

Supplementary Table 3 - Outcomes reported by included studies												
Study ID	Pubertal development	Side effects	Gender-related outcomes	Body image	Psychological health	Psychosocial outcomes	Physical health	Bone health	Fertility	Cognitive/neuro-developmental	Other	Outcomes (measures)
Cohort												
Achille 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Depression (Patient Health Questionnaire-9 modified for teens (PHQ-9), Center for Epidemiologic Studies Depression Scale - Revised (CESD-R)); quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (QLES-Q-SF))
Becker-Hebly 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Psychological functioning (Youth Self Report (YSR) for age 11-18 and Adult Self Report (ASR) for 18+); Global functioning (Children's Global Assessment Scale (CGAS)); Health-related quality of life (Kidscreen-27 for age 11-18 and SF (short form)-8 for 18+)
Beking 2020	Yes	No	No	No	No	No	No	No	No	Yes	No	Lateralization index of the amygdala (during an emotional face matching task with angry and fearful faces - fMRI); hormone levels (testosterone - not explicitly identified as an outcome);
Burke 2016	Yes	No	No	No	No	No	No	No	No	Yes	No	Visuospatial working memory (brain activation pattern by sex, performance - mental rotation task - fMRI); hormone levels (testosterone - not explicitly identified as an outcome)
Cantu 2020	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-9); Suicidality (item 9 on PHQ-9); Anxiety (Generalised Anxiety Disorder Assessment (GAD-7))
de Nie 2022	No	No	No	No	No	No	No	No	Yes	No	No	Exocrine testicular function (Spermatogenesis (Johnsen score), germ cell type (ratio of most advanced germ cell types)); Fertility preservation
Grimstad 2021b	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (adult height); skeletal maturation (Delta bone age)
Jensen 2019	No	Yes	No	No	No	No	No	No	No	No	No	Reported side effects (identified based on those recorded by care team physicians in narrative portions of electronic patient notes); required dose (ending dose of treatment)
Lopez de Lara 2020	No	No	Yes	No	Yes	Yes	No	No	No	No	No	Severity of gender dysphoria (UGDS); Patient strengths and difficulties (Strengths and Difficulties Questionnaire (SDQ)); Level of anxiety (STAI); Mood (BDI); family functioning (Family appaer test)
Tordoff 2022	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-9); Anxiety (GAD-7); Self-harm or suicidal thoughts over previous 2 weeks (PHQ-9 question 9)
Valentine 2021	No	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (BMI); Metabolic parameters (lipid profile - total cholesterol, LDL-C, HDL, triglycerides)
van de Grift 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (height, weight, BMI, waist/hip circumference); puberty development (Tanner staging, breast and genital characteristics - clinical exam); surgical requirements for sex re-assignment
Pre-post												
Allen 2019	No	No	No	No	Yes	Yes	No	No	No	No	No	Suicidality (Ask Suicide-Screening Questions (ASQ) instrument); Well-being (General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory)
Chiniara 2018	No	No	No	No	No	No	Yes	No	No	No	No	Safety (AST, ALT, total cholesterol, HDL, LDL, triglycerides, glucose, HbA1c, hemoglobin, red blood cell count, hematocrit, insulin)
de Vries 2014	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Behavioral and emotional problems (CBCL and YSR); depressive symptoms (BDI); anxiety and anger (STAI); global functioning (CGAS); gender dysphoria (UGDS); body image (BIS); well-being (own questionnaire; Satisfaction with Life Scale (SWLS); Subjective Happiness Scale (SHS)); quality of life (World Health Organization Quality of Life Brief Version (WHOQOL-BREF))
Delemarre-van de Waal 2006	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Puberty development (Tanner stage, skeletal age - left hand); anthropometrics (height, weight, sitting height, hip / waist circumference); bone density (whole body, hip, lumbar spine); body composition (fat mass percentage, lean body mass); cardio-metabolic measures (fasting glucose, insulin, cholesterol, HDL, LDL); hormone levels (gonadotrophins, sex hormones)
Grimstad 2021a	Yes	No	No	No	No	No	No	No	No	No	No	Menstruation (presence of, and risk factors for, breakthrough bleeding)
Hannema 2017	Yes	No	No	No	No	No	Yes	No	No	No	No	Puberty development (Tanner stage, bone age); anthropometrics (weight, height, sitting height, waist/hip circumference/ratio, BMI); hormone levels (LH, FSH, testosterone, estradiol); safety (blood pressure, prolactin, ALT, AST, alkaline phosphatase, γ-glutamyl transferase, creatinine, HbA1c, hematocrit); body composition (fat mass, fat percentage, lean body mass percentage)
Hisle-Gorman 2021	No	No	No	No	Yes	No	No	No	No	No	No	Mental health care visits (number of visits, diagnosis sub-category); psychotropic medications (type)
Jarin 2017	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (height, weight, BMI); Safety (blood pressure, lipids (total cholesterol, LDL, HDL, triglycerides, triglyceride:HDL ratio), AST, ALT, hemoglobin, hematocrit, HbA1c, prolactin, serum urea nitrogen, creatinine); hormone levels (testosterone, estradiol)
Kaltiala 2020	No	No	No	No	Yes	Yes	No	No	No	No	No	Adolescent development (living arrangements, peer relationships, school / work participation, romantic involvement, competence in managing everyday matters); need for specialist level psychiatric treatment (depression, anxiety, suicidality/self-harm, conduct problems, psychotic symptoms, substance abuse, autism, attention deficit hyperactivity disorder, eating disorder)
Khatchadourian 2014	No	Yes	No	No	No	No	Yes	No	No	No	No	Side effects (patient reported); Safety for antiandrogens (electrolyte and urea/creatinine levels)

Klaver 2018	Yes	No	No	No	No	No	Yes	No	No	No	No	Body shape (anthropometrics) (waist-hip ratio, body weight, waist/hip circumference, body height, BMI); body composition (whole-body and regional-body fat, total lean body mass, total body mass)
Klaver 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Anthropometrics (body height, body weight, BMI, waist/hip circumference); cardiovascular risk (blood pressure, glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), lipid values (total cholesterol, HDL, LDL, triglycerides), prevalence of obesity and dyslipidemia)
Klink 2015	Yes	No	No	No	No	No	Yes	Yes	No	No	No	bone health (BMD, BMAD); height, weight, BMI
Kuper 2020	No	No	No	Yes	Yes	No	No	No	No	No	No	Body dissatisfaction (BIS); depression (Quick Inventory of Depressive Symptoms (QIDS) - self- and clinician report); Anxiety (SCARED); suicidality (suicidal ideation, suicide attempt); suicidality and self-harm (passive ideation, suicide attempt, NSSI); mental health treatment (psychiatric medication, therapy, support group)
Laurenzano 2021	Yes	Yes	No	No	No	No	Yes	No	No	No	No	side effects (injection site reaction, acne); hormone levels (total and free testosterone, estradiol); menstruation (time to cessation); safety (hematocrit, AST, ALT, blood pressure (hypertension), lipids (total cholesterol, LDL, HDL, triglycerides)); anthropometrics (BMI)
Madsen 2021	No	No	No	No	No	No	Yes	No	No	No	No	Erythrocytosis (hematocrit levels); hormone levels
Millington 2019	No	No	No	No	No	No	Yes	No	No	No	No	Incidence of hyperkalemia (serum potassium concentration >5.0 mmol/L; relationship between potassium levels and treatment dose and duration)
Millington 2022	No	No	No	No	No	No	Yes	No	No	No	No	Kidney function (serum creatinine, estimated glomerular filtration rate (eGFR)); BMI
Mullins 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Incidence of arterial or venous thrombosis during treatment. Testosterone and estradiol levels.
Olson 2014	Yes	No	No	No	No	No	Yes	No	No	No	No	Menstrual cessation; hormone levels (testosterone (free and total levels), estradiol); anthropometrics (BMI); safety (blood pressure; hemoglobin, ALT, AST, non-fasting total cholesterol)
Olson-Kennedy 2018	Yes	No	No	No	No	No	Yes	No	No	No	No	Safety (total cholesterol, HDL, triglycerides, AST, ALT, potassium, prolactin, hemoglobin, glucose, blood pressure); anthropometrics (BMI); hormone levels (estradiol, testosterone free and total)
Perl 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic-pituitary-gonadal axis suppression); hormone levels (testosterone; estradiol, LH, FSH)
Peri 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Changes in weight status (BMI); Changes in blood pressure (systolic and diastolic); puberty development (hypothalamic-pituitary-gonadal axis suppression); hormone levels (testosterone; estradiol, LH, FSH)
Schagen 2018	No	No	No	No	No	No	Yes	No	No	No	No	adrenal androgen levels (dehydroepiandrosterone (DHEAS), androstenedione)
Schagen 2020	No	No	No	No	No	No	No	Yes	No	No	No	bone health (BMAD (whole body, hip, lumbar spine), serum bone markers)
Segev-Becker 2020	No	Yes	No	No	No	No	No	No	No	No	No	Side effects related to medical treatment (from medical record)
Sequeira 2019	No	No	No	No	No	No	Yes	No	No	No	No	BMI
Stoffers 2019	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Puberty development (acne, hair growth / shaving, voice lowering, menses); anthropometrics (height, weight, BMI); blood pressure; hormone levels (FSH, LH, testosterone, estradiol, SHBG); safety (Creatinine, ALP, total cholesterol, HDL, LDL, triglycerides, hemoglobin, hematocrit, vitamin D, DHEAS, androstenedione); bone health (BMD at lumbar spine, left neck, right hip, BMAD for spine and left neck)
Tack 2016	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Anthropometry (height, weight, BMI); Side effects (acne, hirsutism, patient-reported); Safety (Hemoglobin, hematocrit, electrolytes, creatinine, AST, ALT, total cholesterol, triglycerides, HDL, LDL, hemoglobin and fasting insulin); hormone levels (thyroid stimulating hormone, anti-Müllerian hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG)
Tack 2017	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Puberty development (physical changes); Side effects (patient-reported); Anthropometry (height, weight, BMI); Safety (hemoglobin, hematocrit, creatinine, AST, ALT, triglycerides, total cholesterol, HDL, LDL, DHEAS, prolactin); Hormone levels (thyroid stimulating hormone, free thyroxin, LH, FSH, estradiol, total and free testosterone, SHBG, free androgen index)
van der Loos 2021	Yes	No	No	No	No	No	Yes	No	No	No	No	Bone geometry (subperiosteal width (SPW) and endocortical diameter (ED)); hormone levels (testosterone, estradiol); anthropometrics (height, BMI)
Vlot 2017	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Anthropometrics (height, weight); Tanner stage (clinician assessed, bone age); bone turnover markers (P1NP (Procollagen type 1 N propeptide), osteocalcin, ICTP (Cross-linked carboxyterminal telopeptide of type I collagen)); bone health (BMD, BMAD for lumbar spine and femoral neck)
Cross-sectional												
Arcelus 2016	No	No	No	No	Yes	No	No	No	No	No	No	Psychopathology (Symptom Checklist 90 Revised)
Burke 2020	Yes	No	No	No	No	No	No	No	No	No	No	Click-Evoked Otoacoustic Emissions

Fontanari 2020	No	No	Yes	No	Yes	No	No	No	No	No	No	Anxiety (Overall Anxiety Severity and Impairment Scale (OASIS)); depressive symptoms (Modified Depression Scale (MDS)); gender distress (Gender Distress Scale (GDS)); gender positivity (Gender Positivity Scale (GPS))
Grannis 2021	No	No	No	Yes	Yes	No	No	No	No	Yes	No	Generalized anxiety symptoms (Screen for Child Anxiety Related Emotional Disorders (SCARED)); social anxiety (Liebowitz Social Anxiety Scale (LSAS)); depression (Children's Depression Inventory (CDI)); suicidality/non-suicidal self-injury (Suicidal Behaviors Questionnaire - Revised (SBQ-R)); body image dissatisfaction (BIS); amygdala activation (face processing task with functional MRI)
Green 2022	No	No	No	No	Yes	No	No	No	No	No	No	Depression (PHQ-2, score 3+ coded as depression); Suicidality (considered suicide in last year, if yes how many attempts in last year (dichotomised as 0 or 1+))
Millington 2021b	Yes	No	No	No	No	No	Yes	No	No	No	No	Cardiovascular risk (HDL, HDL-C, LDL, LDL-C, triglyceride-rich lipoprotein (TRL)); testosterone levels
Nokoff 2020	Yes	No	No	No	No	No	Yes	No	No	No	No	Insulin sensitivity (glucose, insulin, HbA1c; leptin); Lipids (total cholesterol, triglycerides, HDL, LDL); Safety (AST, ALT); hormone levels (LH, FSH, SHBG, testosterone, estradiol, free androgen index); body composition (total body fat, fat mass, lean tissue, lean mass); anthropometrics (BMI); blood pressure
Strang 2022	No	No	No	No	No	No	No	No	No	Yes	No	Executive functioning problems (Behavior Rating Inventory of Executive Function (BRIEF-2; Adult BRIEF) - primary outcome BRIEF Global Executive Composite (GEC), subscales - inhibition, cognitive flexibility, updating/working memory)
Turban 2022	No	No	No	No	Yes	Yes	No	No	No	No	No	Severe psychological distress in month before survey (defined as score of 13+ on K6+); Binge drinking in month before survey (defined as 5+ standard alcoholic drinks on single occasion); Life-time illicit drug use; Suicidality (ideation during year prior; attempt requiring hospitalisation in year prior)