Age at start of GnRH:
Age at Tx start	Tanner stages 2-3:
Age in cohort	63.5% (n = 40) Tanner 2
Tanner stage	36.5% (n = 23) Tanner 2
	11.0 ± 1.4 years designated females at birth (DFAB)
	12.1 ± 1.3 years designated males at birth (DMAB)



<b>POPULATION (n) n patients</b> 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)
<b>INTERVENTION (type)</b> Puberty suppression (GnRHa) Cross-sex hormone treatment (CSHT)	Previous intervention: GnRH (not further specified)  <u>Study intervention:</u> DXA and quantitative computed tomography (QCT). Methods and machines used for assessment varied among the study sites: DXA scans of 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.  DXA scan before or 2 months after start of GnRH
<b>INTERVENTION (time)</b> Hormone treatment HT duration FU time, FU age	GnRH duration before DXA: 0-2 months
<b>OUTCOMES - All reported outcomes</b>	Areal and volumetric BMD Z-scores  dietary calcium serum 25-hydroxyvitamin D physical activity (assessed with Physical Activity Questionnaire for Older Children (PAQ-C))
<b>RESULTS - Extracted outcomes</b>	Bone health: Areal and volumetric BMD Z-scores.  BMD assessed before initiation of GnRHa: 90% (57/63) of participants  A 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)  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. At least 1 BMD Z-score was < -2 in: 30% of DMAB 13% of DFAB  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 sex hormone suppression in adolescents.**

<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	Schagen et al (16) 2016 The Netherlands Prospective cohort study, before-after 1998 – 2009
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	<b>Age at start:</b> M-t-F: Tanner G2–G5 Range 11.6–17.9 years Median 13.6 years F-t-M: Tanner B2-B5 Range 11.1–18.6 years Median 14.2 years
<b>POPULATION (n)</b> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	116 49 M-t-F 67 F-t-M 0 discontinued treatment
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Previous intervention:</b> <b>GnRH</b> Triptorelin (Decapeptyl-CR) 3.75 mg i.m. at 0, 2, and 4 weeks, followed by every 4 weeks. <b>Study intervention:</b> Dual energy x-ray absorptiometry (DEXA)
<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b>	<b>GnRH duration</b> 3 to 12 months (depended on when the individual reached the age at which CSHT could be added)
<b>OUTCOMES - All reported outcomes</b>	Physical examination Tanner stage (breast development, testicular volume) Height and weight height SD score Body mass index (BMI) SD score Body composition: (fat mass, fat %, lean body mass %) Hormone levels: LH, FSH, testosterone, estradiol liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase) Creatinine
<b>RESULTS</b> <b>Extracted outcomes</b>	<b>At start GnRH/ at 1 y GnRH (mean (SD))</b> <b>M-t-F</b> 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)/ 7216 (79) Creatinine (mmol/L) 70 (12)/ 66 (13) <b>F-t-M</b> 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), mean (SD) 73 (8)/68 (13)
--	--

<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	<b>Klaver et al (17)</b> <b>2018</b> The Netherlands Retrospective cohort study of medical records, before-after 1998–2014
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	<b>Age at start of GnRH:</b> Min age: 12 years Min Tanner B2 (girls) Min Tanner G3 (boys)  Transwomen: 14.5 ± 1.8 years Transmen: 15.3 ± 2.0 years  <b>Age at start of CSHT</b> Min age 16 years Transwomen: 16.4 ± 1.1 years Transmen: 16.9 ± 0.9 years
<b>POPULATION (n)</b> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	192 71 transwomen (MtF) 121 transmen (FtM)
<b>INTERVENTION (type)</b> <b>Puberty suppression (GnRH)</b> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Previous intervention:</b> GnRH: Cross-sex hormonal treatment (CSHT) 17b-estradiol orally or mixed testosterone esters injections <b>Surgery:</b> Gonadectomy (from age 18)  <b>Study intervention:</b> Whole-body dual-energy x-ray absorptiometry
<b>INTERVENTION (time)</b> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<b>GnRH duration:</b> until gonadectomy at earliest age 18  <b>Follow-up time:</b> <i>GnRH monotherapy:</i> Transwomen (M-t-F): 2.1 years (1.0–2.8) Transmen (F-t-M): 1.0 years (0.5–2.9) <i>GnRH + CSHT:</i> Transwomen (M-t-F): 3.1 years (2.5–3.6) + H5 Transmen (F-t-M): 2.4 years (2.0–3.1) <i>CSHT monotherapy:</i> Transwomen (M-t-F): 2.8 years (1.6–3.4) Transmen (F-t-M): 3.0 years (1.9–3.4).  Follow-up age: 22

<b>RESULTS</b> <b>Extracted outcomes</b>	At start of GnRH ( $\pm 4$ months)/ at start of CSHT( $\pm 4$ months)/ at age 22( $\pm 1.5$ years)
	<b>Transwomen</b>
	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)
	Lean body mass
	Total body (%) 75 (74–77)/ 69 (68–71)/ 66 (64–68)
	<b>Transmen</b>
	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)
	Lean body mass
	Total body (%) 70 (69–71)/67 (66–68)/ 73 (72–74)

<b>Author</b>	<b>Klaver et al (18)</b>
<b>Year</b>	<b>2020</b>
<b>Country</b>	The Netherlands
<b>Study design</b>	Retrospective cohort study, before after 1998–2015
<b>POPULATION (ages)</b>	At min age 12 years
<b>Age at Tx start</b>	Tanner B2 (girls)
<b>Age in cohort</b>	Tanner G3 (boys)
<b>Tanner stage</b>	Started GnRH in adolescence (15 years) addition of sex hormones (17 years)
<b>POPULATION (n)</b>	192
<b>n patients</b>	71 transwomen (M-t-F)
<b>natal male (M-t-F)</b>	121 transmen (F-t-M)
<b>natal female (F-t-M)</b>	
<b>INTERVENTION (type)</b>	<b>GnRH</b> 3.75 mg/4 weeks s.c.
<b>Puberty suppression (GnRH)</b>	<b>Cross sex hormonal treatment (CSHT):</b> (from age 16 years):
<b>Cross-sex hormone treatment (CSHT)</b>	<i>Transwomen (M-t-F):</i> 17-b estradiol (E2) oral, start 5 $\mu$ g/kg/day, increased every 6 months until maintenance dose 2 mg/day
	<i>Transmen (F-t-M):</i> mixed testosterone esters (Sustanon <sup>®</sup> ), 25 mg/m <sup>2</sup> body surface area/2 weeks i.m., increased every 6 months until maintenance dose 250 mg/3–4 weeks.
	<i>When GnRHs were started after age 16:</i> 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>	Hormone treatment duration: From min age 12 years (GnRH) up to age 22 years (sex hormones)
<b>Hormone treatment duration</b>	Follow-up age: 22 years (range 20.5–23.5 years)
<b>FU time, FU age</b>	

<b>OUTCOMES - All reported outcomes</b>	<b>Cardiovascular risk:</b> 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
<b>RESULTS Extracted outcomes</b>	<b>At start of GnRH/ at age 22 years/ change during GnRH treatment/ change between start of CSHT and age 22 years (mean (95% CI))</b>  <b>Transwomen</b> <i>BMI</i> 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) <i>SBP (mmHg)</i> 120 (116 to 123)/117 (113 to 122) /+1 (-3 to 5) /-3 (-8 to 2) <i>DBP (mmHg)</i> 65 (63 to 67) /75 (72 to 78) / +4 (1 to 7) /+6 (3 to 10) <i>Glucose (mmol/L)</i> 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) <i>Insulin (mU/L)</i> 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) <i>HOMA-IR</i> 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) <i>Total cholesterol (mmol/L)</i> 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) <i>HDL cholesterol (mmol/L)</i> 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) <i>LDL cholesterol mmol/L</i> 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) <i>Triglycerides (mmol/L)</i> 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)  <b>Transmen</b> <i>BMI</i> 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) <i>SBP (mmHg)</i> 120 (118 to 122) / 126 (122 to 130) / +2 (-1 to 4) / +5 (1 to 9) <i>DBP (mmHg)</i> 67 (66 to 69) / 74 (72 to 77) / +1 (-1 to 3) / +6 (4 to 9) <i>Glucose (mmol/L)</i> 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) <i>Insulin (mU/L)</i> 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) <i>HOMA-IR</i> 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) <i>Total cholesterol (mmol/L)</i> 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) <i>HDL cholesterol (mmol/L)</i> 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) <i>LDL cholesterol (mmol/L)</i> 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) <i>Triglycerides (mmol/L)</i> 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 Country Setting Study design</b>	<b>Perl et al (19)</b> 2020 Israel Retrospective pilot study 2013 - 2018
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of GnRH: 14.4 ± 1.0 years Tanner stage 4/5  Age at start of testosterone: 15.1 ± 0.9
<b>POPULATION (n) n patients</b> natal male (M-t-F), natal female (F-t-M)	48 transgender male adolescents 15 included  15 GnRH subsequently were 9 treated with testosterone

<b>INTERVENTION (type)</b> Puberty suppression (GnRHa) Cross-sex hormone treatment (CSHT)	Previous intervention: GnRHa D-Trp-6-LHRH depot (3.75mg/4 weeks intramuscular injection)  CSHT: (patients who reached $\geq 14$ 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> Hormone treatment HT duration FU time, FU age	GnRHa duration: $3 \pm 1$ months.  Testosterone duration: $4 \pm 2$ months
<b>OUTCOMES - All reported outcomes</b>	BMI BP (procedure for measurement not given) luteinizing hormone (LH) follicle-stimulating hormone (FSH) estradiol testosterone
<b>RESULTS – Extracted outcomes</b>	Anthropometric (before GnRH; after GnRH; before testosterone; after testosterone) mean – SD  BMI (kg/m <sup>2</sup> ), mean $\pm$ SD $21.3 \pm 4.7$ ; $22.0 \pm 4.8$ ; $23.3 \pm 5.6$ ; $24.2 \pm 4.6$ BMI-SDS did not increase significantly during GnRHa therapy.  Diastolic BP percentiles: mean $\pm$ SD $56\% \pm 26$ ; $74\% \pm 9.0$ ; $74\% \pm 9.0$ ; $56\% \pm 17$ 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 $\pm$ 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</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	Schulmeister et al. (20) 2021 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: $11.0 \pm 2.8$ 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

<p><b>POPULATION (n)</b>  <b>n patients</b>  natal male (M-t-F),  natal female (F-t-M)</p>	<p>92 enrolled  55 in cohort  26 designated male at birth  29 designated female at birth</p> <p>Comparison group:  226 participants:  118 (52%) males,  108 (48%) female</p> <p>Prepubertal, presumed cisgender youth not receiving hormonal intervention from the <i>Bone Mineral Density in Childhood Study</i> (BMDCS)  (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).</p> <p>Exclusions: Serious psychiatric symptoms.</p>
<p><b>INTERVENTION (type)</b>  Puberty suppression (GnRHa)  Cross-sex hormone treatment (CSHT)</p>	<p>GnRH: Drug, dose and frequency not reported.</p> <p>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]</p>
<p><b>INTERVENTION (time)</b>  Hormone treatment  HT duration  FU time, FU age</p>	<p>Duration:  GnRHa: min 10 months max 14 months.</p> <p>FU time:  Prior to beginning GnRHa (baseline), 6- and 12-month follow-up visits.</p>
<p><b>OUTCOMES - All reported outcomes</b></p>	<p>HV (height velocity)  BMI  FSH (follicle-stimulating hormone)  LH (luteinizing hormone)  estradiol  testosterone</p>
<p><b>RESULTS – Extracted outcomes</b></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>

<b>Author</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	<b>Nokoff et al. (21)</b> 2020 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> <b>n patients</b> natal male (M-t-F), natal female (F-t-M)	17 youth 9 transgender males on GnRHa 8 transgender females on GnRHa  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 (GnRHa) Cross-sex hormone treatment (CSHT)	GnRH: Drug, dose and frequency not reported.
<b>INTERVENTION (time)</b> Hormone treatment HT duration FU time, FU age	GnRHa 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 - All reported outcomes</b>	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 – Extracted outcomes</b>	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 gender confirming hormonal treatment started before age of 18 years without previous puberty suppression.**

<b>Author</b> <b>Year</b> <b>Country</b> <b>Study design</b>	Tack et al (22) 2016 Belgium Retrospective cohort study 2010–2015
<b>POPULATION (ages)</b> <b>Age at Tx start</b> <b>Age in cohort</b> <b>Tanner stage</b>	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> <b>n patients</b> <b>natal male (M-t-F)</b> <b>natal female (F-t-M)</b>	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> <b>Cross-sex hormone treatment (CSHT)</b>	<b>Hormone treatment:</b> 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  <b>Psychiatric intervention:</b> 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> <b>Hormone treatment duration</b> <b>FU time, FU age</b>	<b>Treatment duration</b> Min 6 months, up to 18 months Lynestrenol (L): Mean 12.6 months Lynestrenol (L) + testosterone esters (T): Mean 11.4 months
<b>OUTCOMES - All reported outcomes</b>	Anthropometry Safety parameters, side effects Biochemical analysis: complete blood count, electrolytes, liver, and renal function, fasting glucose, insulin, lipid metabolism <b>Hormone levels:</b> 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> <b>Extracted outcomes</b>	<b>Anthropometry</b> (at start of lynestrenol / at 12 months of L/ at start of testosterone / at 12 months of T) Mean height 164.6 cm/ –// 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

	<p>Total cholesterol (mmol/l) 4.153/ 4.237// 4.212/ 4.450  HDL (mmol/l) 1.481/ 1.017// 1.098/ 1.085</p> <p><b>Side effects</b>  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</p>
--	--

<p><b>Author</b>  <b>Year</b>  <b>Country</b>  <b>Study design</b></p>	<p><b>Jarin et al (23)</b>  <b>2017</b>  USA  Retrospective, cohort study  2008-2014</p>
<p><b>POPULATION (ages)</b>  <b>Age at Tx start</b>  <b>Age in cohort</b>  <b>Tanner stage</b></p>	<p>14 – 25 years  Affirmed male:  :  mean 16 years  (min 13, max 22)</p> <p>Affirmed* female (MtF)  Mean 18 year  (min 14, max 25)</p>
<p><b>POPULATION (n)</b>  <b>n patients</b>  <b>natal male (M-t-F)</b>  <b>natal female (F-t-M)</b></p>	<p>161 adolescents:  72 affirmed males (FtM)  44 affirmed females (MtF)</p> <p>7 affirmed males on GnRHa before treatment  2 affirmed females on GnRHa before treatment  2 affirmed males reported hormone use outside medical practice (i.e., street hormones)  5 affirmed females reported exogenous street hormone use.</p> <p>Comorbidities:  35 depression (22 FtM 13 MtF)  11 anxiety (8 FtM 3 MtF)  8 ADHD (5 FtM 3 MtF)  10 HIV (10 MtF)</p>
<p><b>INTERVENTION (type)</b>  <b>Cross-sex hormone treatment (CSHT)</b></p>	<p>CSHT:  Testosterone (s.c.):  initiated at 25 mg/ week, weekly doses of 25, 50, or 100 mg at subsequent visits.</p> <p>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</p>
<p><b>INTERVENTION (time)</b>  <b>Hormone treatment duration</b>  <b>FU time, FU age</b></p>	<p>Follow-up time:  Up to 35 months.</p> <p>1 to 3 months after initiation  4 to 6 months after initiation  6 months and beyond</p>

<b>RESULTS</b> <b>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> <b>Extracted outcomes</b>	<p><b>Affirmed male (FtM):</b>          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 suprphysiologic hematokrit levels (&gt;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 &gt;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).</p> <p><b>Affirmed female (MtF):</b>          No significant changes in any other parameter tested were found.          There was no statistically significant difference in measured metabolic parameters among the various methods of oestrogen administration (patch, oral, or intramuscular).</p>

<b>Author</b> <b>Year</b> <b>Country</b> <b>Setting</b> <b>Study design</b>	<b>Mullins et al (24)</b> 2021 USA Retrospective chart review 2013 - 2019
<b>POPULATION (ages)</b> Age at Tx start Age in cohort Tanner stage	Age at start of CSHT: years (median, IQR) 17 years (15–19) total cohort 18 years (15.5–20) estrogen 17 years (15–19) testosterone range 13 - 24 years
<b>POPULATION (n)</b> <b>n patients</b> 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 (GnRHa) Cross-sex hormone treatment (CSHT)	Estrogen: 4.0 mg (2.0–6.0): oral (90.7%), transdermal (5.5%), intramuscular (3.8%)  Testosterone: 70.0 mg (60.0–80.0) subcutaneous (72.7%), intramuscular (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> Hormone treatment HT duration FU time, FU age	Treatment duration, days (median, IQR) Estrogen 554 days (283.0–1037.5) Testosterone 577 days (283.0–923.0)
<b>OUTCOMES - All reported outcomes</b>	Incidence of arterial or venous thrombosis during GAHT. Prevalence of thrombosis risk factors Additional risk factors for thrombosis, including migraine with aura, elevated BMI, tobacco use, medical diagnoses associated with increased risk of thrombosis, and 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 – Extracted outcomes</b>	<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 regret and discontinuation of treatment 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 to17 years	Puberty blockers, hormone therapy, and 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 gonadotropin releasing hormone agonist (GnRH). Sixty-one of these (83%) eventually started gender affirming treatment	Chart review Median follow-up duration was 1.2 years (range, 0 to 5.1 years).	1.2 years (range, 0 to 5.1 years). median	2/96 (pubertal at start)  16/77 (21%) on GnRH did not start gender affirming treatment
Cohen- Ketten is et al 1997 (27)  The Netherlands	Time period not given	22 patients (15 FtMs and 7 MtFs) Mean age at pretest 17.5 years (range 15 to 20) Mean age at follow-up 22.0 years (range 19 to 27)  Resulting posttreatment sample 14 FtMs and 5 MtFs.	Surgically reassigned (various procedures)	Questionnaire s 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) years, (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 (range15–19) years  Mean age at follow-up 21.0 (range 19–23) years	Surgical reassignment Not specified	Semi- structured interview	1–4 years post- surgery	0/20
Mehringer et al (30) 2021  USA	Not given	30 transmasculine youth aged 13 to 21  mean age 17.5 (14-21) years,  14 had undergone chest surgery. Mean age 16.4	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, and

		years				improved quality of life and functioning
Nieder et al (31)2021 Germany	September 2013 to June 2017	75 11-21 years	Varying, hormones, various surgery	Clinical follow-up	2 years	0/75
Carmichael et al (5) 2021 The UK	April 2011 to 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 (32) 2021 USA	December 2016 to April 2017	100 detransitioners, mean age at detransition 26 years Mean age at transition 22 years	Varying gender affirming treatments	Open survey over Internet		

## References

Numbers in ( ) refers to reference number in the main document.

- (11) de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;134:696-704.
- (10) Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *J Sex Med*. 2015;12:2206-14.
- (8) Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service. *Eur Child Adolesc Psychiatry*. 2021;30:1755–1767
- (9) Cantu AL, Moyer, D.N., Connely, K.J., Holley, A.L. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. *Transgender Health*. 2020;5: 196–200
- (12) Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, et al. 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. *PLoS One*. 2021;16:e0243894.
- (2) Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi A, Roberts TA, et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. *J Sex Med*. 2021;18:1444-54.
- (13) Staphorsius AS, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Burke SM, Schagen SE, et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015;56:190-9.
- (14) Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. *J Pediatr Endocrinol Metab*. 2019;32:1077-81.

9. (17) Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab.* 2015;100:E270-5.
10. (16) Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone.* 2017;95:11-9.
11. (20) Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *J Clin Endocrinol Metab.* 2020;105(12).
12. (15) Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. *J Sex Med.* 2019;16(9):1459-68.
13. (19) Navabi B, Tang K, Khatchadourian K, Lawson ML. Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria. *Pediatrics.* 2021;148(4).
14. (18) van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. 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. *J Bone Miner Res.* 2021;36(5):931-41.
15. (21) Lee JY, Finlayson C, Olson-Kennedy J, Garofalo R, Chan YM, Glidden DV, et al. Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study. *J Endocr Soc.* 2020;4(9):bvaa065.
16. (24) Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. *J Sex Med.* 2016;13(7):1125-32.
17. (23) Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. *J Sex Med.* 2018;15(2):251-60.
18. (22) Klaver M, de Mutsert R, van der Loos M, Wiepjes CM, Twisk JWR, den Heijer M, et al. Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. *Pediatrics.* 2020;145(3).
19. (26) Perl L, Elkon-Tamir E, Segev-Becker A, Israeli G, Brener A, Oren A. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *J Pediatr Endocrinol Metab.* 2021;34(6):741-5.
20. (25) Schulmeister C, Millington K, Kaufman M, Finlayson C, Kennedy JO, Garofalo R, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. *J Adolesc Health.* 2021.
21. (27) Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Juarez-Colunga E, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. *J Clin Endocrinol Metab.* 2020;105(3):e704-14.
22. (28) Tack LJ, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. *Biol Sex Differ.* 2016;7:14.
23. (29) Jarin J, Pine-Twaddell E, Trotman G, Stevens J, Conard LA, Tefera E, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. *Pediatrics.* 2017;139(5).



24. (30) Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LAE, et al. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. *Pediatrics*. 2021;147(4).
25. (33) Pullen Sansfaçon A, Temple-Newhook J, Suerich-Gulick F, Feder S, Lawson ML, Ducharme J, et al. The experiences of gender diverse and trans children and youth considering and initiating medical interventions in Canadian gender-affirming speciality clinics. *International Journal of Transgenderism*. 2019;20:371-87.
26. (32) Segev-Becker A, Israeli G, Elkon-Tamir E, Perl L, Sekler O, Amir H, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. *Endocr Pract*. 2020;26:423-8.
27. (37) Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997;36:263-71.
28. (34) Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr*. 2018;172:431-6.
29. (31) Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001;40:472-81.
30. (36) Mehringer JE, Harrison JB, Quain KM, Shea JA, Hawkins LA, Dowshen NL. Experience of Chest Dysphoria and Masculinizing Chest Surgery in Transmasculine Youth. *Pediatrics*. 2021;147. e2020013300
31. (35) Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. *J Sex Med*. 2021;18:632-45.
32. (38) Littman L. Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners. *Arch Sex Behav*. 2021;50:3353-69.