Bilaga till rapport
Hormonbehandling vid könsdysfori – vuxna
Hormone treatment of adults with gender dysphoria
rapport 348, 2022

Bilaga 3. Inkluderade studier
Appendix 3. Characteristics of included studies: Extracted data

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Terminology*

Male to Female:	**Female to Male:**
MtF	FtM
MF	FM
Natal male	Natal female
Natal boys	Natal girls
Birth assigned boys	Birth assigned girls
Designated male at birth (DMAB)	Designated female at birth (DFAB)
Assigned male at birth (AMAB)	Assigned female at birth (AFAB)
Transfemale	Transmale
Transfeminine (TF)	Transmasculine (TM)
Transgirls	Transboys
Transwomen (TW)	Transmen (TM)
Transgender women	Transgender men
Transgender female	Transgender male
Affirmed female	Affirmed male

** terminology according to the authors of the included studies*

Psychosocial functioning

Author, reference Publication type	**White Hughto et al 2016** (White Hughto and Reisner 2016) Systematic review
Question	**Psychological functioning and quality of life**
End of search	November 2014
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	Three uncontrolled prospective cohort studies, enrolling 247 transgender adults (180 male-to-female [MTF], 67 female-to-male [FTM]) initiating hormone therapy for the treatment of gender identity disorder (prior diagnostic term for gender dysphoria), were identified. The studies measured exposure to hormone therapy and subsequent changes in mental health (e.g., depression, anxiety) and quality of life outcomes at follow-up. Two studies showed a significant improvement in psychological functioning at 3–6 months and 12 months compared with baseline after initiating hormone therapy. The third study showed improvements in quality-of-life outcomes 12 months after initiating hormone therapy for FTM and MTF participants; however, only MTF participants showed a statistically significant increase in general quality of life after initiating hormone therapy. Conclusions: Hormone therapy interventions to improve the mental health and quality of life in transgender people with gender dysphoria have not been evaluated in controlled trials. Low quality evidence suggests that hormone therapy may lead to improvements in psychological functioning

Author, reference Publication type	**Rowniak et al 2019** (Rowniak, Bolt et al. 2019) Systematic review
Question	**Quality of life, depression, anxiety**
End of search	September 2017
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	Seven observational studies met the inclusion criteria for this review. The total number of transgender participants in all the included studies was 552. Population sizes in the studies ranged from 14 to 163. In general, the certainty of the findings was low to very low due to issues with imprecision and indirectness. The use of cross-sex hormones was associated with improved quality of life, depression, and anxiety scores, although no causation can be inferred. Conclusions: Transgender participants who were prescribed cross-sex hormones had statistically significant scores demonstrating improvement on the validated scales that measured quality of life, anxiety and depression when compared to transgender people who had enrolled in a sex-reassignment clinic but had not yet begun taking cross sex hormones. However, because the certainty of this evidence was very low to low, recommendations for hormone use to improve quality of life, depression and anxiety could not be made. High-quality research on this issue is needed, as is the development of a quality-of-life tool specific to the transgender population

Author, reference Publication type	**Nobili et al 2018** (Nobili, Glazebrook et al. 2018) Systematic review
Question	**Quality of life (QOL)**
End of search	July 2017
Methodology	PRISMA
Synthesis	Narrative 29 studies Meta analysis of mental related QOL compared with general population (14 studies)
Population	MtF and FtM
Results/authors' conclusions	From 94 potentially relevant articles, 29 studies were included within the review and data extraction for meta-analysis was available in 14 studies. The majority of the studies were cross-sectional, lacked controls and displayed moderate risk of bias. Findings from the systematic review suggested that transgender people display poor QoL, independent of the domain investigated. Pooling across studies showed that transgender people report poorer mental health QoL compared to the general population (−0.78, 95% CI = −1.08 to −0.48, 14 studies). However, meta-analysis in a subgroup of studies looking at QoL in participants who were exclusively post-CHT found no difference in mental health QoL between groups (−0.42, 95% CI = −1.15 to 0.31; 7 studies). There was insufficient data for a pre-treatment subgroup. Evidence suggests that transgender people have lower QoL than the general population. Some evidence suggests that QoL improves post-treatment. Better quality studies that include clearly defined transgender populations, divided by stage of gender affirming treatment and with appropriate matched control groups are needed to draw firmer conclusions.

Author, reference Publication type	**Baker et al 2021** (Baker, Wilson et al. 2021) Systematic review
Question	**Quality of life, depression, anxiety, suicide**
End of search	June 2020
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	We included 20 studies reported in 22 publications. Fifteen were trials or prospective cohorts, one was a retrospective cohort, and 4 were cross-sectional. Seven assessed QOL, 12 assessed depression, 8 assessed anxiety, and 1 assessed death by suicide. Three studies included trans-feminine people only; 7 included trans-masculine people only, and 10 included both. Three studies focused on adolescents. Hormone therapy was associated with increased QOL, decreased depression, and decreased anxiety. Associations were similar across gender identity and age. Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions. We could not draw any conclusions about death by suicide. Future studies should investigate the psychological benefits of hormone therapy among larger and more diverse groups of transgender people using study designs that more effectively isolate the effects of hormone treatment.

Author, reference Publication type	**Kristensen et al 2021** (Kristensen, Christensen et al. 2021) Systematic review
Question	**Aggressiveness from testosterone**
End of search	November 2019
Methodology	PRISMA
Synthesis	Narrative
Population	FtM
Results/authors' conclusions	Seven prospective cohort studies investigating aggression-dimensions pre- and post-testosterone therapy, reporting on data from 664 transgender men, were eligible. The studies had moderate to high risk of bias due to non-randomization, lack of appropriate control groups, and reliance on self-report. The behavioural tendency to react aggressively increased in three studies out of four (at three months follow-up), whereas only one study out of five found angry emotions to increase (at seven months follow-up). In contrast, one out of three studies reported a decrease in hostility after initiation of testosterone therapy. The remaining studies found no change in aggressive behaviour, anger or hostility during hormone therapy. Discussion and conclusion: Four out of seven studies reported an increase in aggression-related constructs, while one study reported a decrease. In all studies reporting changes, the follow-up period was less than 12 months, indicating that gender-affirming testosterone therapy could have a short-term impact on aggression-related constructs. However, the available studies carried a risk of bias, which indicates a need for further research.

Author, reference Publication type	**Karalexi et al 2020** (Karalexi, Georgakis et al. 2020) Systematic review
Question	**Cognition**
End of search	June 2019
Methodology	Moose guidelines, search only in Medline.
Synthesis	Metaanalysis
Population	MtF and FtM
Results/authors' conclusions	Ten studies (7 cohort and 3 cross-sectional) were eligible representing 234 birth-assigned males (aM)(MtF) and 150 birth-assigned females (aF)(FtM). The synthesis of cohort studies (n = 5) for visuospatial ability following hormone treatment showed a statistically significant enhancement among aF (FtM) (g = 0.55, 95% confidence intervals [CI]: 0.29, 0.82) and an improvement with a trend towards statistical significance among aM (MtF) (g = 0.28, 95%CI: -0.01, 0.58). By contrast, no adverse effects of hormone administration were shown. No heterogeneity was evident in most meta-analyses. Interpretation: Current evidence does not support an adverse impact of hormone therapy on cognitive function, whereas a statistically significant enhancing effect on visuospatial ability was shown in aF. (FtM)

Author, Year Title Country Study design	**Fisher et al 2016** (Fisher, Castellini et al. 2016) *Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons* Italy Cross-sectional 2008-2015 Longitudinal 2012-2015
POPULATION (ages) Age at start Age in cohort	Age in cohort: years (mean, SD) <u>Cross-sectional sample:</u> 33.90 (9.19) CHT group 29.11 (9.28) no CHT group <u>Prospective sample:</u> Age at baseline: 32.52 (11.06) MtF 26.32 (7.29) FtM
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	537 initial sample (calc. by SBU) 178 excluded <u>359 cross-sectional study:</u> 140 female to male (FtM) 219 male to female (MtF) 167 CHT group 192 no-CHT group <u>54 prospective study: (before CHT start)</u> 28 MtF 26 FtM In excluded population (n=178): 23 dropouts during assessment 3 disorders of sexual development 3 personality disorder
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Estradiol valerate, oral ethinyl estradiol, oral estradiol hemihydrate, transdermal estradiol gel Anti-androgens: finasteride, dutasteride, cyproterone acetate, spironolactone Testosterone enanthate Testosterone undecanoate 1000 mg i.m. (repeated after 6 w, after 12 w, then between 10–14 weeks). Testosterone transdermal Mixed CHT profile: more than one type of hormone formulation at the same time. Mental health support every 3 months (details not provided)
INTERVENTION (time) HT duration Follow-up times	Hormone treatment duration: <u>Cross sectional study</u>: CHT group (n=167): Days of hormone therapy (mean, range): 1331 (31; 13445) MtF (n= 125) *[note range 1 month – 36 years]* 323 (33; 1095) FtM (n= 42) *[note range 1 month – 3 years]* <u>Longitudinal study:</u> Follow-up times: 3, 6, 12, 24 months
OUTCOMES - All reported outcomes	**Psychometric measures:** Global severity index (GSI) Body Uneasiness Test (BUT): higher scores indicate greater body uneasiness (max score not indicated) Beck Depression Inventory (BDI) II Gender Identity/ Gender Dysphoria questionnaire (GIDYQ-AA): low score associated with higher dysphoria Symptom Checklist 90 revised (SCL-90-R) Anthropometric: height, weight, waist, BMI Testis volume, Breast development, hair growth, genital features Glutamic-oxaloacetic transaminase, glutamic-pyruvate transaminase

RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Psychological well-being:** (mean ± SE) <u>Cross sectional study:</u> <u>Psychological (BUT-global severity index [GSI]) change ratios:</u> Female-to-male: 2.34 ± 0.09 no-CHT 1.80 ± 0.14 CHT 0.53 ± 0.17 Adjusted Difference Value Male-to-female: 2.42 ± 0.91 no-CHT 1.69 ±1.01 CHT 0.53 ± 0.17 Adjusted Difference Value <u>Beck Depression Inventory (BDI-II):</u> Female-to-male: 7.17 ± 6.97 no-CHT 3.08 ± 3.32 CHT 4.03 ± 2.06 Adjusted Difference Value Male-to-female: 9.41 ± 7.91 no-CHT 7.31 ± 8.55 CHT 1.86 ± 1.67 Adjusted Difference Value <u>Gender Identity/Dysphoria Questionnaire (GIDYQ-AA)</u> Female-to-male: 2.19 ± 0.36 no-CHT 2.10 ± 0.27 CHT 0.11 ± 0.13 Adjusted Difference Value Male-to-female: 2.28 ± 0.34 no-CHT 2.26 ± 0.49 CHT 0.01 ± 0.093 Adjusted Difference Value

Author, Year Title Country Study design	**Ristori et al 2020** (Ristori, Cocchetti et al. 2020) *Hormonal Treatment Effect on Sexual Distress in Transgender Persons* Italy Cross-sectional + longitudinal substudy, 2008-2017
POPULATION (ages) Age at start Age in cohort	Cross-sectional study (mean) 31.56 ± 11.24 transwomen 28.32 ± 8.19 transmen Longitudinal study: 29.57 ± 10.89 transwomen 27.57 ± 10.89 transmen Transmen reported an earlier GD onset (before age of 12) than transwomen (78.1% and 64.9 %)
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	301 transgender persons 160 transwomen 141 transmen 54 excluded Cross-sectional: HT group: 55 transwomen (MtF) 13 transmen (FtM) No HT group: 105 transwomen (MtF) 128 transmen (FtM) Longitudinal: Before HT start: 38 transwomen (MtF) 40 transmen (FtM) at 2 year FU: 36 transwomen (MtF) 36 transmen (FtM)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Transwomen: estradiol valerate, oral (2-6 mg/day) estradiol gel, transdermal (1 mg/3 times day) cyproterone acetate, oral (50 mg) Transmen: testosterone undecanoate, i.m. (1000 mg) , first injection being repeated after 6 weeks and 12 weeks. Psychological support: Standardized mental health support every 3 months (not further specified).
INTERVENTION (time) HT duration Follow-up times	Cross sectional study: Cumulative days of HT: (mean, range) 1825 (range 60 - 11284) days transwomen *[note range 2 months – 31 years]* 590 (range 300 - 1800) days transmen *[note range 1 – 5 years]* Longitudinal study: HT duration: 2 years Follow-up times: 3, 6, 12, 24 months
OUTCOMES - All reported outcomes	**Psychometric measures:** Sexual distress (Female Sexual Distress Scale-Revised) Body uneasiness test (BUT) Beck depression inventory (BDI-II) General psychopathology (Symptom checklist-90 revised, SCL-90) Utrecht Gender Dysphoria Scale (UGDS) Toronto Alexithymia Scale (TAS-20) Autism Spectrum Quotient (AQ) Leibowitz Social Anxiety Scale (LSAS) Humiliation Inventory (HI) Discrimination and Stigma Scale (DISC-12) Female Sexual Function Index (FSFI) Anthropometric measures: height, weight waist, breast development, hair growth cortisol
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Sexual distress:** Reduced across time in both transwomen and transmen. Transmen showed a significant reduction in sexual distress at all time points (3, 6, 12 and 24 months). Transwomen showed a significant reduction only at time points later than 3 months.

Author, Year Title Country Study design	**Van De Grift et al 2017** (van de Grift, Elaut et al. 2017) *Effects of Medical Interventions on Gender Dysphoria and Body Image: A Follow-Up Study* The Netherlands Survey and medical records, applicants for medical interventions 2007 and 2009
POPULATION (ages) Age at start Age in cohort	Minimum age: 17 years or older at clinical entry Age in cohort: (mean SD) 39.2 (SD 12.8) natal male 30.6 (SD 11.3) natal female
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	201 135 natal males 66 natal females
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Cross-sex hormone therapy (type and dose not specified) Surgery (epilation, vaginoplasty, breast augmentation, Adam's apple reduction, facial feminization surgery; mastectomy, oophorectomy/hysterectomy, penis construction)
INTERVENTION (time) HT duration Follow-up times	<u>Years since medical intervention</u> (mean (SD)) Cross-sex hormone therapy: 4.6 (2.3) natal males 4.9 (1.6) natal females <u>Years since last surgery:</u> 2.4 (1.4) natal males 2.6 (1.4) natal females
OUTCOMES - All reported outcomes	Medical Interventions received Utrecht Gender Dysphoria Scale (UGDS) Body Image Scale (BIS) Physical Appearance Scale Body satisfaction Psychological burden: Symptom Checklist 90 (SCL-90), Global Severity Index (GSI)
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Health care pathway:** <u>Medical interventions received n (%)</u> 29 (14%) no intervention 36 (18%) hormone therapy only 136 (68%) hormone therapy & surgery Assigned Male at Birth (n = 135): 110 (83%) hormone therapy 79 (61%) vaginoplasty 38 (30%) mamma augmentation 80 (86%) epilation 9 (8%) Adam's apple reduction 8 (6%) facial feminization surgery Assigned Female at Birth: (n = 66): 59 (91%) hormone therapy 53 (79%) mastectomy 52 (78%) oophorectomy/hysterectomy 18 (27%) penis construction <u>Gender Dysphoria:</u> The average sum scores of GD: UGDS admission: 53.1 (SD 6.7) UGDS no intervention: 20.2 (SD 12.8) UGDS hormones: 20.1 (SD 8.8) UGDS hormones & surgery: 15.5 (SD 4.3) "The scores were significantly lower in all of the follow-up groups when compared with clinical admission, showing a decrease in GD". <u>Body Image: Overall Body Satisfaction:</u> Higher overall body dissatisfaction at admission (BIS admission: 3.34 [SD 0.52]) compared with follow-up: People without medical interventions (BIS no intervention: 3.24 [SD 0.64]) were significantly more dissatisfied with their body than the people who received hormone therapy with(out) surgery (BIS hormones: 2.72 [SD 0.73], BIS hormones & surgery: 2.51 [SD 0.58]).

Author, Year Title Country Study design	**Van Heesewijk et al 2021** (van Heesewijk, Dreijerink et al. 2021) *Long-Term Gender-Affirming Hormone Therapy and Cognitive Functioning in Older Transgender Women Compared with Cisgender Women and Men* The Netherlands Comparative cross sectional
POPULATION (ages) Age at start Age in cohort	Age range 55 - 69 years
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	37 transgender women 222 cisgender women and men
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	CSHT not specified
INTERVENTION (time) HT duration Follow-up times	At least 10 years range 10.2 to 41.6 years
OUTCOMES - All reported outcomes	Cognitive function Mini-Mental State Examination (MMSE) Category Fluency animals Letter Fluency D 15-Word test (15WT) immediate and delayed recall
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Cognitive function:** <u>Mini-Mental State Examination (MMSE) score:</u> +0.9 (95% CI 0.4 - 1.5) transgender women vs cisgender women +1.1 (95% CI 0.4 - 1.8) transgender women vs cisgender men <u>15-Word test (15WT)</u> 15WT immediate recall: -5.5(95% CI -7.6 to -3.4) transgender women vs cisgender women 15WT delayed recall: -2.7 (95% CI -3.7 to -1.7) transgender women vs cisgender women <u>Fluency animals and Fluency D</u> Equal to cisgender women <u>All other tests:</u> Transgender women performed similar to cisgender men.

Mortality

Author, Year Country Title Study design	**de Blok 2021 (de Blok, Wiepjes et al. 2021)** *Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria.* The Netherlands Retrospective cohort study, register, 1972 - 2018
POPULATION (ages) Age at Tx start Age in cohort	At start of hormone treatment (median, IQR): 30 years (24–42) transgender women 23 years (20–32) transgender men
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	8831 at intake 4568 included: 2927 transgender women 1641 transgender men 4263 excluded
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Transgender women: Oestrogen: ethinyl oestradiol (25 - 100 µg /day), conjugated oestrogens (0.625 - 1.25 mg /day), oestradiol patches (50 - 150 µg /day twice weekly), implants (20 mg / 3–6 months), injections (10 - 100 mg / 2–4 weeks), valerate (2 - 6 mg day) gel (0.75 - 3 mg /day) [From 2001: mainly oestradiol valerate, patches, or gel]. Anti-androgens: cyproterone acetate (10 - 100 mg /day) spironolactone (100 - 200 mg /day) Transgender men: testosterone gel (20 - 100 mg daily), intramuscular testosterone esters (125 - 250 mg every 2–3 weeks), or testosterone undecanoate oral [40 - 160 mg /day] or testosterone undecanoate intramuscular [1000 mg / 10–14 weeks]). Progestogens: lynestrenol (5 - 10 mg daily). Surgery: orchiectomy Previous gonadectomy 1891 (64·6%) 1006 (61·3%)
INTERVENTION (time) HT duration Follow-up times	The median follow-up time: 11 years (IQR 4–22) transgender women 5 years (IQR 2–17) transgender men Total follow-up time: 40 232 person-years for transgender women 17 285 person-years for transgender men [Person-time: defined as number of years from start date of hormone treatment to first terminating event]. Terminating events: either date of death, end of study period (Dec 31, 2018) last visit at our clinic for the people who could not be linked to CBS.

OUTCOMES - **All reported outcomes**	Standardised mortality ratios (SMRs): calculated using general population mortality rates stratified by age, calendar period, and sex. Cause-specific mortality calculated. Data were linked to Statistics Netherlands (CBS). Cause of death determined from death certificates, filled out by the medical doctor at time of death. If the cause of death was not known, it was registered on these forms as unknown. Each deceased person is registered with a single death cause (primary cause of death). Non-natural causes of death (only for deaths between 1996 and 2018): suicide other non-natural cause (not further specified)
RESULTS – **Extracted outcomes** (95% confidence interval if not indicated otherwise)	**Mortality:** <u>Standardised mortality ratios (SMRs):</u> Transgender women: 317 (10.8%) of 2927 died, which was higher than expected compared with general population men (SMR 1.8, 95% CI 1.6–2.0) and compared with general population women (SMR 2.8, 2.5–3.1). Transgender men: 44 (2.7%) of 1641 died, which was higher than expected compared with general population women (SMR 1.8, 95% CI 1.3–2.4) but not compared with general population men (SMR 1.2, 95% CI 0.9–1.6). <u>Cause-specific mortality:</u> Transgender women: high for cardiovascular disease, lung cancer, HIV-related disease, and suicide. Transgender men: high for non-natural causes of death. <u>Suicide:</u> Transwomen: 18 individuals; SMR 3.1 (1.8–4.7) compared with general population men SMR 6·8 (4.1–10.3) compared with general population women Transmen: <10 individuals; SMR 2.8 (0.6–6.8) compared with general population women SMR 1·2 (0.3–3.0) compared with general population men No decreasing trend in mortality risk was observed over the five decades studied. "Increased mortality risk in transgender people using hormone treatment, regardless of treatment type. This increased mortality risk did not decrease over time. The cause-specific mortality risk because of lung cancer, cardiovascular disease, HIV-related disease, and suicide gives no indication to a specific effect of hormone treatment".
Comments	Exclusions: 4263 people excluded: 3022 had never used hormone treatment 574 started hormone treatment younger than age 17 years 294 previously used puberty blockers before gender-affirming hormone treatment 335 had no follow-up visit data available after the start of hormone treatment 38 alternated between testosterone and oestradiol use

Tumours

Benign brain tumours

Author, Year Title Country Study design	**Nota et al. 2018** (Nota, Wiepjes et al. 2018) *The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment* The Netherlands Retrospective chart study, 1972 - 2015
POPULATION (ages) Age at start Age in cohort	At start of CSHT (median, IQR): 31 years (IQR 23–41) transwomen 23 years (IQR 18–31) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	3928 2555 transwomen 1373 transmen
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	<u><18 years:</u> triptorelin cyproterone acetate, lynestrenol <u>From age 16:</u> oestrogens: oestradiol valerate, ethinylestradiol, or oestradiol hemihydrate) testosterone esters <u>Adults:</u> oestrogens (ethinylestradiol, conjugated oestrogens, oestradiol patches, oestradiol implants, oestradiol injections, oestradiol valerate, oestradiol gel) cyproterone acetate (CPA) spironolactone testosterone gel, testosterone esters i.m., testosterone undecanoate im or oral) lynesterol (if uterine bleeding) Surgery: Most transwomen had received orchiectomy but still cyproterone acetate at time of diagnosis.
INTERVENTION (time) HT duration Follow-up times	Follow up time: (median) 6.22 years transwomen range 0.01–54.77 years *[Note range 3 days – 54 years]* 4.16 years transmen range 0.02–41.66 years *[Note range 7 days – 41 years]* 23 935 person-years transwomen 11 212 person-years transmen
OUTCOMES - All reported outcomes	Benign brain tumors: meningiomas pituitary adenomas vestibular schwannomas
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Benign brain tumors.** Standardized incidence ratio (SIR, 95% CI): Transwomen: 8 meningiomas Incidence higher than in: female population (SIR 4.1, 1.9–7.7) male population (SIR 11.9, 5.5–22.7) 9 prolactinomas Incidence higher than in: female population (SIR 4.3, 2.1–7.9) male population (SIR 26.5, 12.9–48.6) Transmen: 2 somatotrophinomas Incidence higher than in: a general European population (incidence rate females = incidence rate males; SIR 22.2, 3.7–73.4)

Breast cancer

Author, Year Title Country Study design	**Gooren et al 2013** (Gooren, van Trotsenburg et al. 2013) *Breast Cancer Development in Transsexual Subjects Receiving Cross-Sex Hormone Treatment* The Netherlands Retrospective register, cohort 1975 - 2011
POPULATION (ages) Age at start Age in cohort	16–83 years Age at start: (mean ± SD) 29.3 ± 12.7 (16 - 83 years) MtF 23.2 ± 6.5 (16 - 66 years) FtM
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	3102 2307 male-to-female (MtF) 795 female-to-male (FtM)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	estrogen anti-androgen testosterone Note: *Not indicated how many FtM individuals that underwent mastectomy* *Not indicated how many FtM individuals that underwent ovariectomy*
INTERVENTION (time) HT duration Follow-up times	HT duration: 5 to >30 years Follow-up time: 21.4 ± 8.7 years (range 6-43 years) MtF 20.1 ± 7.3 years (range 6-36 years) FtM 52,370 person-years of exposure MtF 15,974 total years of exposure FtM
OUTCOMES - All reported outcomes	Number of people with breast cancer
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Incidence of breast cancer** (per 100 000 patient-years of follow-up): MtF: 1 observed case 1 probable case Estimated rate: 4.1 per 100,000 person-years (95% CI 0.8–13.0) lower than expected for female breast cancer, within expectations if viewed as male breast cancer. FtM: 1 observed case Estimated rate: 5.9 per 100,000 person-years (95% CI 0.5–27.4) lower than expected for female breast cancer, within expected norms for male breast cancer.

Author, Year Title Country Study design	**Brown** et al 2015 (Brown and Jones 2015) *Incidence of breast cancer in a cohort of 5,135 transgender veterans* USA Veterans Health Administration data chart review (encounter and prescription data), 1996 - 2013
POPULATION (ages) Age at start Age in cohort	Age in cohort, years (mean ± SD) 55.76 ± 13.48 overall 55.65 ± 12.90 female *(Note: not specified if natal female or transfemale)* 55.80 ± 13.73 male *(Note: not specified if natal male or transmale)*
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	5135 transgender veterans 1579 female (not specified if natal female or transfemale) 3556 male (not specified if natal male or transmale)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	52 % ≥1 dose of CSH treatment " ≥1 dose " not specified further CSH use: Estrogen: 1116 (70.68%) female 1112 (31.27%) male Testosterone: 218 (13.81%) female 361 (10.15%) male
INTERVENTION (time) HT duration Follow-up times	Exposure CSH treatment: Patient-years: (mean ± SD) 9.73 ± 4.62 overall 9.72 ± 4.61 female 9.73 ± 4.62 male
OUTCOMES - All reported outcomes	Incidence of breast cancer
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Incidence of breast cancer:** 10 observed cases: 7 in FtM 2 in MtF 1 in natal male transvestic fetishism* (*unclear hormonal treatment) Overall incidence rate: 20/ 100 000 (95 % CI 9.6–36.8) patient-years of CSH treatment. Average age at diagnosis: 63.8 years (SD 8.2)

Author, Year Title Country Study design	**De Blok** et al 2019 (De Blok, Wiepjes et al. 2019) *Breast cancer risk in transgender people receiving hormone treatment* The Netherlands Retrospective, nationwide cohort study, 1991-2016
POPULATION (ages) Age at start Age in cohort	Age at start: median (IQR) 28 years (21-38) overall 31 years (23-41) transwomen 23 years (19-31) transmen Age in cohort: median (IQR) 47 years (31-57) overall 51 years (38-60) transwomen 39 years (26-51) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	3489 2260 male at birth (MtF) 1229 female at birth (FtM)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Estrogen (mainly estradiol valerate, estradiol patches, or estradiol gel): ethinyl-estradiol (25 to 100 µg /day), conjugated oestrogens (0.625 to 1.25 mg/ daily), estradiol patches (50 to 150 µg/24 hours twice weekly), estradiol implants (20 mg every 3 to 6 months), estradiol injections (10 to 100 mg every 2 to 4 weeks), estradiol-valerate (2 to 6 mg daily), or estradiol gel (0.75 to 3.0 mg daily). Anti-androgen (cyproterone acetate or spironolactone) Testosterone gel (20 to 100 mg daily), intramuscular testosterone esters (150 to 250 mg every 2 to 3 weeks), or oral or intramuscular testosterone undecanoate (orally: 40 to 160 mg daily, intramuscularly: 1000 mg every 10 to 14 weeks) Progestogens (lynestrenol (5 to 10 mg daily) if continued menstruation Surgery: Gonadectomy: 68% *Not indicated how many FtM individuals that underwent mastectomy.* *Not indicated how many FtM individuals that underwent ovariectomy.*
INTERVENTION (time) HT duration Follow-up times	HT duration: (median, range) range 2-37 years: 18 years (2-37) transwomen 15 years (2-17) transmen Follow-up time: Transwomen: 33 991 years total person time Transmen: 14 883 years total person time
OUTCOMES - All reported outcomes	Incidence of breast cancer Hormone levels, Hormone receptor status BMI
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Incidence of breast cancer** Transwomen: 18 observed cases of breast cancer 15 invasive breast cancer 3 noninvasive breast cancer Invasive breast cancer: diagnosis at median 50 years (IQR 43-55) after 18 years (range 7-37) of HT 67% ductal type 83 % estrogen receptor positive, 67% progesterone receptor positive SIR (standardized incidence ratio): 46.7 (27.2 - 75.4) Ref: incidence ratio cisgender men 0.3 (0.2-0.4) Ref: incidence ratio cisgender women Transmen: 4 observed cases invasive breast cancer SIR (standardized incidence ratio): 58.9 (18.7-142.2) Ref: incidence ratio cisgender men 0.2 (0.1-0.5) Ref: incidence ratio cisgender women

Prostate cancer

Author, Year Title Country Study design	**Gooren & Morgentaler 2014** (Gooren and Morgentaler 2014) *Prostate cancer incidence in orchidectomised M-t-F transsexual persons treated with oestrogens* The Netherlands Review of Medical records, 1975 and 2006
POPULATION (ages) Age at start Age in cohort	At start of treatment: range 15–83 years 29.3 ± 12.7 years
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	2306 MtF orchidectomised
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Oestrogens: up to 1993: ethinyl oestradiol (100 µg /day) after 1993: oestradiol valerate (4 mg /day) or transdermal 17beta-oestradiol (100 µg /day). Anti-androgens: usually cyproterone acetate 100 mg /day) Surgery: Orchiectomy (all individuals)
INTERVENTION (time) HT duration Follow-up times	Follow-up time: min 6 years mean 21.4 years range <5 years - >30 years 51 173 person-years of exposure and follow-up
OUTCOMES - All reported outcomes	Prostate cancer incidence.
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Prostate cancer incidence:** 1 case of prostate cancer Overall incidence of PCa: 0.04% (0.13% for individuals who had initiated hormonal treatment after at 40 years or later) Only a limited number of transwomen (MtF) had reached older age.

Author, Year Title Country Study design	**de Nie et al 2020** (de Nie, de Blok et al. 2020) *Prostate Cancer Incidence under Androgen Deprivation:* *Nationwide Cohort Study in Trans Women Receiving Hormone Treatment* The Netherlands Retrospective cohort study of medical files, 1972 - 2016
POPULATION (ages) Age at start Age in cohort	Age at start of hormonal treatment: (median (IQR) 31 (23–41) years Age at time of study: (median (IQR) 50 (37–59) years
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	2281 transwomen
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Cyproterone acetate Spironolactone (sporadically) Antiandrogenic treatment discontinued after bilateral orchiectomy. estradiol valerate estradiol patches estradiol gel ethinyl estradiol conjugated estrogens estradiol implants estradiol injections From 2001 onward: mainly estradiol valerate, estradiol patches, or estradiol gel. People <18 years when started on hormone treatment: triptorelin
INTERVENTION (time) HT duration Follow-up times	Follow-up time (median): 14 years (IQR 7-24) 37 117 years total follow-up time
OUTCOMES - All reported outcomes	Hormone use Data on gender-affirming surgery Database was linked to the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands (PALGA) to obtain data regarding prostate cancer histology and the date of prostate cancer diagnosis
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Prostate cancer diagnosis:** 6 transwomen diagnosed after a median 17 years (range 10-24 years), hormone treatment at median age 47 years (range 38-58) 4 had undergone orchiectomy, median 11 years (range 2-14), prior to the prostate cancer diagnosis. Median age at time of prostate cancer diagnosis: 64 years (range 53-77). Incidence rate: 16.2 cases per 100 000 years. 30 expected prostate cancer cases, based on age-specific incidence rates. A lower prostate cancer risk in transwomen than in Dutch reference males (SIR 0.20, 95% confidence interval 0.08-0.42). Androgen deprivation had a preventive effect on the initiation and development of prostate cancer.

Author, Year Title Country Study design	**Silverberg et al 2017** (Silverberg, Nash et al. 2017) *Cohort study of cancer risk among insured transgender people* USA Cohort medical record review, 2006 - 2014
POPULATION (ages) Age at start Age in cohort	At index date: 39 years TF 32 years TM
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	2791 transfeminine 2098 transmasculine
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Not reported
INTERVENTION (time) HT duration Follow-up times	Follow-up time (mean): 4 years TF 3.5 years TM Follow-up from index date until first occurrence of a cancer diagnosis, disenrollment from the plan for more than 90 days, death, or end of the follow-up. Index date: defined as date of first recorded evidence of transgender status
OUTCOMES - All reported outcomes	Incident primary cancer cases ascertained via linkages to each health plan's Surveillance Epidemiology and End Results (SEER) affiliated cancer registry All cancers combined Individual cancer sites with at least five cases Grouped categories of cancers with shared risk factors: including smoking-related cancers, viral infection-induced cancers, screening-detectable cancers)
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	Cancer incidence rates and adjusted hazard ratios (95% CI) compared with matched males and females. Reference males and females matched on year of birth, enrollment at index date, race, and site. Transfeminine (MtF): Any incident cancer (54 cases) 495 (379, 646) incidence rate 1.0 (0.7, 1.3) aHR vs reference males 1.0 (0.7, 1.3) aHR vs reference female Prostate cancer (8 cases) 72 (36, 145) 0.4 (0.2, 0.9) reference males Transmasculine (FtM): Any incident cancer (25 cases) 337 (228, 499) incidence rate 1.3 (0.8, 1.9) aHR vs reference males 1.0 (0.6, 1.4) aHR vs reference females Breast cancer (7 cases) 82 (10, 673) aHR vs reference males 0.9 (0.4, 1.9) aHR vs reference females Lymphatic and hematopoietic cancers: included leukemias, myelomas, and Hodgkin and non-Hodgkin lymphomas. Endocrine gland cancers: included cancers of the thyroid gland, adrenal gland, pituitary gland, and pineal gland.

Other tumors

Author Pulblication year	**McFarlane et al 2018** (McFarlane, Zajac et al. 2018) Systematic review
Question	Cancer mortality,
End of search	April 2018
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	The search strategy identified 307 studies. Excluding those that did not meet inclusion criteria, 43 studies (7 cohort studies, 2 cross-sectional studies and 34 case reports) were reviewed. Retrospective cohort studies suggest no increase in risk of tumour development in transgender individuals receiving GAHT compared to the general population. Notably, the mean ages of cohorts were young and were treated with GAHT for insufficient durations to assess tumour risk. Case reports raise potential associations between high-dose oestradiol and anti-androgen therapy with prolactinoma and meningioma, respectively.

Author, Year Title Country Study design	**de Nie et al 2022** (de Nie, Wiepjes et al. 2022) *Incidence of testicular cancer in trans women using gender-affirming hormonal treatment* The Netherlands Nationwide retrospective cohort study, 1972 - 2017
POPULATION (ages) Age at start Age in cohort	Age at start (median, IQR) 29 years (22–41)
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	3026 transwomen (MtF) 1112 no bilateral orchidectomy 1914 bilateral orchidectomy: 722 histopathological analysis of resected specimens
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Oestrogens: transdermal, oral, or intramuscular: oestradiol patches (50–150 µg/24 h twice weekly) oestradiol gel (0.75–3.0 mg daily) oestradiol valerate (2–6 mg daily) ethinyl oestradiol (25–100 µg daily) conjugated oestrogens (0.625–1.25 mg daily) oestradiol implants (20 mg every 3–6 months) oestradiol injections (10–100 mg every 2–4 weeks) [from 2001: mainly oestradiol patches, oestradiol gel, or oestradiol valerate] Anti-androgens: cyproterone acetate (10–100 mg daily) spironolactone (100–200 mg daily) sporadically. GnRH: people who started hormonal treatment when they were aged <18 years: often GnRHa (triptorelin), prior to the start with oestrogens and continued until orchidectomy. Orchidectomy: bilateral orchidectomy at median 2.3 years (IQR 1.7–3.4) after commencing CSHT. Data linked to national pathology database to obtain testicular cancer diagnoses. Subgroup analyses performed in testicular tissues sent for histopathological analysis at the time of bilateral orchidectomy, and when follow-up exceeded 5 years.
INTERVENTION (time) HT duration Follow-up times	Follow-up time (median, IQR): 2.3 (1.6–3.7) years Follow-up > 5 years subgroup (n= 523): 8.9 years (6.4–13.9)
OUTCOMES - All reported outcomes	Testicular cancer Standardised incidence ratio (SIR) calculated using number of observed testicular cancer cases and number of expected cases based on age-specific Dutch incidence rates.
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Testicular cancer:** In transwomen with no bilateral orchidectomy (n=1112): 2 cases identified (2.4 cases expected), SIR 0.8 (95% CI 0.1–2.8) In transwomen with bilateral orchidectomy (n=1914): 1 testicular cancer case encountered in an orchidectomy specimen (0.1%) In trans women with a follow-up time of >5 years (n=523): no testicular cancer was observed (median follow-up 8.9 years [IQR 6.4–13.9] years).
	Excluded: people who never used GAHT those who underwent bilateral orchidectomy prior to the start of GAHT those of whom the start date of GAHT was unknown. aged <18 years at the time of the study (2020) having used female and male hormones alternatingly during the follow-up period

Bone health

Author, reference Publication type	**Delgado-Ruiz et al 2019** (Delgado-Ruiz, Swanson et al. 2019) Systematic review
Question	Bone mineral density, bone metabolism, bone turnover.
End of search	December 2018
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	The initial search returned 564 articles. After reading the titles and abstracts, 471 articles were excluded. The remaining 93 articles were read in full, and 84 articles were excluded. Nine manuscripts that fulfilled the inclusion criteria were included for this review. The considerable variability between studies did not allow a meta-analysis. All the studies were completed' Calcium, phosphate, alkaline phosphatase, and osteocalcin levels remained stable. PINP increased in transwomen and transmen meanwhile, CTX showed contradictory values in transwomen and transmen. Finally, reduced BMD was observed in transwomen patients receiving long-term cross-sex pharmacotherapy Considering the limitations of this systematic review, it was concluded that long-term cross-sex pharmacotherapy for transwomen and transmen transgender patients does not alter the calcium, phosphate, alkaline phosphatase, and osteocalcin levels, and will slightly increase the bone formation in both transwomen and transmen patients. Furthermore, long-term pharmacotherapy reduces the BMD in transwomen patients.

Author, reference Publication type	**Sing-Ospina et al 2017** (Singh-Ospina, Maraka et al. 2017) Systematic review
Question	Bone mineral density
End of search	April 2015
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	Thirteen studies evaluating 639 transgender individuals were identified [392 male-to female (MTF), 247 female-to-male (FTM)] In FTM individuals and compared with baseline values before initiation of masculinizing hormone therapy, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip bone mineral density (BMD) when assessed at 12 and 24 months. In MTF individuals and compared with baseline values before initiation of feminizing hormone therapy, there was a statistically significant increase in lumbar spine BMD at 12 months (0.04 g/cm2; 95% CI, 0.03 to 0.06 g/cm2) and 24 months (0.06 g/cm2; 95% CI, 0.04 to 0.08 g/cm2). Fracture rates were evaluated in a single cohort of 53 MTF and 53 FTM individuals, with no events at 12 months. The body of evidence is derived mostly from observational studies at moderate risk of bias.

Author, Year Title Country Study design	**Vlot et al 2019** (Vlot, Wiepjes et al. 2019) *Gender-Affirming Hormone Treatment Decreases Bone Turnover in Transwomen and Older Transmen* The Netherlands Part of the European Network for Investigation of Gender Incongruence (ENIGI) study, 2012 – 2016
POPULATION (ages) Age at start Age in cohort	Age in cohort (median, IQR): 30 years (IQR 24 - 41) transwomen 24 years (IQR 21 - 33) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	253 121 transwomen 132 transmen
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Estrogen: estradiol valerate, oral (2 - 4mg/ day) or estradiol patches, transdermal (50 - 100 µg/24 h/twice a week) Cyproterone acetate (50 to 100 mg daily, oral) Testosterone gel, transdermal (50 mg/day), testosterone esters, i.m. (250 mg/2 to 3 weeks) testosterone undecanoate, i.m. (1000 mg/12 weeks) lynestrenol for a short period if menses persisted while using testosterone
INTERVENTION (time) HT duration Follow-up times	Duration of CSHT: 1 year
OUTCOMES - All reported outcomes	Bone turnover markers (BTMs): P1NP Alkaline phosphatase (ALP) Sclerostin CTx BMD of the total hip, the femoral neck, and the lumbar spine Hormone levels 25OHD creatinine AST = aspartate transaminase; ALT = alanine transaminase; γGT = gamma-glutamyltransferase.
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Bone turnover markers:** % change (95% CI) Transwomen: ALP decreased in 19% (–21 to –16) CTx decereased in 11% (–18 to –4) Sclerostin decreased in 8% (–13 to –4) Transmen: P1NP increased in 33% (24 to 42) ALP increased in 16% (12 to 20) Sclerostin increased in 15% (10 to 20) Opposite effect on bone turnover in transmen aged ≥50 years after 1 year of HT compared with younger transmen: In transmen aged ≥50 years: P1NP decrease –19% (–35 to -4) CTx decease –32% (–50 to –13) Sclerostin decrease –10% (–19 to 0)

Author, Year Title Country Study design	**Dobrolińska** et al 2019 (Dobrolinska, van der Tuuk et al. 2019) *Bone Mineral Density in Transgender Individuals After Gonadectomy and Long-Term Gender-Affirming Hormonal Treatment* The Netherlands Retrospective, 1979 - 2014
POPULATION (ages) Age at start Age in cohort	Age at start of CSHT (mean ± SD) 36 ± 12 transwomen 30 ± 8 transmen Age at gonadectomy: 38 ± 12 transwomen 32 ± 9 transmen Age at first DXA scan: 44 ± 11 transwomen 39 ± 10 transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	111 68 transwomen 43 transmen
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	estradiol, oral or subcutaneous anti-androgens testosterone, intramuscular or transdermal Surgery: gonadectomy Study intervention: Dual-energy x-ray absorptiometry (DXA) Standard reference databases used to calculate T- and Z-scores: Data for the lumbar spine from a study on healthy American men and women [*Kelly 1990 J Bone Min Res 5 (Suppl 1): S249*]. Data for total hip from the National Health and Nutrition Examination Survey III study [*Looker 1998 Osteoporos Int 8: 468-490*]. Osteoporosis: defined as having a T-score ≤ -2.5 SD compared to normal values for young adults. Low bone density for age: defined as a Z-score < -2.0 SD compared to normal values for young adults.
INTERVENTION (time) HT duration Follow-up times	First DXA scan: within 5 years after gonadectomy, repeated every 5 years thereafter, up to > 20 years after gonadectomy. Time (months, median (1st, 3rd quartile) Interval of HT to gonadectomy: 22.5 months (16.0, 30.5) 20.0 months (16.0, 24.0) Interval of HT to first DXA: 83.5 months (66.5, 111.5) 87.0 months (73.0, 150.0) Interval of gonadectomy to first DXA: 60.0 months (41.0, 87.5) 62.0 months (49.0, 129.0)
OUTCOMES - All reported outcomes	BMD at the lumbar spine and total hip. Sex hormone levels

RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	In transwomen: BMD (mean) at first DXA scan: 0.99 ± 0.15 g/cm2 lumbar spine 0.94 ± 0.28 g/cm2 total hip In transmen: BMD (mean) at first DXA scan: 1.08 ± 0.16 g/cm2 lumbar spine 1.01 ± 0.18 g/cm2 total hip A significant decrease in total hip BMD was found in both transwomen and transmen after 15 years of HT compared with 10 years of HT. Osteoporosis based on male scores: 18 % transwomen 33 % transmen Osteoporosis based on female scores 5 % transwomen 4 % transmen Low bone density based on male scores 5 % transwomen 20 % transmen Low bone density based on female scores 5 % transwomen 0 % transmen

Author, Year Title Country Study design	**Motta et al 2010** (Motta, Marinelli et al. 2020) *Fracture risk assessment in an Italian group of transgender women after gender-confirming surgery* Italy Retrospective cross-sectional study 2012 - 2018
POPULATION (ages) Age at start Age in cohort	Age in cohort: 45.3 ± 11.3 years
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	57 transwomen (MtF)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Estrogens: oral estradiol valerate 2–6 mg/day transdermal estradiol hemihydrate 1.5–3 mg/day cyproterone acetate 25–100 mg/day spironolactone 100–200 mg/day Surgery: orchiectomy and phallectomy plus vaginoplasty
INTERVENTION (time) HT duration Follow-up times	CSHT duration: 11 years [7.00–11.0] before and after surgery 3 years [2.00–6.25] before surgery 5 years [3.00–12.0] after surgery Frequency of low compliance: 51 % (38–64)
OUTCOMES - All reported outcomes	Fracture incidence Prevalence of low bone mass (Z-score ≤ -2) Lumbar spine BMD vitamin D (25OHD) levels anthropometric parameters compliance to estrogen treatment biochemical and hormonal levels
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Ten-year fracture risk:** 7% (3–31) according to natal gender Intermediate–high fracture risk found in 14% of subjects Ten-year fracture risk according to natal gender: 4.5 % ± 0.89 normal bone mass (n = 34) 10.6 % ± 5.80 low bone mass (n = 23) Prevalence of low bone mass (Z-score ≤ -2): 40% (28–53) according to natal gender 30% (18–42) according to affirmed gender BMD at lumbar spine L1-L4: 0.91 ± 0.13 (g/cm2) Z-score: − 0.68 ± 1.19 according to affirmed gender − 1.4 ± 1.18 according to natal gender Hypovitaminosis D: 93%

Author, Year Title Country Study design	**Bretherton et al 2022** (Bretherton, Ghasem-Zadeh et al. 2022) *Bone Microarchitecture in Transgender Adults: A Cross-Sectional Study* Australia Cross-sectional study 2017-2018
POPULATION (ages) Age at start Age in cohort	Age in cohort (median, IQR): 28.6 years (24.6, 30.9) transmen 37.6 years (26.3, 52.7) transwomen 28.2 years (24.2, 31.7) ciswomen 41.6 years (32.4, 54.4) cismen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	81 41 transmen 40 transwomen 71 cisfemale controls 51 cismale controls
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Testosterone: testosterone undecanoate i.m. (1000 mg 8 to 14 weekly, n = 30) testosterone enanthate i.m. (250mg/ 2weeks, n=9) transdermal testosterone gel (1%, 5 g/d, n = 2) Estradiol: oral estradiol valerate, dose range 1–6 mg daily, n = 33) transdermal estradiol (100 mcg/24 hours, n = 4) oral ethinyl estradiol (dose range 30–100mcg daily, n=3) Androgen-blocking therapy(n=31): 78% of the feminizing hormone therapy group: cyproterone acetate (n = 21) spironolactone (n = 4) progesterone (n = 5) GnRH (n = 1) Surgery: orchidectomy: 28% (n = 11) oophorectomy: n=0 Study intervention: Imaging of the nondominant distal radius and distal tibia using high-resolution peripheral quantitative computed tomography (HR-pQCT, XtremeCT)
INTERVENTION (time) HT duration Follow-up times	Duration of hormone therapy (median, IQR): 42.5 months (21.4, 65) transmen 39.1 months (21.8, 60) transwomen
OUTCOMES - All reported outcomes	Bone health: Total CSA, vBMD (mg/cc) thickness (mm), separation (mm), porosity (%) BV/TV (%) hormone levels, SHBG, vitamin D, eGFR
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	Transmen: Relative to cis women, transmen had 0.63 SD higher total volumetric bone mineral density (vBMD). Cortical vBMD and cortical porosity did not differ, but cortices were 1.11 SD thicker ($p < 0.01$). Trabeculae were 0.38 SD thicker ($p = 0.05$) but otherwise no different. Transwomen: Compared with cismen, transwomen had 0.68 SD lower total vBMD ($p=0.01$) cortical vBMD was 0.70 SD lower ($p < 0.01$) cortical thickness was 0.51 SD lower ($p = 0.04$) cortical porosity was 0.70 SD higher ($p < 0.01$) Trabecular bone volume (BV/TV) was 0.77 SD lower ($p < 0.01$), with 0.57 SD fewer ($p < 0.01$) and 0.30 SD thicker trabeculae ($p = 0.02$). 0.56 SD greater trabecular separation ($p = 0.01$). Findings at the distal radius were similar.
Comments	Exclusion criteria: presence of metabolic bone disease, receiving therapy that affects bone (glucocorticoids, bisphosphonates, anti-epileptic medication, use of HIV pre-exposure prophylaxis), participants presumed to be menopausal (trans men and cis females age >50 years).

Cardiovascular events and metabolism

Acute cardiovascular events

Author, reference Publication type	**Ignacio et al 2022 (Ignacio, Diestro et al. 2022)** Systematic review
Question	Risk for stroke
End of search	November 2020
Methodology	PRISMA
Synthesis	Narrative Metaanalysis (5 studies)
Population	MtF
Results/authors' conclusions	Results: Fourteen studies were included in the qualitative analysis while five studies were included in the quantitative analysis. A total of 109 MTF transgenders (Mean 14; range 1–53) suffered a cerebrovascular event. Random-effect modeling analysis showed an overall estimated frequency of 2% for cerebrovascular events in transgenders with a moderate degree of heterogeneity (I2 = 62%). Conclusion: Hormonal therapy in MTF transgenders may confer cardiovascular risks in this population. However, more population-based studies that include clinical characteristics and outcomes of chronic health diseases in MTF transgenders are warranted. Such studies may be crucial in directing future guidelines on the health care and management of MTF transgenders.
Comment	Two studies with ethinyl estradiol, three included in the metanalysis (of five studies) 'varied preparations of estrogen either orally, transdermally, or via injection with or without antiandrogens'.

Author, Year Title Country Study design	**Getahun et al 2018** (Getahun, Nash et al. 2018) *Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons* USA Medical record-based cohort, 2006 - 2014
POPULATION (ages) Age at start Age in cohort	Age at index date*: 18 to >55 years (mean age not indicated) *Index date: defined as the first recorded evidence of transgender status.
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	4960 transgender 2842 transfeminine 2118 transmasculine Matched to: 48 686 cisgender men 48 775 cisgender women
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Feminizing drugs (estradiol and spironolactone) in a participant recorded as male at birth masculinizing drugs (testosterone) in a participant documented as female at birth
INTERVENTION (time) HT duration Follow-up times	Follow-up (average, years): 4.0 (SD 3.0) transfeminine group 4.4 (SD 3.1) matched reference cohort 3.6 (SD 2.7) transmasculine group 3.9 (SD 2.9) matched reference cohort
OUTCOMES - All reported outcomes	Acute Cardiovascular Events: VTE ischemic stroke myocardial infarction events Body mass index blood pressure total blood cholesterol level
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	Acute Cardiovascular Events since the index date: Transfeminine: 148 ACVE: 61 VTE 54 ischemic stroke 33 myocardial infarction Transmasculine: 48 ACVE: 23 VTEs 16 ischemic strokes 9 myocardial infarctions Transfeminine cohort: VTE post-index date incidence increase compared with either reference cohort: 2-year risk difference: 4.1 (1.6 to 6.7) per 1000 persons relative to cisgender men 2-year risk difference: 3.4 (1.1 to 5.6) per 1000 persons relative to cisgender women 8-year risk difference: 16.7 (6.4 to 27.5) per 1000 persons relative to cisgender men 8-year risk difference: 13.7 (4.1 to 22.7) per 1000 persons relative to cisgender women. Ischemic stroke incidence was about the same in all 3 cohorts. Myocardial infarction incidence greater than in reference women but no different from reference men.

Author, Year Title Country Study design	**Nota et al 2019** (Nota, Wiepjes et al. 2019) *Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy* The Netherlands Cohort study, review of medical records, 1972 – 2015
POPULATION (ages) Age at start Age in cohort	Age in cohort: (years, median) 30 transwomen 23 transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	6793 registered 3927 screened Included in cohort: 3875 2517 transwomen 1358 transmen Reference group: Age groups comparable to those used by reference studies examining the occurrence of CVEs in the general Dutch or Norwegian populations
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Puberty suppressors From age 16: estrogens (± antiandrogens) testosterone
INTERVENTION (time) HT duration Follow-up times	Transwomen: 9.07 years (SD 8.72) mean 5.95 years (range 0.01–54.77) median *[note range 3 days – 54 years]* 22 830 years total follow-up time Transmen: 8.10 years (SD 8.82) mean 4.10 years (range 0.02–41.66) median *[note range 7 days – 41 years]* 11 003 years total follow-up time
OUTCOMES - All reported outcomes	Acute cardiovascular events
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	**Acute Cardiovascular Events** Standardized incidence ratio (SIR (95% CI)): Transwomen: Stroke 2.42 (1.65–3.42)† women as reference 16.08 1.80 (1.23–2.56)† men as reference Myocardial infarction 2.64 (1.81–3.72)† women as reference 0.79 (0.54–1.11) men as reference Venous thromboembolism 5.52 (4.36–6.90)† women as reference 4.55 (3.59–5.69)† men as reference Transmen: Stroke 1.72 (0.70–3.58) women as reference 1.46 (0.59–3.04) men as reference Myocardial infarction 3.69 (1.94–6.42) women as reference 1.00 (0.53–1.74) men as reference Venous thromboembolism 0.41 (0.07–1.37) women as reference 0.36 (0.06–1.19) men as reference

Blood pressure

Author, reference Publication type	**Connelly et al. 2021** (Connelly, Clark et al. 2021) Systematic review
Question	Blood pressure
End of search	January 2020
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	Six hundred articles were screened, of which 14 studies were included in this systematic review encompassing 1309 individuals (approximately 50% transgender men and women) treated with gender affirming hormone treatment between 1989 and 2019. These articles were all pre–post observational studies without control groups. Mean ages ranged between 23.0–36.7 years (transgender men) and 25.2–34.8 years (transgender women). Interventions were diverse and included oral, transdermal and injectable hormonal preparations with 4 months to 5 years follow-up. Most studies in transgender men did not demonstrate a change in BP, whereas transgender women on GHT demonstrated both increases and decreases in SBP. These studies were heterogenous with significant methodological limitations and only two were determined to have a good quality rating. Conclusion: There is currently insufficient data to advise the impact of GHT on BP in transgender individuals.

Author, reference Publication type	**Velho et al.2017** (Velho, Fighera et al. 2017) Systematic review
Question	Blood pressure
End of search	March 2017
Methodology	PRISMA, search limited to PUBMED and EMBASE
Synthesis	
Population	FtM
Results/authors' conclusions	455 potentially eligible articles were identified; 438 were excluded after reading the abstracts and/or titles; and 17 articles were read in full. Thirteen articles were included in the systematic review Slight but significant increases in BMI were reported (from 1.3 to 11.4%). Three out of seven studies assessing the impact of different testosterone formulations on blood pressure detected modest increases or clinically irrelevant changes in this variable. In another study, however, two patients developed hypertension, which was resolved after cessation of testosterone therapy. Decreases in HDL-cholesterol and increases in LDL-cholesterol were consistently observed. Eight studies observed a relationship between testosterone and increased haemoglobin (range: 4.9–12.5%) and hematokrit (range: 4.4–17.6%), but discontinuation of androgen therapy was not necessary. Six studies assessing liver function showed slight or no changes. Overall, the quality of evidence was low, Exogenous testosterone administration to transgender men was associated with modest increases in BMI, haemoglobin/hematokrit, and LDL-cholesterol, and with decreases in HDL-cholesterol. Long-term studies are needed to assess the long-term risks.

Author, Year Title Country Study design	**Pyra et al 2020** (Pyra, Casimiro et al. 2020) *An Observational Study of Hypertension and Thromboembolism Among Transgender Patients Using Gender-Affirming Hormone Therapy* USA Retrospective cohort
POPULATION (ages) Age at start Age in cohort	Age in cohort (median): 30 years (range 20-70) transwomen 26 years (range 20-67) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	4402 patients 2509 trans women (TW) 1893 trans men (TM)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Hormone use (assessed by blood concentrations and prescriptions from electronic medical records): Ever use estrogen: 99.0% (2485) TW 8.0% (152) TM Ever use androgen antagonist/finasteride: 94.2% (1364) TW 4.6% (87) TM Ever use progestin: 29.8% (748) TW 2.8% (53) TM Ever use testosterone: 1.6% (41) TW 99.6% (1886) TM
INTERVENTION (time) HT duration Follow-up times	HT duration: Range: 0.5 – 12 years: Years since first hormone prescription (median, range) 2.6 years (0.5-12.0) transwomen 2.2 years (0.5-11.9) transmen
OUTCOMES - All reported outcomes	Outcomes by ICD-10 codes in electronic medical records. Associations between hormone treatment and hypertension and thromboembolism.
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Hypertension and Thromboembolism** Transwomen (TW): 19 (0.8%) TE event 49 (2.1%) hypertension development Associations with TE: No association between TE and hormone treatment as assessed by blood concentrations. Progestin prescriptions associated with increased odds of TE (aOR 2.95 [95% CI 1.02–8.57]), (possibly differential effects for medroxyprogesterone acetate versus micronized progesterone). Associations with hypertension: Higher total testosterone blood concentrations associated with greater odds of hypertension (aOR 1.16 [95% CI 1.01–1.33]), after controlling for BMI. Ever having a progestin prescription was protective for hypertension (aOR 0.36 [95% CI 0.15–0.87]). Transmen (TM): 27 (1.5%) developed hypertension. No significant associations between hypertension and hormone treatment.

Thromboembolism

Author, reference Publication type	**Kahn et al 2019** (Khan, Schmidt et al. 2019) Systematic review
Question	Deep venous thrombosis
End of search	April 2018
Methodology	PRISMA
Synthesis	Narrative
Population	MtF
Results/authors' conclusions	952 abstracts were screened. Abstract screening indicated that 868 of the references were irrelevant; 84 references proceeded to full text re-view. Case reports and review articles were the most com-mon exclusion (n=18 each), while wrong outcome (n=10) and wrong study design (n=11) also excluded a significant percentage. After excluding commentaries (n=9), duplicates (n=4), and wrong patient population or wrong (n =1 each), 12 articles/abstracts remained for data extraction Our study estimated the incidence rate of venous thromboembolism in transgender women pre-scribed oestrogen to be 2.3 per 1000 person-years, but because of heterogeneity this estimate cannot be reliably applied to transgender women as a group. There are insufficient data in the literature to partition by subgroup for subgroup prohibiting the analysis to control for tobacco use, age, and obesity, which is a major limitation. Additional studies of current oestrogen formulations, modes of administration, and combination therapies, as well as studies in the aging transgender population, are needed to confirm thrombotic risk and clarify optimal therapy regimens.

Author, reference Publication type	**Defreyne et al 2019** (Defreyne, Van de Bruaene et al. 2019) Systematic review
Question	Cardiometabolic risk factors and thrombosis
End of search	June 2018
Methodology	Prisma
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	After screening 734 abstracts, 77 full text articles were retained, of which 11 were review articles This review includes 4 original studies on cardiovascular mortality, 12 on cardiovascular morbidity, 12 on blood pressure, 25 on lipids, 24 on body composition and 19 on markers of increased thrombosis. Studies describing a higher risk for cardiometabolic and thromboembolic morbidity and/or mortality in transgender women (but not transgender men) mainly covered data on transgender women using the now obsolete ethinyl oestradiol and, therefore, are no longer valid. Currently, most of the available literature on transgender people adhering to standard treatment regimens consists of retrospective cohort studies of insufficient follow-up duration. When assessing markers of cardiometabolic disease, the available literature is inconclusive, which may be ascribed to relatively short follow-up duration and small sample size.

Author, reference Publication type	**Kotamarti et al 2021** (Kotamarti, Greige et al. 2021) Systematic review
Question	Risk for Venous Thromboembolism in Transgender Patients Undergoing Cross-Sex Hormone Treatment:
End of search	March 2020
Methodology	PRISMA like/ PRISMA not mentioned specifically Review process not described
Synthesis	Metaanalysis
Population	MtF and FtM
Results/authors' conclusions	Overall, 22 studies were included with 11 reporting VTE rates among transgender patients, 6 in cis-female patients, and 5 in cis-male patients. Data from 9,180 transgender patients (6,068 assigned male at birth [AMAB] and 3,112 assigned female at birth [AFAB]) undergoing hormone treatment and 103,713 cis-gender patients (18,748 female and 84,965 male) undergoing HRT were pooled. The incidence of VTE was higher in AMAB patients compared to AFAB patients (42.8 vs 10.8 VTE per 10,000 patient years;(p= .02). The rate of VTE incidences in AMAB patients appears similar or higher than the rate demonstrated in cis-females on HRT.VTE incidence in AFAB patients, however, is similar to the published rates in cis-males on HRT. Clinical Implications: AMAB patients on hormone therapy have higher VTE rates than AFAB patients. AMAB and AFAB patients may have similar VTE incidence to cis-female and cis-male patients on hormone replacement therapy, respectively. Strengths & Limitations: This is the first study to aggregate and quantify the development of VTE events in association with hormone therapy in transgender patients. It places these values in the context of rates published in more widely studied populations. It is limited by its retrospective data and heterogenic data. Conclusion: Surgical planning regarding perioperative and postoperative VTE prophylaxis or cessation of hormone therapy should take into account each patient's Caprini risk assessment and the nature of each intervention.

Author, reference Publication type	**Totaro et al 2021** (Totaro, Palazzi et al. 2021) Systematic review
Question	Risk of Venous Thromboembolismin Transgender People Undergoing Hormone Feminizing Therapy:
End of search	April 2021
Methodology	PRISMA
Synthesis	Metaanalysis and metaregression
Population	MtF
Results/authors' conclusions	The eighteen studies included gave information about 11,542 AMAB undergoing gender affirming hormone therapy. The pooled prevalence of VTE was 2%(95%CI:1-3%), with a large heterogeneity (I2= 89.18%, P<0.0001). Trim-and-fill adjustment for publication bias produced a negligible effect on the pooled estimate. At the meta-regression analysis, a higher prevalence of VTE was significantly associated with an older age (S=0.0063; 95%CI:0.0022,0.0104, P=0.0027) and a longer length oestrogen therapy (S=0.0011; 95%CI:0.0006,0.0016, P<0.0001). When, according to the meta-regression results, the analysis was restricted to series with a mean age≥37.5years, the prevalence estimate for VTE increased up to 3% (95%CI:0-5%), but with persistence of a large heterogeneity (I2= 88,2%, P<0.0001); studies on younger participants (<37.5 years) collectively produced a pooled VTE prevalence estimate of0% (95%CI:0-2%) with no heterogeneity (I2= 0%, P=0.97). Prevalence estimate for VTE in series with a mean length of estrogen therapy≥53 months was 1% (95%CI:0-3%), with persistent significant heterogeneity (I2= 84,8%, P=0.0006); studies on participants subjected to a shorter length of estrogen therapy (<53 months), collectively produced a pooled VTE prevalence estimate of 0% (95%CI:0-3%) with no heterogeneity (I2= 0%, P=0.76). Conclusions: The overall rate of VTE in AMAB trans people undergoing gender affirming hormone therapy was 2%. In AMAB population with <37.5 years undergoing estrogen therapy for less than 53 months, the risk of VTE appears to be negligible. Further studies are warranted to assess whether different types and administration routes of estrogen therapy could decrease the VTE risk in AMAB trans people over 37.5 years subjected to long-term therapy

Author, Year Title Country Study design	**Lim et al 2020** (Lim, Leemaqz et al. 2020) *Global Coagulation Assays in Transgender Women on Oral and Transdermal Estradiol Therapy* Australia Cross-sectional case-control
POPULATION (ages) Age at start Age in cohort	Age in cohort: 32.8 years (26.7-44.7) transgender women 28.7 years (24.9-57.3) cisgender male 44.9 years (25.5- 58.3) cisgender female
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	26 transgender women 98 cisgender women 55 cisgender men
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	estradiol valerate, oral (4-8 mg) (n=16) estradiol transdermal (median 100 mcg/24 day) (n=10) cyproterone acetate (mean 12.5 mg/day) spironolactone (mean 100 mg/day)
INTERVENTION (time) HT duration Follow-up times	Follow-up time: 25.5 months (22.5–31.2)
OUTCOMES - All reported outcomes	Global coagulation assays profiles: Thromboelastography (TEG) Calibrated automated thrombogram (CAT): thrombin generation Overall hemostatic potential: fibrin generation hormone levels blood examination renal and liver function tests coagulation studies von Willebrand studies
RESULTS – Extracted outcomes (95% CI if not indicated otherwise)	Transgender women compared with cisgender men: Thromboelastography (TEG): max amplitude +6.94 mm (3.55, 10.33) Calibrated automated thrombogram (CAT): endogenous thrombin potential (nM.min) +192.62 (38.33, 326.91) peak thrombin +38.10 nM (2.27, 73.94) Overall Hemostatic Potential (OHP): overall fibrinolytic potential increased (+4.89% (0.52, 9.25) No significant changes observed relative to cisgender women.
Comments	Not included in systametic review of Totaro 2021 or Kotamarti 2021.

Author, Year Title Country Study design	**Scheres et al 2021** (Scheres, Selier et al. 2021) *Effect of gender-affirming hormone use on coagulation profiles in transmen and transwomen* *The Netherlands* Before - after study 2012 - 2015
POPULATION (ages) Age at start Age in cohort	Age at start of CSHT: (mean (SD)) 33.7 years (12.9) transwomen 26.9 years (9.7) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	98 transwomen (male sex at birth) 100 transmen (female sex at birth) 5 excluded due to anti-androgen monotherapy
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	transdermal estradiol (Systen® 100 mg twice a week) oral estradiol valerate (Progynova® 2 mg twice a day) oral anti-androgen, cyproterone acetate (Androcur® 50 mg daily) intramuscular testosterone (Sustanon® 250 mg per 2 weeks or Nebido® 1000 mg per 2 weeks) transdermal testosterone (Androgel® 50 mg per day)
INTERVENTION (time) HT duration Follow-up times	CSHT duration: 12 months
OUTCOMES - All reported outcomes	Venous thromboembolism (VTE) risk coagulation FII, coagulation FIX, coagulation FXI fibrinogen hematocrit protein S, protein C APCr SHBG BMI,height
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	Number thrombotic events during 12 months follow-up. **Coagulation profiles:** pro-coagulant change, anti-coagulant change Transwomen: more procoagulant profiles (absolute mean paired difference (95% CI): FIX mean increase (relative change +7.8%) : 9.6 IU/dL (3.1-16.0) FXI mean increase (relative change +11.6%) : 13.5 IU/dL (9.5-17.5) Protein C mean decrease (relative change -7.1%) : -7.7 IU/dL (-10.1 to -5.2) Changes in measures of coagulation influenced by route of administration and age (reduced with transdermal administration and lower age). Higher sex-hormone binding globulin (SHBG) level after 12 months associated with a lower activated protein C resistance. Transmen: Changes were not procoagulant overall and influenced by age. Small differences for route of administration.
Comments	Exclusion criteria: psychotic disorder Part of the European Network for the Investigation of Gender Incongruence (ENIGI)

Diabetes and insulin sensitivity

Author, reference Publication type	**Spanos et al 2020** (Spanos, Bretherton et al. 2020) Systematic review
Question	Insulin residence
End of search	March 2019
Methodology	PRISMA
Synthesis	Narrative
Population	MtF and FtM
Results/authors' conclusions	The search strategy identified 221 studies. After exclusion of studies that did not meet inclusion criteria, 26 were included (2 cross-sectional, 21 prospective uncontrolled and 3 prospective controlled). 751 transgender males and 689 transgender females. Evidence in transgender men suggests that testosterone therapy increases lean mass, decreases fat mass, and has no impact on insulin resistance. Evidence in transgender women suggests that feminising hormone therapy (estradiol, with or without anti-androgen agents) decreases lean mass, increases fat mass, and may worsen insulin resistance. Changes to body composition were consistent across almost all studies: Transgender men on testosterone gained lean mass and lost fat mass, and transgender women on oestrogen experienced the reverse. No study directly contradicted these trends, though several small studies of short duration reported no changes. Results for insulin resistance are less consistent and uncertain. There is a paucity of prospective controlled research, and existing prospective evidence is limited by small sample sizes, short follow up periods, and young cohorts of participants.

Author, Year Title Country Study design	**Shadid et al 2020** (Shadid, Abosi-Appeadu et al. 2020) *Effects of Gender-Affirming Hormone Therapy on Insulin Sensitivity and Incretin Responses in Transgender People* Cohort, Before -After study, Part of European Network for the Investigation of Gender Incongruence (ENIGI)
POPULATION (ages) Age at start Age in cohort	Age at baseline: 26.1 ± 1.3 TM (FtM) 34.4 ± 1.5 TW (MtF)
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	90 35 transgender men (TM) 55 transgender women (TW)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	testosterone i.m. (1000 mg/12 weeks) estradiol valerate oral (2 mg twice daily) cyproterone acetate (50 mg/ day) In patients > 45 years: estradiol patches (100 mg/72 h) transdermal gel (1.5 mg twice daily)
INTERVENTION (time) HT duration Follow-up times	HT duration 1 y Follow-up time 1y
OUTCOMES - All reported outcomes	body composition body weight fat-free mass (FFM) waist-hip-ratio glucose insulin GLP-1 GIP
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	TM: Body weight, fat-free mass (FFM), and waist-to-hip ratio increased Fasting insulin (-1.46 ± 0.8 mU/L) decreased HOMA of insulin resistance (HOMA-IR) (2.26 ± 0.3 vs. 1.86 ± 0.2) decreased AUC for GIP and AUC for GLP-1 ([pmol/L] x min) increased Fasting glucose, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 unchanged. TW: Body weight increased FFM and waist-to-hip ratio decreased Insulin (3.4 ± 0.8 mU/L) increased HOMA-IR (1.7 ± 0.1 vs. 2.4 ± 0.2) increased Fasting GIP and AUC GIP decreased Fasting glucose and AUC GLP-1 unchanged

Author, Year Title Country Study design	**Islam et al 2022** (Islam, Nash et al. 2022) *Is There a Link Between Hormone Use and Diabetes Incidence in Transgender People?* *Data From the STRONG Cohort USA* Review of medical records 2006 -2014
POPULATION (ages) Age at start Age in cohort	Age at index date: range 18 - >55 years range 18-35 years: 54% of subjects* Index date was defined as the first recorded evidence of TGD status
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	5002 transgender (TGD): 2869 transfeminine (TF) 2133 transmasculine (TM) TF cohort matched to: 28 300 cisgender females 28 258 cisgender males TM cohort matched to: 20 997 cisgender females 20 964 cisgender males
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	CSHT: not reported. Approximately 32% of TFs and 24% of TMs were on GAHT on or before the index date. Data collection methods and determination of GAHT described in ref 18.
INTERVENTION (time) HT duration Follow-up times	Follow-up time (mean) among transgender members who initiated GAHT after the index date and who did not have a prior T2DM diagnosis: 3.1 years for TF 2.8 years for TM Follow-up times (median (IQR)) 2.5 (1.4, 4.1) years TF 2.2 (1.1, 3.6) years TM
OUTCOMES - All reported outcomes	T2DM incidence and prevalence. Identification of diabetes: based on 2 or more hemoglobin A1c levels ≥ 6.5% or 2 or more, fasting plasma glucose levels ≥ 126 mg/dL no more than 2 years apart. T2DM timing of diagnosis BMI
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	Diabetes (type 2 diabetes mellitus (T2DM): TGD cohort members with T2DM, n (%): TF: 287 (10%*) TM: 131 (6%*) Timing of T2DM diagnosis: Number of patients with a diagnosis of T2DM: At baseline (on or before the index date): 175/ 287 (61%) TF patients 77 / 131 (59%) TM patients Incident cases within follow-up period: 94 TF 44 TM Prevalent and incident T2DM more common in the transfeminine cohort relative to cisgender females: Odds ratio OR 1.3 (1.1-1.5) Hazard ratio HR 1.4 (1.1-1.8) No significant differences in prevalence or incidence of T2DM were observed across the remaining comparison groups, both overall and in TGD persons with evidence of GAHT receipt.
Comments	Study of Transition Outcomes and Gender (STRONG): electronic health record (EHR)-based cohort of TGD persons. Receipt of GAHT determined through EHR linkages to prescription data by using national drug codes. Identification of diabetes: "T2DM cases were ascertained using the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) Data Link algorithm, adopted by a consortium of multiple integrated health care systems that include the 3 KP health plans participating in STRONG. The SUPREME-DM methods of T2DM identification have been described in detail previously (19). Briefly, the algorithm identifies enrolled members in the health systems with diabetes by searching inpatient and outpatient diagnosis codes, laboratory test results, and pharmacy records."

Author, Year Title Country Study design	**van Velzen et al 2022** (van Velzen, Wiepjes et al. 2022) *Incident Diabetes Risk Is Not Increased in Transgender Individuals Using Hormone Therapy* The Netherlands Retrospective data linked to nationwide health data registry 1972 - 2018
POPULATION (ages) Age at start Age in cohort	Age at start of hormone therapy (mean ± SD) 30 years (23–41) transwomen 23 years (20–31) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	8831 total population 3022 excluded (did not start hormone therapy) 1710 excluded (other reasons) 4099 included in study 2585 transwomen 1514 transmen
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	No puberty blockers prior to the start of hormone therapy. Transwomen: estradiol patches (50-150 µg/24 hours twice a week) oral estradiol valerate (2-4 mg daily) estradiol gel (0.75-1.5 mg daily) [1972 - until 2001, 2005, and 2014 respectively: ethinyl estradiol (50-150 µg daily) conjugated estrogens (0.625-2.5 mg daily) 17-beta estradiol implants (20-40 mg per 3 months) Anti-androgen: Cyproterone acetate (25-100 mg daily) Transmen: testosterone gel (20-60 mg daily) intramuscular testosterone undecanoate (1000 mg per 12-14 weeks) oral testosterone undecanoate (40-240 mg daily) intramuscular testosterone esters (250 mg or 125 mg every 2-3 weeks) Surgery: (min age 18 and after at least one year of hormone therapy): vaginoplasty with orchiectomy hysterectomy with oophorectomy Gonadectomy (% yes) 63.4 % transwomen 61.4 % transmen
INTERVENTION (time) HT duration Follow-up times	Follow-up period (median, IQR) from start of hormone therapy until censoring: 11.3 years (3.6-22.4) in transwomen 5.2 years (2.2-16.4) in transmen Effective median time under observation (from 2007 until censoring) in years: 9.0 years (3.3-12.0) in transwomen 4.9 years (2.2-12.0) in transmen Age at end of study: 48 years (33-58) 32 years (24-49) Total number of effective person-years under observation (after 2007): 20 129 in transwomen 9492 in transmen

OUTCOMES - All reported outcomes	Incidence of type 2 diabetes: occurrence of diabetes inferred from first dispense of a glucose-lowering agent identified by codes A10A and A10B using Anatomical Therapeutic Chemical (ATC) classification. Standardized incidence ratios (SIR) computed for transwomen and transmen in comparison with the same birth sex from the general population. Body mass index (BMI) gonadectomy smoking habits alcohol consumption comorbidity comedication
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Incidence of type 2 diabetes:** No difference in the incidence of type 2 diabetes mellitus was observed: 90 type 2 diabetes cases in 2585 transwomen, SIR 0.94 (95% CI 0.76-1.14) 32 type 2 diabetes cases in 1514 transmen, SIR 1.40 (95% CI 0.96-1.92) Mean age of individuals who developed type 2 diabetes: 55 ± 11 years transwomen 50 ± 13 years trans men
Comments	Study design and initially included study population of cohort described in detail in other publication. Participants with at least one follow-up visit after initiation of hormone therapy were included. Excluded: if starting date of hormone therapy was unknown if alternating the use of testosterone and estradiol Distinction between type 2, type 1 diabetes, and gestational diabetes could not be made based on these data.

Liver enzymes

Author, Year Title Country Study design	Hashemi et al 2021 (Hashemi, Zhang et al. 2021) *Longitudinal Changes in Liver Enzyme Levels Among Transgender People Receiving Gender Affirming Hormone Therapy* USA Longitudinal study, review of medical records 2006 - 2013
POPULATION (ages) Age at start Age in cohort	Age at index date: range 18 - >55 years range 18-35 years: 64% of subjects* index date (calendar year of the first recorded evidence of transgender status
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	1062 transgender subjects 624 transfeminine (TF) 438 transmasculine (TM) 4090 cisgender males and 4797 cisgender females Each transgender subject was matched to 20 cisgender subjects (10 female and 10 male)
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	CSHT: not reported. *[Note: study based on prescriptions but prescriptions not indicated]*
INTERVENTION (time) HT duration Follow-up times	Observation times: from the first blood test to the date of the first filled GAHT prescription from GAHT initiation to the most recent ALT or AST measurement
OUTCOMES - All reported outcomes	alanine aminotransferase (ALT) aspartate transaminase (AST)
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	Liver enzymes: Transmasculine (TM): post GAHT ratios-of-ratios (95% CI): AST 1.61 (1.13, 2.31) relative to cisgender males AST 1.57 (1.06, 2.31) relative to cisgender females ALT 2.06 (1.67, 2.54) relative to cisgender males ALT 1.90 (1.50, 2.40) relative to cisgender females Transfeminine (TF) participants: No statistically significant changes observed. Other factors associated with higher liver enzyme levels included alcohol use/abuse and obesity.
Comments	Details of the study (Study of Transition, Outcomes and Gender (STRONG)) described in other publications. TM and TF assignment methodology described and validated in other publications. Study based on prescriptions but prescriptions not indicated Limitations: lack of information on hormone levels inability to take into account GAHT doses and routes of administration.

Author, Year Title Country Study design	**Stangl et al 2021** (Stangl, Wiepjes C et al. 2021) *Is there a need for liver enzyme monitoring in people using gender-affirming hormone therapy?* The Netherlands Multicentre prospective study 2010 and 2020
POPULATION (ages) Age at start Age in cohort	Age in cohort (median, IQR): 33 years (23–42) transwomen 26 years (20–29) transmen
POPULATION (n) **n patients** natal male (M-t-F) natal female (F-t-M)	2391 subjects 458 excluded 1933 individuals in cohort 889 transgender women 1044 transgender men
INTERVENTION (type) Cross-sex hormone treatment (CSHT)	Transgender women: oral oestradiol valerate (2–4 mg/ day) oestradiol patches (100 µg/24 h twice per week) transdermal 17-β oestradiol gel (1.5 mg twice daily) cyproterone acetate (25–100 mg daily) Transgender men: testosterone gel (50 mg/day) testosterone esters injections (250 mg/2–3 weeks) testosterone etnanthate injections (250 mg/2–3 weeks) testosterone undecanoate injections (1000 mg/12 weeks)
INTERVENTION (time) HT duration Follow-up times	CSHT duration: 12 months Follow up: 3 months, and after 12 months of hormone therapy 381 individuals and analysed their measurements 36 months after start of hormone treatment
OUTCOMES - All reported outcomes	Incidence of liver injury alanine aminotransferase (ALT) aspartate aminotransferase (AST) alkaline phosphatase (ALP) gamma-glutamyltransferase (GGT) Liver injury was defined as either an elevation (upper limit of normal (ULN)) 2× ULN of ALP 3× ULN of ALT 3× ULN of AST BMI (kg/m2) SBP (mmHg) alcohol (units/week)
RESULTS – **Extracted outcomes** (95% CI if not indicated otherwise)	**Incidence of liver injury:** [within 12 months after start of hormone therapy, without attribution to alcohol abuse, medical history, or comedication]: 0.1 (95% CI 0.0–0.7) and 0.0% in transgender women (according to female and male reference intervals) 0.6 (95% CI 0.3–1.3) and 0.4% (95% CI 0.1–1.0) in transgender men (according to female and male reference intervals)

Studies investigating regret, detransition and discontinuation of treatment

Adults ≥ 18 years						
Surgical reversal or application for surgical reversal						
Author, Year Country	**Inclusion period**	**Population**	**Treatment**	**Follow-up method**	**Follow-up time**	**Regret**
Dhejne et al 2014 (Dhejne, Öberg et al. 2014) Sweden	1960–2010	767 people (289 natal females 478 natal males) applied for legal and surgical sex reassignment. 681 persons were granted a new legal gender and had undergone sex confirmation surgery. Age range 16-65 years	Surgically reassigned (genital)	Application for reversal of sex reassignment.	Up to 50 years	15/ 681 applied for surgical reversal to initial sex.
Landen et al 1998 (Landen, Walinder et al. 1998) Sweden	1972–1992	218 subjects with gender identity disorder who were approved for sex reassignment in Sweden	Surgical reassignment genital	Register	Time from application for reassignment and initial evaluation ranged from 4 to 24 years.	13/ 218, application for surgical reversal
Wiepjes et al 2018 (Wiepjes, Nota et al. 2018) The Netherlands	1972–2015.	6793 people (4432 birth-assigned male, 2361 birth-assigned female) visiting gender identity clinic. 2627 underwent gonadectomy	Surgical reassignment, genital Gonadectomy	Chart review/ clinical follow-up	Not given Estimated median approximately 20 years	14/ 2627 10 underwent reversal surgery

Adults ≥ 18 years Expressed regret or detransitioned from hormonal treatment						
Author, Year Country	**Inclusion period**	**Population**	**Treatment**	**Follow-up method**	**Follow-up time**	**Regret**
Blanchard et al 1989 (Blanchard, Steiner et al. 1989) Canada	Up to oct 1985	134 -transsexuals 111 with follow-up 1 year or more	Surgically reassigned: Vaginoplasty for males and mastectomy for females	Questionnaire, mail or at clinical visit	1–13.6 years, mean 4.4 years	4/ 111
Bodlund et al 1996 (Bodlund and Kullgren 1996) Sweden	1989/ 1990	19 transsexuals applying for sex reassignment	18 started hormonal treatments where of 12 had reassignment surgery (genital)	Questionnaires	At 5 years after start of hormonal treatment	1/ 19 regretted after name shift but before surgery
de Cuypere et al 2006 (de Cuypere, Elaut et al. 2006) The Netherlands	1986–2001	107 Dutch- transsexuals	Surgical reassignment (genital)	Questionnaires and personal interviews	Follow-up time mean (SD) MtF 4.1 (3.8) FtM 7.6 (7.1)	0/ 107
Garcia et al 2014 (Garcia, Christopher et al. 2014) The UK / USA	Time period not given	25 FtM transexuals Means age 34 -39 years depending of surgical technique	Phalloplasty with various techniques	Interviews	Mean time post-surgery 2.2 to 6.8 years	0/ 25
Hall et al. (Hall, Michell et al. 2021) The UK	2010-2017	182 discharged from service (sept 2017 to aug 2018) 175 completed assessments 67 transmen 108 transwomen Median age 25 years 17 or older)	Hormonal treatment and varying surgery	Retrospective review of medical records	7 to 8 years	12/175 detransitioned. ”Regret was specifically documented in 2 cases” “6 cases did not strictly meet the criteria for detransitioning but showed some overlap of experience”.
Imbimbo et al 2009 (Imbimbo, Verze et al. 2009) Italy	1992–2006	163 male patients had undergone gender-transforming surgery (MtF)	Surgical reassignment (genital)	Questionnaire from September 2007 to March 2008	1–15 years	8/ 139
Johansson et al 2010 (Johansson, Sundbom et al. 2010) Sweden	Time period not given.	60 patients approved for sex reassignment in two geographical regions 42 completed follow-up assessments.	Surgical reassignment or waiting for surgery	Semi-structured interview	After ≥ 5 in the process or ≥ 2 years after completed surgery	0/ 60
Judge et al 2014 (Judge, O'Donovan et al. 2014) Ireland	2005 - 2014	218 referred patients	Hormonal or surgical treatment (various procedures).	Retrospective review of medical records	0–9 years from referral Median approximately 3 years (table 2)	4/ 218

Lawrence et al 2003 (Lawrence 2003) USA	1994–2000	232 MtF transsexuals	Surgical reassignment genital	Written questionnaire	≥1 year after surgery	0/ 232
Author, Year Country	Inclusion period	Population	Treatment	Follow-up method	Follow-up time	Regret
Nelson et al 2009 (Nelson, Whallett et al. 2009) The UK	2000–2005	17 patients FtM, identified retrospectively 12 responded	Reduction mammaplasty	Questionnaire	Mean follow-up after surgery 10 months (range 2-23 months)	0/ 12
Ott et al 2010 (Ott, van Trotsenburg et al. 2010) Germany	1998–2008	32 FtM transsexuals Mean age 30.0±5.8 years.	Hysterectomy, bilateral salpingo-oophorectomy, bilateral mastectomy in one single operative	Clinical follow-up examinations	≥ 6 months after surgery	0/ 32
Richards & Doyle (Richards and Doyle 2019) 2019' The UK	Time period not given.	303 transsexuals number FtM and MtF not given Age not given	Detransition (not specified)	Retrospective review of medical records	Not given	3/ 303 All re-transitioned at later time
Smith et al 2005 (Smith, Van Goozen et al. 2005) The Netherlands	Time period not given	325 consecutive adolescent and adult applicants for sex reassignment. M ean age 30.9 years (range 17.7–68.1 years)	188 completed various surgical reassignment. 103 patients never started hormone treatment.	Interview/questionnaire data were gathered from 126 adults	Mean time from surgery to follow-up 21.3 months (range 12–47)	2/ 126 103/ 325 (40%) did not start cross-sex hormonal treatment
van de Grift et al 2018 (van de Grift, Elaut et al. 2018) Europe	2007–09	546 eligible persons 201 (37%) responded 136 had undergone gender affirming surgery Mean age 36 (17–63) years	Various gender affirming surgery	Questionnaires	4–7 years	8/136 dissatisfaction 2/136 minor regret
Vujovic et al 2009 (Vujovic, Popovic et al. 2009) Serbia	1987–2006	71 MtF transsexuals and 76 FtM from persons applying for sex reassignment	Surgical reassignment, genital. 12% of MTF and 18% of FTM transsexuals were satisfied with hormonal treatment only	Retrospective, no information on method	no information on follow-up time.	0/ not defined in the paper
Zavlin et al 2018 (Zavlin, Schaff et al. 2018) Germany	September 2012–2014	49 adult MTF transgender patients who underwent two-stage SRS followed prospectively	Surgical reassignment (genital)	40 patients filled out both parts of the questionnaire sets:1 day before the first stage surgery and 6 months after the second stage.	6 months	1/ 40

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