

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	No of patients		Effect Result (95% CI)		
				Intervention	Comparator			
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales								
1 cohort study Klaver et al. 2020	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001) Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5)	Important VERY LOW

Abbreviations: BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

¹ Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

² Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	No of patients		Effect Result (95% CI)		
				Intervention	Comparator			
Liver enzymes (1 uncontrolled, retrospective observational study)								
Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)								

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator			
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alanine aminotransferase (ALT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in gamma-glutamyl transferase (GGT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alkaline phosphatase (ALP) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Median (IQR), U/L T0: 102 (78 to 136) T6: 115 (102 to 147) T12: 112 (88 to 143) T24: 81 (range 69 to 98) Statistically significant increase from T0 at T6 and T12 (p<0.001)	Important	VERY LOW

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients	Effect		
					Intervention	Comparator	Result (95% CI)	
Kidney markers (1 uncontrolled, retrospective observational study)								
Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)								
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Mean (SD), umol/L T0: 62 (7) T6: 70 (9) T12: 74 (10) T24: 81 (10) Statistically significant increase from T0 at all timepoints (p<0.001)	Important VERY LOW
Change from start of testosterone in serum urea² level in transmales (up to 24 months follow-up)								
1 cohort study Stoffers et al. 2019	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important VERY LOW
Adverse effects (1 uncontrolled, retrospective observational study)								
Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))								
1 cohort study Khatchadorian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	No participants permanently discontinued gender-affirming hormones.	Important VERY LOW
Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))								
1 cohort study Khatchadorian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	3/37 transmales receiving testosterone temporarily discontinued treatment, 2 due to concomitant mental health	Important VERY LOW

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients			
					Intervention	Comparator	Result (95% CI)	
							comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment	
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))								
1 cohort study Khatchadourian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	All 12 were transfemales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1) No transfemales receiving oestrogen had minor complications	Important VERY LOW
Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3))								
1 cohort study Khatchadourian et al. 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=63	None	No severe complications reported during gender-affirming treatment	Important VERY LOW

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
 2 Referred to as 'ureum' in original publication
 3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales

Study	QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect Result (95% CI)		
					Transfemales	Transmales			
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	<p>Transfemales T0 (baseline) = 1.21 (SE 0.36) T1 (final assessment) = 0.24 (SE 0.19)</p> <p>Transmales T0 (baseline) = 1.01 (SE 0.23) T1 (final assessment) = 0.29 (SE 0.13)</p> <p>No statistically significant difference in change from baseline between transfemales and transmales (p=0.79)</p>	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.									
1 cohort study Allen et al. 2019	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	<p>Transfemales T0 (baseline) = 58.44 (SE 4.09) T1 (final assessment) = 69.52 (SE 3.62)</p> <p>Transmales T0 (baseline) = 64.95 (SE 2.66)</p>	Critical	VERY LOW

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients			
					Transfemales	Transmales	Result (95% CI)	
							T1 (final assessment) = 70.94 (SE 2.35) No statistically significant difference in change from baseline between transfemales and transmales (p=0.32)	

Abbreviations: ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

¹ The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)

Study type and number of studies Author year	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients% (n/N%)	Comparator	Effect		
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=40	None	Baseline = 7.5 (SD 4.9) Follow-up = 6.6 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=45	None	Baseline = 4.2 (SD 3.2) Follow-up = 5.4 (SD 3.4) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients% (n/N%)	Effect		
					Intervention	Comparator	Result (95% CI)	
Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 26.4 (SD 14.2) Follow-up = 24.3 (SD 15.4) No statistical analysis reported for this sub-group	Critical VERY LOW
Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 5.7 (SD 4.9) Follow-up = 5.1 (SD 4.9) No statistical analysis reported for this sub-group	Critical VERY LOW
Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 8.6 (SD 5.1) Follow-up = 8.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical VERY LOW
Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 7.1 (SD 3.9) Follow-up = 6.8 (SD 4.4) No statistical analysis reported for this sub-group	Critical VERY LOW
Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 3.4 (SD 3.3) Follow-up = 2.7 (SD 2.3) No statistical analysis reported for this sub-group	Critical VERY LOW
Change from baseline in mean school avoidance symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								

Study type and number of studies Author year	QUALITY				Summary of findings			CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients% (n/N%)		IMPORTANCE	
					Intervention	Comparator		
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Result (95% CI) Baseline = 1.8 (SD 1.7) Follow-up = 1.9 (SD 2.1) No statistical analysis reported for this sub-group	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)								
1 cohort study Achille et al. 2020	Serious limitations ²	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	Wave 1 (baseline) = 11.8% (2/17) Wave 2 (approx. 12 months) = 5.9% (1/17) No statistical analysis reported	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)								
Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.								
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=30	None	Baseline = 67.5 (SD 19.5) Follow-up = 49.0 (SD 21.6) No statistical analysis reported for this sub-group	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

¹ Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

² Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

³ Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect		
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=76	None	Baseline = 10.4 (SD 5.0) Follow-up = 7.5 (SD 4.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=78	None	Baseline = 6.7 (SD 4.4) Follow-up = 6.2 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 35.4 (SD 16.5) Follow-up = 29.8 (SD 15.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 9.3 (SD 6.5) Follow-up = 7.9 (SD 6.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 10.4 (SD 5.0) Follow-up = 9.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean social anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 8.5 (SD 4.0) Follow-up = 7.8 (SD 4.1)	Critical	VERY LOW

QUALITY				Summary of findings				CERTAINTY
Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect	IMPORTANCE	
				Intervention	Comparator	Result (95% CI)		
Study Kuper et al. 2020						No statistical analysis reported for this sub-group		
Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group	VERY LOW	
Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.								
1 cohort study Kuper et al. 2020	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group	VERY LOW	
Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9 Modified for Teens (approximately 12-month follow-up)								
1 cohort study Achille et al. 2020	Serious indirectness ³	No serious inconsistency	Not calculable	N=33	None	Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported	VERY LOW	
Impact on body image (1 uncontrolled, prospective observational study)								
Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.								
1 cohort study Kuper et al. 2020	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group	VERY LOW	

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

¹ Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems

Study	QUALITY					Summary of findings			CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	No of patients		Effect	
						Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.27) Numerical scores not reported	Critical	VERY LOW
Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.43) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9 Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.07) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transmales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9 Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.67) Numerical scores not reported	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator	Result (95% CI)		
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in mean quality of life score in transfemales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.06)	Critical	VERY LOW
Change from baseline in mean quality of life score in transmales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations ¹	Serious indirectness ²	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.08)	Critical	VERY LOW
Psychosocial Impact (1 uncontrolled, retrospective observational study)									
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 47% (15/32) functioning well Did not need mental health treatment: 82% (14/17) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									
1 cohort study Kaltiala et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 72% (23/32) managing well Did not need mental health treatment: 94% (16/17) managing well	Important	VERY LOW

QUALITY				Summary of findings			IMPORTANCE	CERTAINTY	
Study	Risk of bias	Indirectness	Inconsistency	No of patients		Effect			
				Intervention	Comparator		Result (95% CI)		
						No statistically significant difference p=0.06			
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaitiata et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 42% (10/24) functioning well Did not need mental health treatment: 74% (20/27) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaitiata et al. 2020	Serious limitations ³	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 67% (16/24) managing well Did not need mental health treatment: 93% (25/27) managing well Statistically significant difference p=0.02	Important	VERY LOW

Abbreviations: CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Serious indirectness in Achille 2020.- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

3 Downgraded 1 level - the cohort study by Kaitiata et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding and no control).

Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age

Study	QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect			
					Intervention	Comparator		Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)										
Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)										
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in outcomes found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Critical	VERY LOW	
Impact on body image (1 uncontrolled, prospective observational study)										
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.										
1 cohort study Kuper et al. 2020	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Important	VERY LOW	

Abbreviations: BIS: Body Image Scale

1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Glossary

Ask Suicide-Screening Questions (ASQ)	ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ (“Have you ever tried to kill yourself?”) and prefaced it with “In the past few weeks . . .” as they were not investigating lifetime suicidality. A response of ‘no’ was scored as 0 and a response of ‘yes’ was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation.
Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents.
Center for Epidemiologic Studies Depression scale (CESD-R)	The CESD-R is a valid, widely used tool to assess depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 (“not at all or less than one day”) to 3 (“5–7 days” and/or “nearly every day for 2 weeks”). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms.
Cisgender	Cisgender is a term for someone whose gender identity matches their birth-registered sex.
Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test	The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points.
Gender	The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person’s gender identity (how they see themselves regarding their gender) and that person’s sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).

General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory score	The GWBS of the Pediatric Quality of Life Inventory uses a 5-point response scale, contains seven items, and measures two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. High scores reflect fewer perceived problems and greater well-being.
GnRH analogue	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in LH and FSH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Patient Health Questionnaire Modified for Teens score (PHQ 9_Modified for Teens)	The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10-14 moderate, 15-19 moderate and 20-27 severe symptoms.
Quick Inventory of Depressive Symptoms (QIDS)	Both the clinician- and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) are added to give a total score ranging from 0 to 27. A score of 0 to 5 is suggestive of no depressive symptoms, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16-20 severe symptoms and 21 to 27 very severe symptoms.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)	QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good).
Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire	<p>SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders:</p> <p>A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these.</p> <p>A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this.</p> <p>A score of 5 or more in questions related to separation anxiety may indicate the presence of this.</p> <p>A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this.</p> <p>A score of 3 or more in questions related to significant school avoidance may indicate the presence of this.</p>
State-Trait Anxiety Inventory (STAI) score	STAI is a validated and commonly used measure of state anxiety (current state of anxiety) and trait anxiety (general state of calmness, confidence and security). It has 40 items, the first 20 covering state anxiety, the second 20 covering trait anxiety. STAI

	can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Each subtest (state and trait) is scored between 20 and 80, with higher scores indicating greater anxiety. There is no published minimal clinically meaningful difference (MCID) for STAI or thresholds for anxiety severity.
Strengths and Difficulties Questionnaire (SDQ, Spanish version)	The SDQ, Spanish version includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 is considered indicative of risk of having a disorder (normal: 0-15; borderline: 16-19, abnormal: 20-40).
Tanner stage	Tanner staging is a scale of physical development.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transfemale is a person who identifies as female and a transmale is a person who identifies as male.
Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. Higher scores indicate higher levels of gender dysphoria.

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RESEARCH

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Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development

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Abstract

Background: Increasing numbers of adolescents present in adolescent gender identity services, desiring sex reassignment (SR). The aim of this study is to describe the adolescent applicants for legal and medical sex reassignment during the first two years of adolescent gender identity team in Finland, in terms of sociodemographic, psychiatric and gender identity related factors and adolescent development.

Methods: Structured quantitative retrospective chart review and qualitative analysis of case files of all adolescent SR applicants who entered the assessment by the end of 2013.

Results: The number of referrals exceeded expectations in light of epidemiological knowledge. Natal girls were markedly overrepresented among applicants. Severe psychopathology preceding onset of gender dysphoria was common. Autism spectrum problems were very common.

Conclusion: The findings do not fit the commonly accepted image of a gender dysphoric minor. Treatment guidelines need to consider gender dysphoria in minors in the context of severe psychopathology and developmental difficulties.

Keywords: Transsexualism, Gender dysphoria, Sex reassignment, Adolescent development

Introduction

According to the ICD-10 [1], transsexualism involves a desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make one's body as congruent as possible with one's preferred sex through surgery and hormonal treatment. **The desire has to be persistent and not a symptom of a mental disorder.** Gender dysphoria refers to dysphoria experienced due to the incongruence between a person's inner perception of her/his gender, and the incongruous bodily reality. The term Gender Dysphoria has also recently been adopted as the diagnostic category in DSM-5 [2]. Psychotherapeutic approaches have not proven successful in relieving gender dysphoria, and social, juridical, medical and surgical sex reassignment (SR) is nowadays the treatment of choice [3]. Sex reassignment with

hormonal and/or surgical treatments has been reported to improve social, psychological and sexual well-being and functioning.

Surveys based on the Child Behaviour Checklist [4] report that 2-5% of children aged up to seven, as reported by their parents, "behaves like opposite sex" and 1-2% "wishes to be of opposite sex", but cultural issues likely play a major role in whether a child's behavior is perceived as gender atypical. Consultations due to gender identity are generally more often sought for boys than girls, which may suggest greater gender variation in boys, but also that effeminate behaviours in boys are perceived as more of a problem than tom-boyishness in girls [5,6].

Of children with even severe gender dysphoria and cross-sex identification, about 85% do not develop a persistent transsexual identity in adolescence (reviewed in [7]). Reliable indicators are not so far available regarding which gender dysphoric children cease to be so in puberty and who develop transsexual identity [8]. Medical interventions are therefore not warranted in pre-

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pubertal children. In light of current knowledge, transsexual identity in adolescence is persistent and medical interventions may be appropriate. According to the treatment model developed in the Netherlands (Dutch model), early treatment may include delaying puberty after its first stages with GnRh analogues, and administering cross-sex hormones from about age 16 [9,10]. This approach is recommended when childhood gender dysphoria exacerbates in puberty, no (primary) severe psychopathology is present, and the young person has appropriate developmental support and support for the process from her/his primary caregivers (parents). The rationale with GnRh analogue treatment is to prevent the undesired development of secondary sex characteristics and thereby facilitating later transition to the desired role, and postponing complicated and irreversible treatment decisions to a more mature age. **Psychopathology largely attributed secondary to gender dysphoria is expected to be relieved by puberty blocking and resolved by sex reassignment [5,11,12].**

In the past decade, the numbers of referrals to child and adolescent gender identity services have been on the increase across Europe (personal communications in 2013 and 2014 from UK, NL, Spain, Sweden child and adolescent gender identity teams) and in Canada [13]. It is not known whether this represents a true increase in gender dysphoria, lowered thresholds for seeking help for it or perhaps cultural developments that promote the conceptualization of developmental challenges as being rooted in sex and gender.

In Finland, the legislation stipulates that a transsexual person may be recognized in law as a member of the desired sex and have access to hormonal and surgical sex reassignment (in public health care) (act 2002/563). **A psychiatric assessment by a specialized gender identity team is a prerequisite for legal as well as surgical sex reassignment, both of which have a lower age limit of 18.** The specialized psychiatric assessment by a gender identity team is centralized to two university hospital psychiatric clinics, Tampere and Helsinki University Hospitals, in the country (codes 1053/2002 and 476/2010).

Since 2011, specialized adolescent psychiatric gender identity teams have been available for minors at the above mentioned two university hospitals. The excessive number of referrals, exceptional sex ratio and severity of general psychopathology among the applicants compared to what might have been anticipated on the basis of the literature called for clinical attention from the beginning of the service. The aim of this study is to describe the adolescent applicants for legal and medical sex reassignment in terms of sociodemographic, psychiatric and gender identity related factors and adolescent development in order to initiate a scientific discussion on the meaning of these observations.

Materials and methods

The study comprises a retrospective chart review of all the SR applicants attending for assessment by one of the two adolescent gender identity services in Finland (Tampere University Hospital, Department of Adolescent Psychiatry) in 2011–2013. Altogether 49 adolescents were referred to assessment for sex reassignment and invited to their first meeting during the study periods, but two adolescents declined to start the evaluation. Thus 47 adolescents are included in this study. Of these, one was autistic and did not provide any information; for this young person, information on personal experiences is missing but information from case records and parents could be used.

The assessments take place in an outpatient setting and comprise structured and free format assessments and interviews with an adolescent psychiatrist, a psychiatric nurse, a social worker and a psychologist. The adolescent and her/his parents/guardians are seen together and separately by all the multi-disciplinary team members. Psychiatric and medical files are requested from all previous health care contacts of the adolescent, with due permission from her/him and her/his parents. After completing all the assessments, the multi-disciplinary team discusses the diagnosis as to gender identity and mental disorders, eligibility for hormonal SR treatments and possible other needs to be met and recommendations to be given regarding gender identity needs and mental health needs when appropriate. All the below described measures were collected using all the material available after the assessment. The study received approval from the ethics committee of Pirkanmaa Hospital District.

Measures

Sociodemographic variables collected were age, natal sex, family structure (living with both parents/one parent/neither parent) and parental education (professional/intermediate/skilled non-manual/skilled manual/unskilled or not in employment). Further background information included the reason for referral (sex reassignment, definite wish/sex reassignment, possible reassignment/other) and parental homosexuality or transsexualism (yes/no).

Throughout the discussion of our own research we use the terms “gender dysphoria” and “gender dysphoric” to refer to the experienced gender incongruence among our applicants, regardless of whether they fulfill the diagnostic criteria for Gender Dysphoria in the DSM-5. For the present study we recorded whether there had been signs of gender dysphoria/gender incongruence in childhood (before age 12) (Table 1). Age of onset of conscious gender concerns and age when the applicant was convinced that s/he is transsexual were recorded. If the adolescent was already living in the desired role (Table 1), it was recorded for how long.

Table 1 Variable descriptions for childhood gender dysphoria, bullying and social isolation**Gender dysphoria/gender incongruence in childhood (<12 years of age)**

Childhood gender dysphoria/incongruence present

- explicit gender dysphoria or marked and persistent cross-gender identification on behavioural level even without explicit verbalization of one's gender related thoughts and feelings in childhood

Gender presentation, living in desired role

Classified as living in the desired role

- the applicant had officially changed her/his name to a gender neutral one or arranged his/her registration in school, and being consistently called, by a name suggesting the desired sex; being always presented to new people as being of the desired sex; being treated by family, teachers/employers, friends, schoolmates as well as by new people as a member of the desired sex
- some of these young people had explicitly "come out" in school and openly made a transition to the desired role; some, with the support of some community key adults, had adults, had totally concealed their natal sex from the school/workplace

Bullying

Significantly subjected to bullying

- the applicant and/or her/his parents considered that there had been significant and traumatic victimization.
- a) related to gender presentation or sexual identity: name-calling, spreading rumours and the like related to gender presentation/sexual identity
- b) not related to gender or sexual identity: bullying was related to other issues like weight, interests, belonging or not belonging to a certain group etc.

Isolation

Periods of isolation

- periods of not having contact with peers outside of arranged study-related activities at school - or not even that, if not attending school
- having same-age contacts only with one's own siblings
- keeping (tenuous, infrequent) contact with one or two peers only despite previously having been normatively engaged with peers
- contacts outside the family only via Internet

Childhood gender dysphoria/incongruence not present

- no signs of gender dysphoria/incongruence in childhood

Not classified as living in the desired role

- the adolescent had not made any attempt to live and be treated in the desired role
- the adolescent dressed gender neutrally and asked the family to use a name indicative of the desired sex, but was actually not living in any social role outside the family due to isolation from social interactions
- some of the adolescents in this group were almost totally isolated in their homes (not going to school or work, not meeting peers), some attended school but were isolated from social interactions there and elsewhere

Not subjected to bullying

- no recollection of being bullied
- if ever bullied, the adolescent described it as non-significant ("maybe sometimes", "not more than anyone else").

No isolation

- no interruptions in attending age appropriate daily programme (usually school), having age-appropriate contacts with peers

Previous and current psychiatric history was recorded. Previous files were not always complete, and diagnoses were not always accurately defined in terms of ICD-10 diagnostic codes. Thus, we recorded 1) whether the young person had been in contact with psychiatric services prior to entering the gender identity service (yes/no), 2) whether the previous contact had been because of gender concerns or psychiatric symptoms (gender issues only/psychiatric symptoms only/both), 3) what kind of problems the young person had displayed (anxiety, depression, suicidal behaviours, conduct problems, autism spectrum related problems, substance abuse, psychotic symptoms, other; all recorded yes/no), and 4) the temporal relationship between psychiatric symptoms and gender dysphoria/identity concerns (psychiatric symptoms emerged earlier/gender dysphoria and gender identity concerns emerged first).

Peer-related difficulties were recorded being subjected to bullying at school (yes/no) and isolation from peers (yes/no) (Table 1). Of bullying it was recorded whether it happened before, after or both before and after of the onset of gender dysphoria, and whether it was related to gender presentation or sexual orientation. Of social isolation it was recorded whether it occurred before, after or both before and after the onset of gender dysphoria.

Statistical analyses

All the variables were recorded in a structured form developed for this research. Descriptive analysis was conducted using statistical methods for quantitative data. We report frequencies and means (sd) where appropriate. Between groups comparisons are made with cross-

tabulations and chi-square statistics/Fisher's exact test, and with t-test where appropriate.

Qualitative observations

The qualitative content analysis approach [14] was applied to illustrate, based on all material recorded in case histories, different groups of gender dysphoric adolescents, or different developmental pathways resulting in the adolescent now perceiving the need to apply for sex reassignment. This was carried out by condensing and extracting from all material recorded in the case histories similar and different developmental patterns and descriptions of experiences that could be used to create mutually exclusive model stories, or trajectories that would include all the studied adolescents and not allow for assigning a given adolescent to more than one trajectory. The model stories were not defined in advance but they were formed in a data-driven process, the outcome of which is presented.

Results

Demographics

Of the applicants included in the present study, 41 were natal girls and 6 were natal boys. Their mean age (sd) at entering assessment was 16.04 (0.57) years for natal boys and 16.66 (1.07) for natal girls ($p = 0.18$). Of these, 49% (23) were living with both their biological parents, 39% (18) with one biological parent, and 13% (6) in child welfare foster placements or independently. Parental education was distributed as follows: 16% (8) professional, 5% (2) intermediate, 22% (10) skilled non-manual, 43% (20) skilled manual, and 14% (7) were unskilled or not participating in work life. None of the applicants had transsexual or homosexual parents.

Gender dysphoria

Of the applicants, 32% (14/47) reported having started to consciously question their gender before age 12, 62% (30/47) at 12 or later, and three applicants (6%) could not define this. Most commonly (one in five) these concerns had started at age 14. There were altogether five applicants (11%) who during childhood had persistently expressed gender dysphoria and/or identified with the opposite sex, and three (6%) who during childhood had transiently displayed gender dysphoria and a desire to be of the opposite sex. A further nine applicants (19%) had been tomboyish girls but had not questioned their gender or experienced dysphoria, and as to most of the applicants (30/47, 64%), neither the young person nor her/his parents recalled gender dysphoria or cross-gender behaviors during childhood.

During the assessment process, 72% (34/47) of the applicants were sure about feeling they were of the opposite sex to their natal and about pursuing sex reassignment,

but 28% (13/47) were not sure about their feelings regarding gender identity and/or sex reassignment. There was no difference between natal girls and natal boys in this regard. Of those who felt sure about their cross-gender identity, 15% (5/34) recalled reaching the conclusion before age 12, 79% (27/34) at 12 or later, and two (6%) could not define at what age they had reached the conclusion. There was no difference between natal girls and natal boys. The time frame from first becoming aware of gender dysphoria to being sure of one's own cross-gender identity ranged from 0 to 7 years, with mean 1.6 (sd 2.1) years.

Of all the applicants, 38% (17/47) were living in the desired role when the assessment was completed, 50% (3/6) of the natal boys and 37% (15/41) of the natal girls ($p = 0.41$). Of those applicants who expressed certainty about being of other than their natal sex and desiring physical and legal sex reassignment, 47% (16/34) were living in the desired role. Of those who were living in the desired role, the mean (sd)/median time of living in the role was 28.3 (17.9)/24.0 months for natal boys, and 29.8 (39.2)/12 months for natal girls ($p = ns$).

Peer relationship difficulties

Of the applicants, 57% (27/47) had been significantly bullied at school, 53% (25/47) in primary school (grades 1–6, ages 7–13 yrs) and 45% (21/47) in secondary school (grades 7–9, ages 13–16 yrs). Of those who had been victims of bullying, 73% (19/27) had been bullied before they came to think about their gender identity, 8% (2/27) after starting to think about gender issues, and 19% (5/27) both before and after. Of those bullied, 27% (7/26) reported that bullying had been related to gender presentation or sexual identity, and 73% (19/26) had been bullied due to some other reasons (see Table 1).

Natal girls and natal boys had been bullied equally frequently. Natal girls tended more often to report having been bullied only before the onset of gender dysphoria, and natal boys more often both before and after the onset of gender dysphoria (girls: 78% (17/23) only before, 9% (2/23) only after, 13% (3/23) before and after vs. boys: 33% (1/3) only before, none only after, 67% (2/3) both before and after, $p = 0.08$). Among natal boys gender presentation and/or sexual identity had always been the topic of the bullying, among natal girls 83% (19/23) had been bullied for something else and 17% (4/23) due to gender presentation/sexual identity ($p = 0.01$).

Of the applicants, 45% (21/47) had presented with periods of isolation from peer relationships; 32% (15/47) before and 40% (19/47) after the onset of gender dysphoria, and 43% (20/47) were socially isolated during the SR assessment. Twenty-eight per cent (13/47) were isolated in all three observed periods. Social isolation was equally common among natal boys and girls applicants.

41 girls
6 boys

PARENTS

49% both
39% one
13% foster

GENDER ?
BEGAN

32% before 12
62% after 12
6% unknown

20% most
common at age
14

64% —no
recollection
of early gender
issues

11%, early onset
persistent
6% early onset
transient
19% tomboy
girls w/o ? gender
or dysphoria

Psychiatric treatment and psychopathology

Seventy-five per cent of the applicants (35/47) had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria when they sought referral to SR assessment, and two more were contacted with general adolescent psychiatric services soon after entering the SR assessment. Sixty-four per cent (30/47) were having or had had treatment contact due to depression, 55% (26/47) due to anxiety disorders, 53% (25/47) due to suicidal and self-harming behaviours, 13% due to psychotic symptoms (6/47), 9% (4/47) due to conduct disorders, 4% (2/47) due to substance abuse, 26% (12/47) due to autism spectrum disorder, and 11% (5/47) due to ADHD. One severe case of anorexia nervosa was noted. Of the applicants, 68% (32/47) had had their first contact with psychiatric services due to other reasons than gender identity issues. Natal boys and natal girls had equally commonly been treated for psychiatric disorders except for ADHD which had been more commonly treated in natal boys (50% vs.5%, $p = 0.01$). The mean number of distinct psychiatric problems was 2.3 (sd 1.7), with no difference between natal girls and natal boys.

The different groups

Five different mutually exclusive groups (a - e below) were identified that differed as to onset of gender dysphoria and cross-gender identification, psychopathology and adjustment/difficulties in social relationships, and the temporal relationships between these. They are presented in Table 2.

We carried out logistic regression analyses to detect what kind of presenting features were associated with belonging to the last, confused group of adolescents with gender dysphoria (e) when entered in the model simultaneously. This was appropriate because psychiatric symptoms and psychosocial functioning are strongly interrelated. Age and natal sex were not predictive of belonging to the confused group. Each psychiatric problem, being subjected to bullying, presenting with periods of isolation, number of different psychiatric problems, and months living in desired role were each in turn entered as independent variables, controlling for age and natal sex. When controlling for age and natal sex, group memberships was predicted by anxiety (OR 4.8, 95% CI 1.4-17.0), suicidality (OR 5.7, 95% CI 1.7-20.3), number of different psychiatric symptoms (OR

Table 2 The different groups of gender dysphoric adolescents seeking SR

Early onset gender dysphoria, exacerbates in puberty

a) with no with no significant psychopathology and developmental problems (n = 2)

- very mild or no psychopathology across childhood and until the assessment

b) with considerable psychopathology and developmental problems (n = 3)

- severe psychopathology that had previously and currently required specialist level child and adolescent psychiatric care (autism spectrum disorder, OCD, Tourette, anorexia nervosa, suspected psychotic episodes or psychosis high risk, specific learning difficulties)

Adolescent onset gender dysphoria, where transsexual identity appeared established

c) without, or with only mild psychopathology and developmental difficulties (n = 10)

- mild to moderate depression or anxiety, could be considered secondary to gender dysphoria, or was transient, and did not impair functioning in social relationships or school
- age-appropriate social relationships and leisure time activities, participation in age-appropriate educational activities (comprehensive, vocational or upper secondary school)

d) with severe psychopathology and developmental difficulties (n = 9)

- psychiatric problems that warranted specialist level adolescent psychiatric treatment, either in treatment at the beginning of their SR assessment, or treatment contact was arranged during the SR assessment
- autism spectrum disorders (3), major depression (3), social phobia (5), substance abuse problems (1) or a history of conduct disorder and trauma (2) (several had two disorders); clearly more severe psychopathology than what was seen in group c

e) Adolescent onset gender dysphoria, identity confused development (n = 23)

- In childhood, no gender dysphoria nor cross-gender behaviors
- For most of their primary school years (age 7–12 years) felt excluded
- Persistent experiences of bullying before the onset of gender dysphoria
- In adolescence, social anxiety and depression, most often with self-harm and suicidal preoccupation if not suicide attempts
- Isolated
- Long periods of not attending school, or if attended school, did not engage in peer contacts outside learning situations arranged by teachers.
- Did not meet with same-aged peers in leisure time, or they met with few peers and only if their parents arranged it; many in contact only with their family members.
- Socially and/or academically marginalized
- Very high expectations that SR would solve their problems in social, academic, occupational and mental health domains

75% seeing psych for issues other than GD
64% depression
55% anxiety
53% SI or self harm
13% psychosis
9% conduct d/o
4% substance abuse
26% ASD
11% ADHD
68% first contact with psych was not for GD

1.7, 95% CI 1.1-2.6), and presenting with periods of isolation (OR 9.0, 95% CI 2.3-34.7). However, when presenting with periods of social isolation was entered into any other model, the other independent variables were leveled out, suggesting that social isolation was the strongest factor predicting membership of the problematic, identity confused group.

Discussion

The number of referrals exceeded expectations. Given the most cited epidemiological figures among adults, 1:10 000–1:30000 MtF and 1:40 000–1:100 000 FtM [6], in Finnish population, 6–18 boy-to-girl adolescents and 2–4 girl-to-boy adolescents aged 13–18 would be expected. The number of referrals to the study unit already doubled the less conservative estimates based on adult figures. Referrals to the other adolescent gender identity unit amount to equal numbers, and the natal girl:boy ratio in referrals is also similar in the other unit (Tainio V-M, personal communication). Valid epidemiological research on incidence and prevalence of transsexualism or gender dysphoria at large among adolescents is not available [6]. The adult figures cited above are based on treatment seeking, as are the numbers presented in the present study. Gender dysphoria may be more common among adolescents than among adults, or it may be increasing in younger age cohorts.

Not all applicants could be seen as presenting with established transsexual identity, even though they suffered gender dysphoria. **Excluding the confused (e) group in our data, 3 boy-to-girl and 21 girl-to-boy applicants were identified who displayed transsexual identity that appeared established, unique, and not part of more general identity confusion or secondary to severe mental disorders.** Given that these numbers are based on half of the adolescent gender identity assessments in Finland, the findings further suggest that severe and persistent gender dysphoria/transsexualism in adolescence may be more common than hitherto assumed.

The natal girl:boy ratio among the adolescent SR applicants was very high. In prepubertal children referred to gender identity services, boy:girl ratio is reportedly 3–6:1, with some variation across countries presumably due to cultural reasons [5,13]. Previously a more even boy:girl ratio has been suggested in adolescents seeking sex reassignment than among child samples [13], and a recent paper from Germany reported natal boy:natal girl ratio of 0.81 among 268 minors diagnosed with gender identity disorder from 1987–2013 [15]. Among adults, there seems to be remarkable variation across countries in the ratio of natal men:natal women seeking for sex reassignment [16]. In Western countries natal male transsexuals exceed natal females transsexuals. A German study demonstrated that the natal male:natal female

ratio among transsexual people has changed to more equal towards 2000's that what it was in earlier decades [16]. However, the overrepresentation of girls on our sample differs still from these more recent trends, and it is similar in both the two Finnish centers. We have so far no explanation for this great overrepresentation of natal girls seen in our material, and equalizing of sex ratio demonstrated by others [13,15,16]. Cultural trends may somehow influence this. May be more permissive societal attitudes allow “coming out” as gender variant more easily than before. However, why this would concern primarily girls remains an open question.

Of children and adolescents, 10-15% are regularly (weekly) involved in school bullying [17]. Of the adolescent SR applicants, more than a half had been subjected to bullying. Even if in the present study it was not possible to verify exactly how frequently the applicants had been bullied, we only recorded bullying that the adolescent and her/his parents perceived as significant: particularly intensive, vicious, long-term and traumatizing. However, in more than two thirds of the cases, bullying had occurred before the onset of gender dysphoria, and was not targeted at gender or sexual identity. Bullying is an unspecific risk factor for developmental problems rather than a problem specifically related to gender identity. That natal boys were more commonly bullied because of gender presentation suggests that effeminate characteristics in boys are less tolerated than masculine self-presentation in girls.

Peer relationships are of the utmost importance during adolescent development [18-20], and social isolation from peer relationships suggests developmental difficulties and impaired mental health [21-24]. In the present sample, isolation was extremely common and also the strongest predictor of membership of the “confused” group.

More than three quarters of the adolescent SR applicants had needed and/or currently needed specialist level child and adolescent psychiatric services due to psychiatric problems other than gender dysphoria. Specialist level child and adolescent psychiatric services are provided exclusively for severe disorders in Finland [25,26]. The recorded comorbid disorders were thus severe and could seldom be considered secondary to gender dysphoria. This utterly contradicts the findings in the Dutch child and adolescent gender identity service, where two thirds of adolescent SR applicants did not have psychiatric comorbidity [27]. In a recent German study, 43% of children and adolescents seen in a specific gender identity unit suffered from major psychopathology [15]. For the time being, we are unable to explain why Finnish adolescent SR applicants appear psychiatrically much more disturbed than has been reported elsewhere, but our findings warrant attention. The

treatment guidelines for adolescent gender dysphoria may require extensions taking into account the needs of those with severe psychopathology and identity confusion, very unlikely currently eligible to medical SR.

The overlap between autism spectrum disorders and gender dysphoria has been recognized before [28]. In a Dutch gender identity service, 9.4% of adolescents presented with autism spectrum disorder. In our sample, 26% of the adolescent SR applicants were diagnosed to be on the autism spectrum. These diagnoses had mainly been made during the adolescents' previous psychiatric treatment in our hospital or elsewhere, but three such diagnoses were also made by our team. In our hospital, the ADOS [29] is used with the minors, and the 3Di [30] or ADI-R [31] with parents to diagnose autism spectrum disorders. We could not systematically review with which protocols the diagnoses had been made elsewhere in the country, but in our clinical opinion there was no reason to doubt them. It is currently not known why autism spectrum is overrepresented in gender dysphoric children and adolescents. The conditions could be truly co-occurring. Prenatal exposure to high levels of testosterone could be involved in the development of both conditions, especially for girls with autism spectrum disorder, but this leaves the comorbidity in males unexplained. Gender identity issues could arise from autism spectrum people's predisposition toward unusual interests, or gender dysphoria in ASD could represent OCD rather than genuine gender identity issues. The cross-gender behaviour in ASD minors could also rather represent non-normative sexual interests or unusual sensory preferences [28]. Our clinical impression is that a long-standing feeling of being different and an outsider among peers could play a role in ASD children developing gender dysphoria in adolescence. In our clinical sample of gender dysphoric adolescents, autism spectrum disorders by far exceeded the prevalence of 6/1000 suggested for general population [32], and almost three-fold that in the sample of deVries et al. [28]. **Autism spectrum needs to be taken seriously in considering treatment guidelines for child and adolescent gender dysphoria.** Given the nature of ASD, particularly ASD children's and adolescents' difficulties in adjusting to changes, profound changes in their own bodies with SR treatments may pose a major challenge to psychological adjustment, and ASD adolescents may be particularly rigidly unwilling to consider this in advance.

In the international literature on gender dysphoria in minors, the most often portrayed picture is that of childhood cross-gender identification/gender dysphoria, where gender dysphoria exacerbates in puberty due to the development of secondary sex characteristics. Our findings suggest that there are many more developmental pathways that may also need different treatment

approaches. In our data, most of the adolescents first presented with gender dysphoria and cross-gender identification well after the onset of puberty, and the vast majority suffered significant psychopathology and broader identity confusion than gender identity issues alone. It is important to be able to openly discuss these alternative presentations of gender dysphoria in order to find appropriate treatment options.

Adolescence is a period of identity formation. From early to late adolescence, identity develops from fragmented and contextual identity experience to endogenous, permanent and integral identity that remains constant across contexts and interactions [33]. Identity is formed through diverse physical and psychological developments and in relation to other people and the social environment [34,35]. An adolescent also faces fundamental identity challenges in the domains of religion, worldview, ethnicity, sexuality and the like. Identification with various groups is often passionate during adolescence, but the object of identification may also change, even several times [34-37]. Adolescents are more suggestible and submit more readily to group pressure to gain acceptance [38]. Adolescence is a period of maturation of social cognition, and a prerequisite for the maturation of social cognition is the maturation of the central nervous system that continues to the third decade of life [39]. During puberty and adolescent development there may be some overlap between normative testing of sexuality and gender roles in the one end, and gender dysphoria as a disorder in the other end of the spectrum. This would implicate that GD in adults and in adolescence may not be the same issue in general. For these reasons it is more challenging to assess whether the gender identity of an adolescent is so firmly established that physical intervention is indicated than it is to assess this among adults.

In the majority of the applicants, gender dysphoria presented in the context of wider identity confusion, severe psychopathology and considerable challenges in the adolescent development. At this point it is not possible to predict how gender dysphoria in this group will develop: will gender dysphoria in these adolescents cease with the resolution of wider developmental problems, or perhaps consolidate later into transsexual identity, with the completion of the developmental tasks of adolescence.

Methodological considerations

The present paper is based on information on all adolescents who entered the assessment for sex reassignment in Finland in 2011–2013 by one of the two centralized adolescent gender identity teams in the country. The basis for choosing one or another of the two centers was geographical and not likely to create bias due to subject selection. It is further known that number of referrals

during the study period well as natal girl:natal boy ratio are similar in both centers.

The data collection was systematic and structured, which adds to the reliability of the findings. The data collection took place in the form of retrospective chart review of files created during a comprehensive assessment period by a multi-disciplinary team. Thus data collection was unlikely to bias the assessments in any way. Comprehensive assessments by a multi-disciplinary team are likely to provide reliable and valid data. The multi-disciplinary team collected information from the applicants themselves, from their parents, from previous case histories and by their own psychometric measurements. The applicants themselves might be prone to interpret a variety of their problems as being a result of gender incongruence, even if the problems actually were independent of gender identity issues or even predisposing to gender incongruence. In this study we attempted to avoid bias due to subjects' interpretation by using multiple source of information.

However, the data is relatively small and does not permit complex analyses. The study remains descriptive and cannot shed light on causal relationships. Some information of interest for the research was occasionally missing in the files, because the files were primarily created for clinical purposes, not for research.

The validity of the diagnoses in previous psychiatric contacts needs to be considered with certain caution. Previous files were not always complete and did not provide diagnoses according to ICD-10, and we were not able to check in the databases of the previous treatment providers what ICD diagnoses were recorded there. Thus, we recorded reasons for previous treatment based on verbalizations in the referrals and available copies of previous files. This only allowed a rough descriptive classification to problems related to anxiety, depression, suicidal behaviours, conduct problems, autism spectrum related problems, substance abuse, psychotic symptoms and other. We only recorded these problems if the adolescent had had a psychiatric treatment contact. The data gives a picture of the primary problems in previous psychiatric treatment contacts but not of all possible symptoms. Thus, our figures for problems related to anxiety, depression etc. are likely underestimates. It was also not possible to obtain exact information of when the various symptoms and disorders had been present and for how long time, except for autism which is of course assumed a lifetime condition. However, as clinical research on adolescent SR applicants is scarce, descriptive studies are valuable in providing a basis for discussion and international comparisons that are needed in order to create optimal clinical treatment guidelines.

Psychotic symptoms in our data mainly comprise brief and limited hallucinatory experiences. Psychotic symptoms

were recorded if there were descriptions of hallucinations in the files, or of the previous files mentioned "psychotic symptoms" even when not giving more detailed descriptions. However, none of the applicants had a diagnosis of schizophrenia or schizoaffective disorder. Assessing gender dysphoria in the context of schizophrenia spectrum psychoses would be inappropriate. Doctors/units primarily contacted would very unlikely refer a patient with schizophrenia or schizoaffective disorder in gender identity assessments. Current psychotic symptoms would result in the gender identity team promptly referring the young person to general adolescent psychiatric care.

The findings cannot be generalized to all adolescents experiencing gender variation. Not all gender incongruent people perceive a need to seek for SR, or find it timely during adolescence.

Conclusion

Adolescents seeking sex reassignment represent a variety of developmental pathways differentiated by the timing of onset of gender dysphoria, psychopathology and developmental difficulties. It is important to be aware of the different groups, or developmental pathways, in gender dysphoric adolescents in order to be able to find appropriate treatment options. In the presence of severe psychopathology and developmental difficulties, medical SR treatments may not be currently advisable. Treatment guidelines need to be reviewed extended to appreciate the complex situations.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors participated in designing the present study and formulating the study questions. RKH and MS collected the data from case files. RKH performed the data analysis. All the authors participated in discussing the results and writing the manuscript. All authors read and approved the final manuscript.

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