

EPATH Endocrinology Update

EPATH Rome

12 April 2019

Professor Gary Butler

Paediatric and Adolescent Endocrinology

University College London Hospital

UK Gender Identity Development Service



The Tavistock and Portman 
NHS Foundation Trust

in partnership with

The Leeds Teaching Hospitals 
NHS Trust

University College London Hospitals 
NHS Foundation Trust

What will I cover?

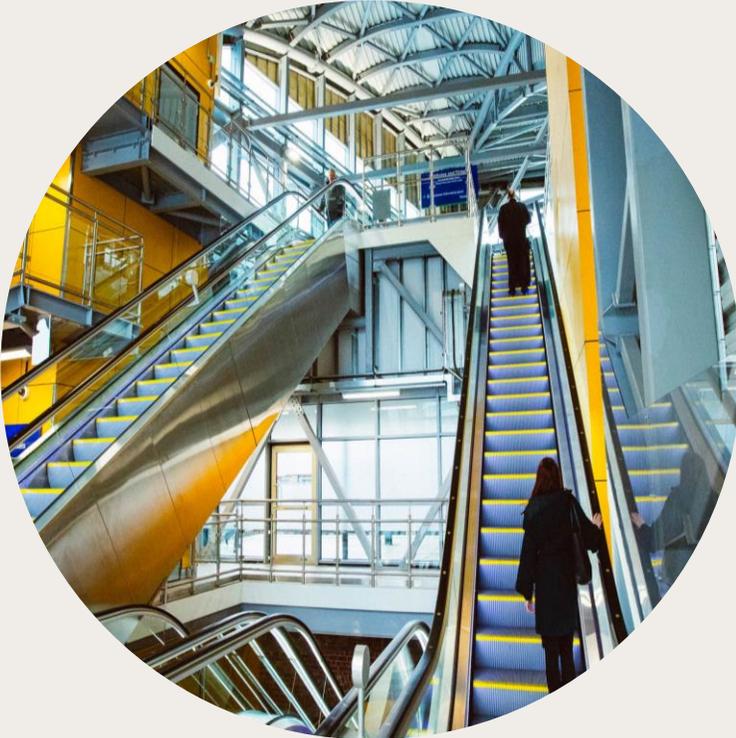
Major publications
2018-9

Selected from PubMed
with data/evidence

General interest to all present

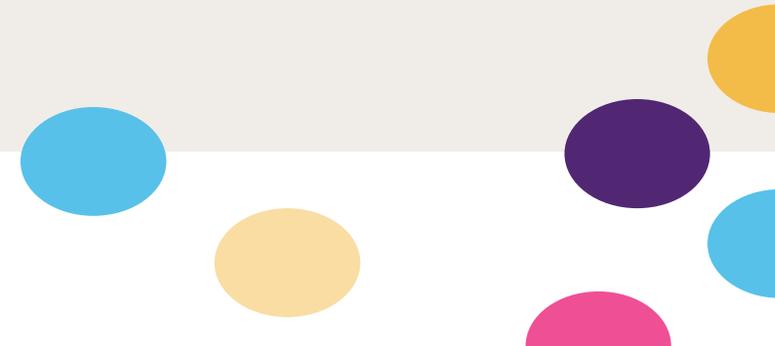
Apologies if time does not permit
a full representation

Headings



- Safety and efficacy
 - Adults
 - Adolescents
- Bone health
- Behaviour
- Comings and goings

NB presentation based on published literature and reviewed by EPATH Board



Safety and Efficacy

Adults



Risks of stroke and heart attack with CSH

Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons A Cohort Study

Darios Getahun, MD, PhD, MPH; Rebecca Nash, MPH; W. Dana Flanders, MD, MPH, DSc; Tisha C. Baird, MD; Tracy A. Becerra-Culqui, PhD; Leo Cromwell, MS; Enid Hunkeler, MA; Timothy L. Lash, PhD; Andrea Millman, MA; Virginia P. Quinn, PhD; Brandi Robinson, MPH; Douglas Roblin, PhD; Michael J. Silverberg, PhD; Joshua Safer, MD; Jennifer Slovis, MD; Vin Tangpricha, MD, PhD; and Michael Goodman, MD, MPH

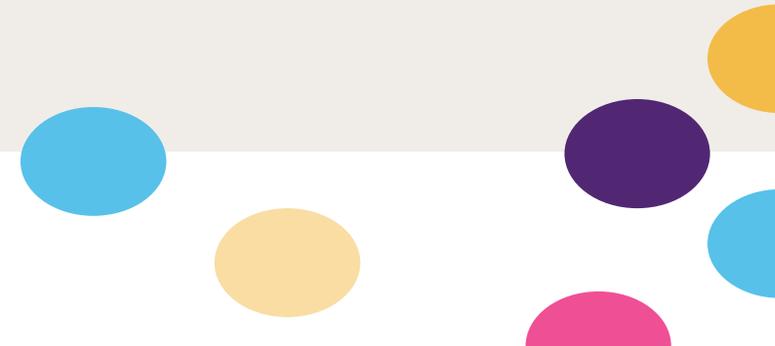
Ann Intern Med. 2018 Aug 21;169(4):205-213

Aim: To examine the incidence of these events in a cohort of transgender persons.

Methods: Electronic medical record-based cohort study index date (transgender status) from 2006 to 2014

10 male and 10 female cisgender enrollees were matched to **each** transgender participant

Transgender 2842/2118; Cisgender 48 686/48 775



Findings: Transwomen had a higher incidence of venous thromboembolism (VTE), with **2** and **8** year risk differences per 1000 persons of:

4.1 and **16.7** relative to cismen

3.4 and **13.7** relative to ciswomen

The overall analyses for ischaemic stroke and myocardial infarction demonstrated similar incidence across groups

Conclusion: The patterns of increases in VTE and ischaemic stroke rates among transwomen are higher than those observed in ciswomen

Need for long-term vigilance

Figure 1. Adjusted cumulative incidence curves comparing rates of VTE among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (left) and reference women (right) from KPNC, KPSC, and KPGA, 2006-2016.

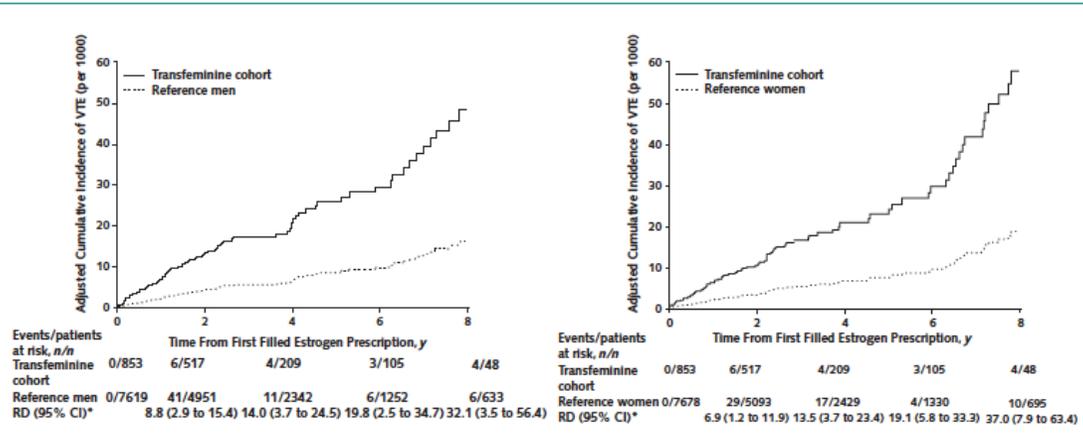
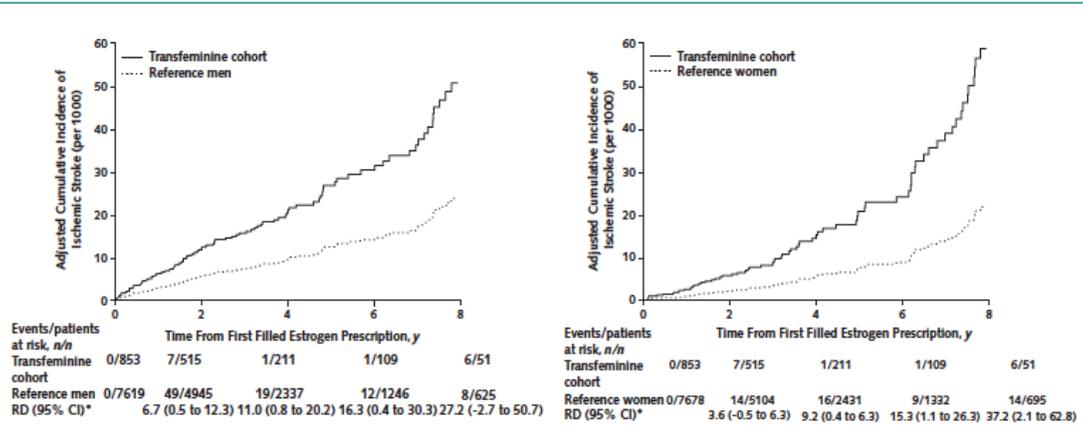


Figure 2. Adjusted cumulative incidence curves comparing rates of ischemic stroke among transfeminine cohort members who initiated estrogen therapy after the index date with matched reference men (left) and reference women (right) from KPNC, KPSC, and KPGA, 2006-2016.



Oestrogen

HORMONE REPLACEMENT THERAPY AND VENOUS THROMBOEMBOLISM

Hormone replacement therapy: transgender studies show safety of estradiol

Richard Quinton *consultant and senior lecturer in endocrinology*¹, Du Soon Swee *consultant endocrinologist*²

BMJ 2019; 364: l600 (Published 11 Feb 2019)

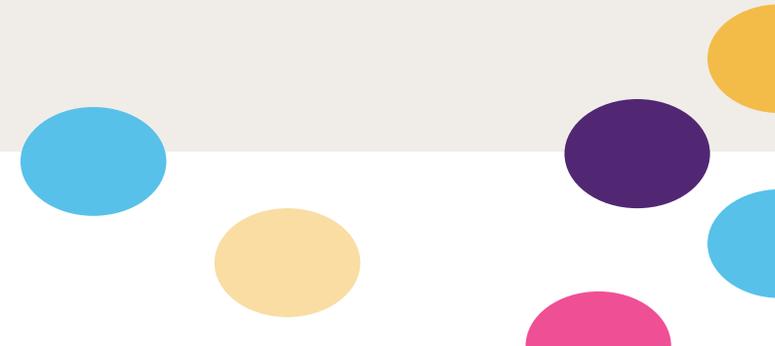
RESEARCH

Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases

Yana Vinogradova,¹ Carol Coupland,¹ Julia Hippisley-Cox¹

BMJ 2019;364:k4810 (Published 09 January 2019)

Aim: To assess the association between risk of VTE and use of different types of hormone replacement therapy



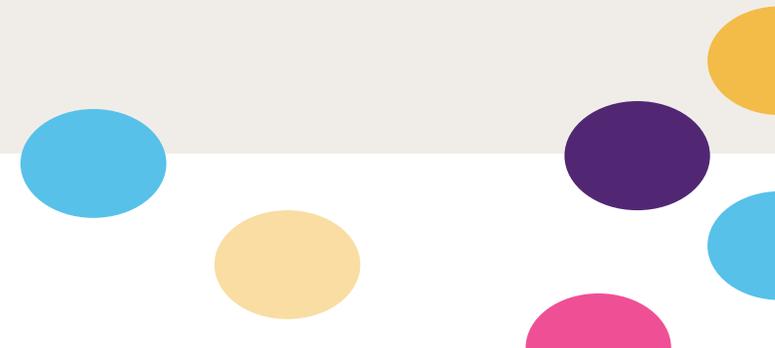
Oestrogen

Methods:

80 396 ciswomen aged 40-79 with a primary diagnosis of venous thromboembolism (VTE) between 1998 and 2017

Matched by age, general family practice, and index date to 391 494 ciswomen in the community

5795 (7.2%) with VTE and 21 670 (5.5%) had hormone replacement therapy HRT within 90 days



Oestrogen

Findings:

- Significantly increased risk of VTE **vs no exposure**
Odds Ratio for oestrogen only preparations (1.40)
Combined with progestogen preparations (1.73)
NB not needed in women without a uterus
- Oestrogen only preparations:
oestradiol **lower risk** (1.27) than conjugated equine oestrogen (1.49)
- Transdermal oestradiol **NO INCREASED RISK VTE** (0.93)

Conclusion: Transdermal treatment has the lowest risk of VTE



Testosterone

EXOGENOUS TESTOSTERONE DOES NOT INDUCE OR EXACERBATE THE METABOLIC FEATURES ASSOCIATED WITH PCOS AMONG TRANSGENDER MEN

Chan, Kelly J, MS; Liang, Jennifer J, BS; Jolly, Divya, BS; Weinand, Jamie D, MD; Safer, Joshua D, MD.

Endocrine Practice; Jacksonville Vol. 24, Iss. 6, (Jun 2018): 565-

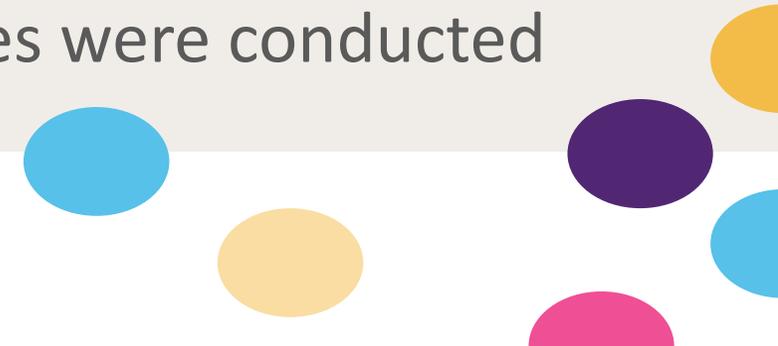
572.

DOI:10.4158/EP-2017-0247

Aim: Polycystic Ovarian Syndrome (PCOS) can cause metabolic changes in ciswomen

The aim was to examine metabolic changes due to T in transmen

Methods: 34 transmen, serum metabolic factors and BMI levels were examined over 6 years of T treatment. Bivariate analyses were conducted



Testosterone 2

Findings:

No significant changes in levels of glycosylated haemoglobin (HbA1c), triglycerides, or low-density-lipoprotein cholesterol

Significant decrease in BMI with increasing testosterone

Significant decrease in high-density lipoprotein levels

Conclusion:

T therapy did not result in the dyslipidaemia or abnormalities in HbA1c seen with PCOS

Only saw shift of metabolic biomarkers towards the physiologic cis male body



Brain tumours

Aim:

to compare the incidence of common benign brain tumours: meningiomas, pituitary adenomas (non-secretive and secretive), and vestibular Schwannomas in transgender individuals receiving GAH treatment, with those reported in general Dutch or European populations.

Methods:

VU University Medical Centre in the Netherlands: 2555 transwomen (median 31 years) and 1373 transmen (median 23 years) who were followed for 23 935 and 11 212 person-years, respectively.

The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment

Nienke M. Nota,¹ Chantal M. Wiepjes,¹ Christel J. M. de Blok,¹ Louis J. G. Gooren,¹ Saskia M. Peerdeman,² Baudewijntje P. C. Kreukels³ and Martin den Heijer¹

Brain tumours 2

Findings:

The incidence of meningiomas was higher in transwomen than in a general European cisfemale population (*SIR* 4.1) and cismale population (**11.9**)

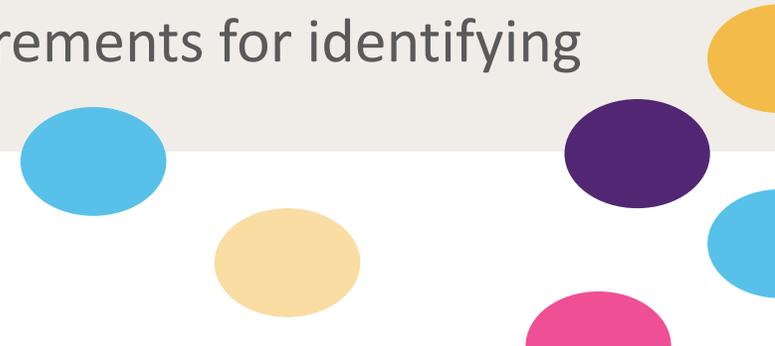
Prolactinomas occurred more often in transwomen compared with general Dutch cisfemale population (**4.3**) and cismale population (**26.5**)

Conclusion:

GAH is associated with a higher risk of

- meningiomas and prolactinomas in *transwomen* (which may be linked to cyproterone acetate usage)
- somatotrophinomas in *transmen*

Regular screenings for such tumours (e.g. regular prolactin measurements for identifying prolactinomas) does not seem necessary as quite rare



Safety and Efficacy

Adolescents



Assessment

Assessment and support of children and adolescents with gender dysphoria

Gary Butler,^{1,2,3} Nastasja De Graaf,³ Bernadette Wren,³
Polly Carmichael³

Aim: Evidence base for investigating adolescents

Arch Dis Child 2018;103:631-636

Methods: UK GIDS clinics review 2009-17

Findings: genetic and extensive investigations not needed

Table 1 Karyotypes performed in young people attending GIDS England and Wales, and from Scotland and Northern Ireland (2009–2015), and frequencies of aneuploidy^{10 11}

46,XX	269		
46,XY	177		
Total	446		
New sex chromosome aneuploidies	47,XXY	GIDS: 1 in 446	Population: 1 in 426–523
New autosomal aneuploidies	46XX, t(7;13) (p21;q31)mos 47,XX,+mar[10]/46,XX[20]	GIDS: 1 in 223	Population: 1 in 138–164

GIDS, Gender Identity Development Service.

Box 4 Useful first-line investigations in a child or adolescent presenting with gender dysphoria

- ▶ Full blood count.
- ▶ Iron/ferritin.
- ▶ U&E, LFT. Renal and liver function tests
- ▶ Bone profile.
- ▶ Vitamin D.
- ▶ Testosterone.
- ▶ Oestradiol.
- ▶ Follicle stimulating hormone FSH and luteinising hormone LH.
- ▶ Prolactin.
- ▶ Bone age in premenarchal female to male or prepuberty/inpuberty male to female.
- ▶ Bone density scan.

Monitoring



JOURNAL OF
ADOLESCENT
HEALTH

www.jahonline.org

Original article

Physiologic Response to Gender-Affirming Hormones Among Transgender Youth



Johanna Olson-Kennedy, M.D. ^{a,b,*}, Vivian Okonta, M.P.H. ^a, Leslie F. Clark, Ph.D., M.P.H. ^{a,b}, and Marvin Belzer, M.D. ^{a,b}

Aim: follow-up data in trans young people aged 12-23 yr over 2 yr GAH

Methods: 59 (25 transgirls, 34 transboys) had follow-up physiologic data collected between 21 and 31 months after initiation GAH

Findings: Metabolic parameter changes were not clinically significant, lipids, potassium, haemoglobin, and prolactin

Exception - sex steroid levels (target of intervention)

Conclusion: Extensive and frequent laboratory examination may be unnecessary. GAH appears to be safe over 2yr



Body composition

THE JOURNAL OF
SEXUAL MEDICINE

TRANSGENDER HEALTH

Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents

Maartje Klaver, MD,¹ Renée de Mutsert, PhD,² Chantal M. Wiepjes, MD,¹ Jos W. R. Twisk, PhD,³ Martin den Heijer, MD, PhD,¹ Joost Rotteveel, MD, PhD,⁴ and Daniël T. Klink, MD, PhD^{4,5}

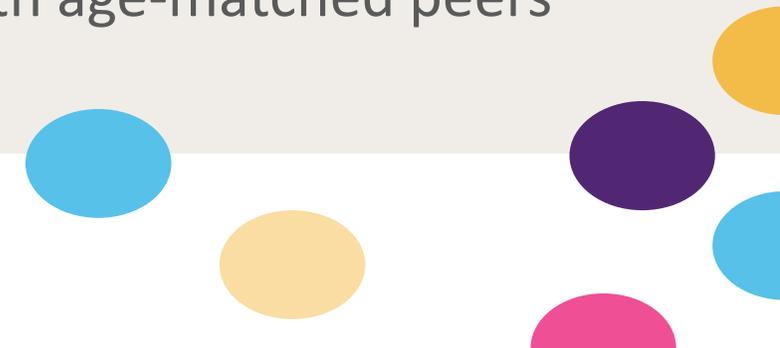
J Sex Med. 2018 Feb;15(2):251-260

Aim: Unknown how body shape and composition develop during treatment and whether transgender persons obtain the desired body phenotype

Methods: To examine the change in body shape and composition from the start of GnRHa until 22 years: **71** transwomen and **121** transmen from **1998 - 2014**

Change in waist-hip ratio (WHR), total body fat (TBF), and total lean body mass (LBM) during hormonal treatment

SDS of measures of body shape and composition compared with age-matched peers at 22 years of age



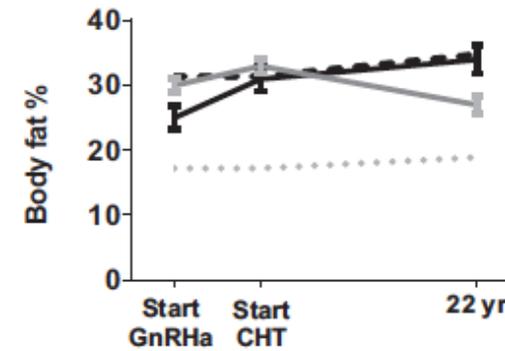
Body composition 2

Findings:

WHR and body composition changed towards the affirmed sex

Conclusion: At 22 years of age, transwomen compared better to age-matched ciswomen than to cismen

Transmen were *between* reference values for ciswomen and cismen



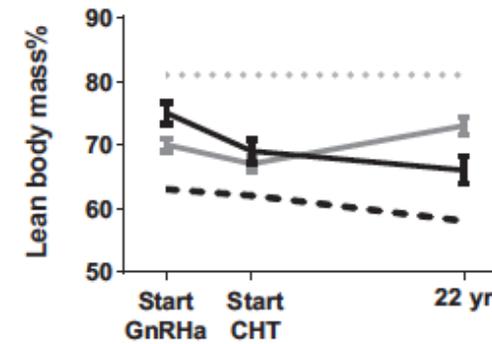
Mean changes (95% confidence interval):

Transwomen

Δ during GnRHa alone: +6% (4;7)
 Δ after addition of CHT: +3% (1;5)

Transmen

Δ during GnRHa alone: +3% (2;4)
 Δ after addition of CHT: -6% (-8;-4)

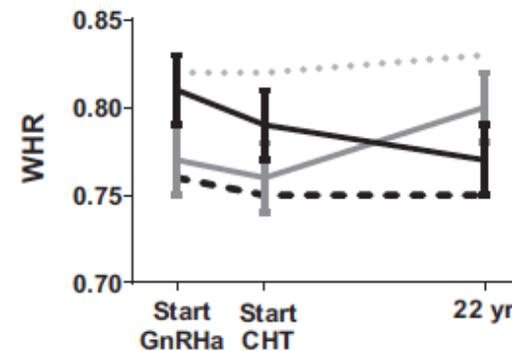


Transwomen

Δ during GnRHa alone: -6% (-7;-4)
 Δ after addition of CHT: -3% (-5;-1)

Transmen

Δ during GnRHa alone: -3% (-4;-2)
 Δ after addition of CHT: +6% (4;8)



Transwomen

Δ during GnRHa alone: -0.02 (-0.03;-0.00)
 Δ after addition of CHT: -0.02 (-0.04;0.01)

Transmen

Δ during GnRHa alone: -0.01 (-0.02;0.00)
 Δ after addition of CHT: +0.04 (0.02;0.05)

Progestins

Proandrogenic and Antiandrogenic Progestins in Transgender Youth: Differential Effects on Body Composition and Bone Metabolism

Lloyd J. W. Tack,¹ Margarita Craen,¹ Bruno Lapauw,^{2,3} Stefan Goemaere,^{2,3} Kaatje Toye,^{2,3} Jean-Marc Kaufman,² Sara Vandewalle,² Guy T'Sjoen,² Hans-Georg Zmierzczak,^{2,3} and Martine Cools¹

J Clin Endocrinol Metab. 2018;103(6):2147-2156

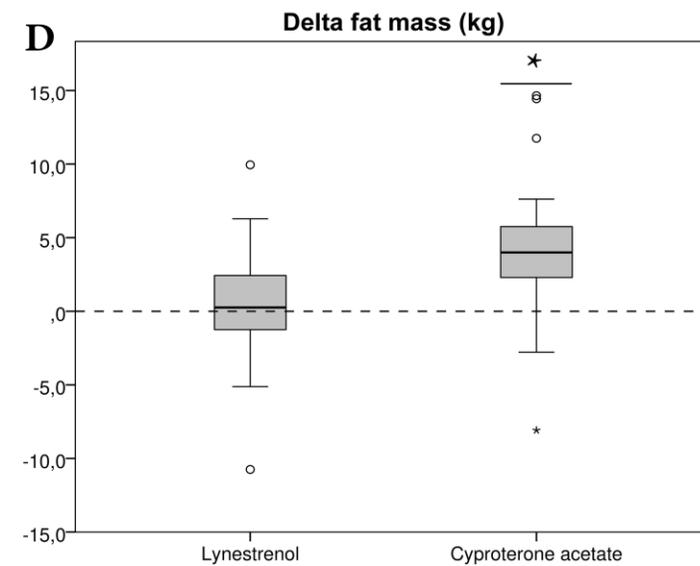
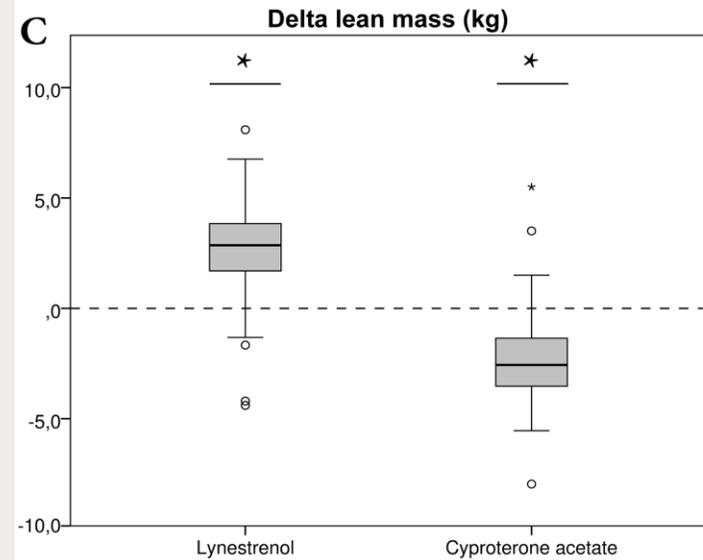
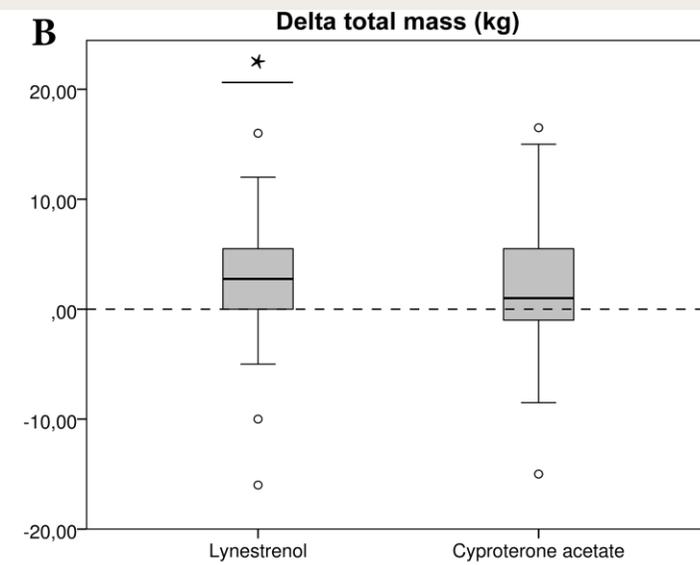
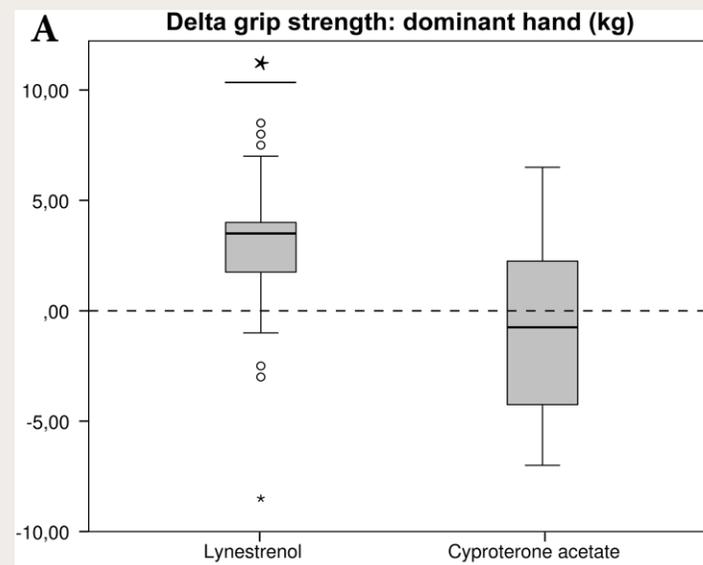
Aims: no data are available on the effects of progestins on the development of bone mass or body composition in late-pubertal transgender adolescents

Methods: 44 transboys, 21 transgirls were treated with *lynestrenol* or *cyproterone acetate* for 11.6 (4 to 40) and 10.6 (5 to 31) months, respectively. Anthropometry, grip strength, body composition, and bone mass, size, and density were determined by DEXA and qCT



Progestins 2

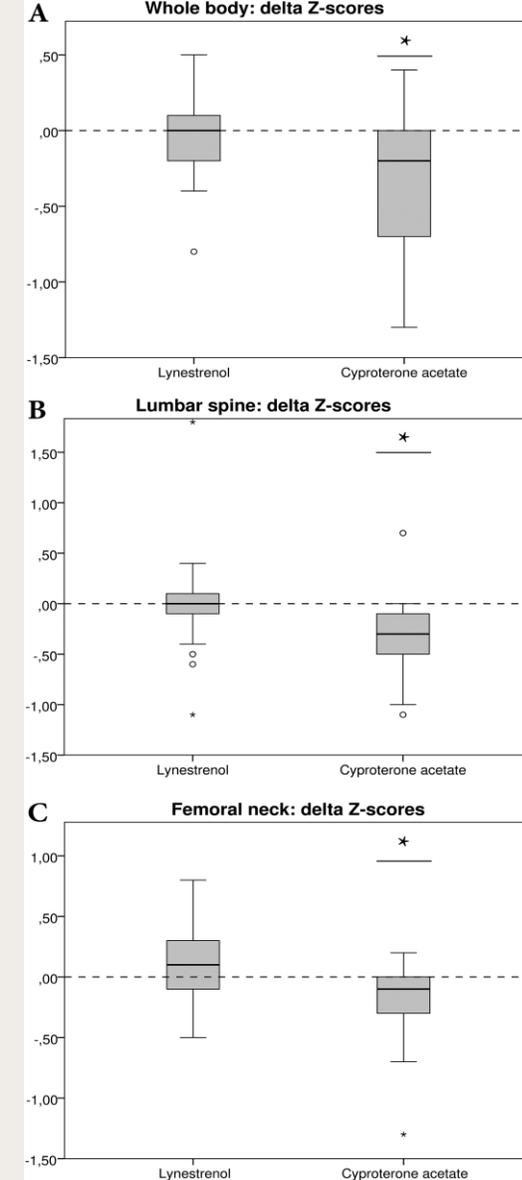
Findings:



Progestins 3

Conclusions: Pro-androgenic and anti-androgenic progestins induce body composition changes in line with the desired appearance within 1 year of treatment

Bone density (lumbar spine) in transgirls is severely affected by androgen suppressive therapy



Bone health



Adult bones

Eighteen-Year Effect of Androgen Therapy on Bone Mineral Density in Trans(gender) Men

Authors

Petr Dan Broulik¹, Václav Urbánek², Petr Libanský³

Horm Metab Res. 2018 Feb;50(2):133-137

Aim: to examine effect of long-term androgen supplementation on bone metabolism in transmen

Methods: 35 transmen aged 47 ± 4 yr were treated with T for 18 years
BMD was measured by DEXA at lumbar spine and neck and *T-score* was determined (cismale + cisfemale references)

Biochemical parameters of bone turnover were measured



Adult bones 2

Findings:

No significantly different T-score at spine, **1.2** in transmen vs **1.2** in ciswomen

BMD in the hip skeleton in transmen (**0.95 g/cm²**) was statistically higher than ciswomen (**0.82**) but not statistically different from cismen (**0.98**)

Circulating biochemical markers of bone formation, and resorption were not different between the transmen, and matched controls

Conclusion:

In transmen after 18 years of T, BMD in the hip is higher than ciswomen, but not different in the spine



Young bones

The effect of GnRH analogue treatment on Bone Mineral Density in young adolescents with gender dysphoria: findings from a large national cohort

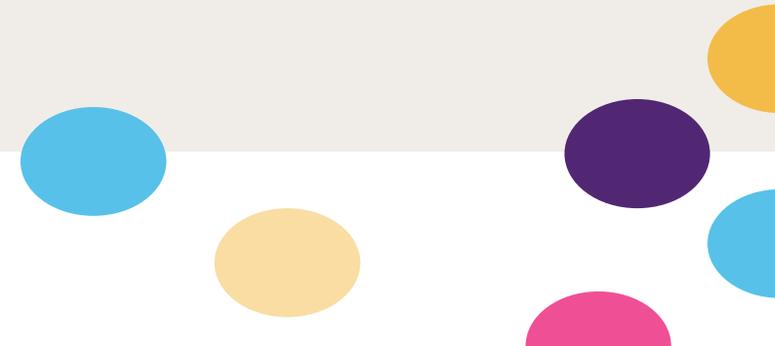
Tobin Joseph, Joanna Ting, Gary Butler

J Ped Endocrinology Metabolism 2019

Aim: to investigate whether there were any clinically significant changes in BMD and BMAD in young adolescents on GnRHa

Methods: 70 subjects yearly DXA scans (31 with 3 yr data) aged 12-14 years, referred to UK GIDS endocrine clinic (2011-16)

BMAD scores were calculated from available data



Young bones 2

Findings:

There was a significant fall in lumbar spine BMD and lumbar spine BMAD Z-scores and a lower fall in BMD/BMAD Z-scores in the second year

There was no significant change in the **absolute** values of hip or spine BMD or lumbar spine BMAD after 2 years on GnRHa

Conclusion:

We suggest that reference ranges may need to be re-defined for this patient cohort

Characteristic Mean (SD)	Scan 1	Scan 2	Scan 3
Transgirls (n)	10	10	10
Age (y)	13.0	14.5	15.8
Spine BMAD [g/cm³]	0.24	0.24	0.24
Spine BMAD Z- Score	0.48	-0.09	-0.27
Transboys (n)	21	21	21
Age (y)	12.9	14.3	15.6
Spine BMAD [g/cm³]	0.19	0.19	0.19
Spine BMAD Z- Score	-0.36	-1.00	-0.91

Hormones and behaviour



Anger

Hormones and Behavior 110 (2019) 29–39

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

No correlation between serum testosterone levels and state-level anger intensity in transgender people: Results from the European Network for the Investigation of Gender Incongruence 

Defreyne Justine^{a,*}, Kreukels Baudewijntje^b, TSjoen Guy^c, Staphorsius Annemieke^d, Den Heijer Martin^e, Heylens Gunter^f, Elaut Els^g

Aim: To assess whether anger intensity increases in transmen and decreases in transwomen with GAH therapy

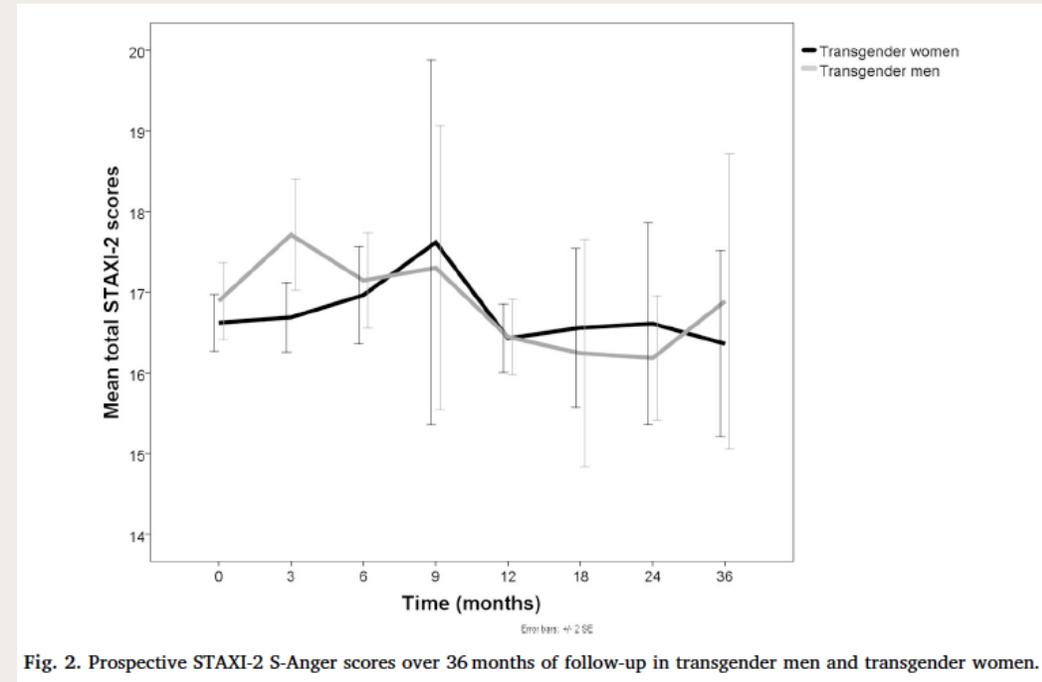
To identify predictors for anger intensity in transgender people

Methods: Part of the European Network for the Investigation of Gender Incongruence (ENIGI). Anger intensity was assessed in 898 (440 transmen, 468 transwomen) by STAXI-2 (State-Trait Anger Expression Inventory-2)

3yr follow-up

Anger 2

Findings: No overall change in STAXI-2 S-Anger Score at 3, 12, 36 months of GAH
STAXI-2 S-Anger scores did not correlate with serum T levels in transmen or transwomen



Transmen experiencing menstrual spotting after three months had higher STAXI-2 S-Anger scores compared to those without

Conclusion: State-level anger intensity is associated with psychological and/or psychiatric vulnerability, but not exogenous T therapy or T levels in transpeople

Comings and goings



ESPE and PES International Survey of Centers and Clinicians Delivering Specialist Care for Children and Adolescents with Gender Dysphoria

Nicos Skordis^{a,b} Gary Butler^{c-e} Martine C. de Vries^{f,g} Katharina Main^h
Sabine E. Hannema^g

Table 2. Number of children and adolescents treated in the participating centers

Centers	Total	MtF	FtM
Europe	834	293	541
Santiago	8	6	2
USA	1,282	492	790
Total	2,124	791	1,333
USA	685		
Total	2,809		

The majority of young people (63%) were transitioning from female to male (FtM). Some centers in the USA reported only the total number of individuals. MtF, male to female transitioning.

Table 4. Age from which adolescents are treated with gender-affirming hormones varied between centers

Centers	Age, years
Europe	
6	16
2	15–16
2	15
1	17
USA/Chile	
7	>14
4	>15
3	16

None of the European centers started this treatment before age 15 years whereas half of the centers from the USA/Chile started from age 14 years.

Comings

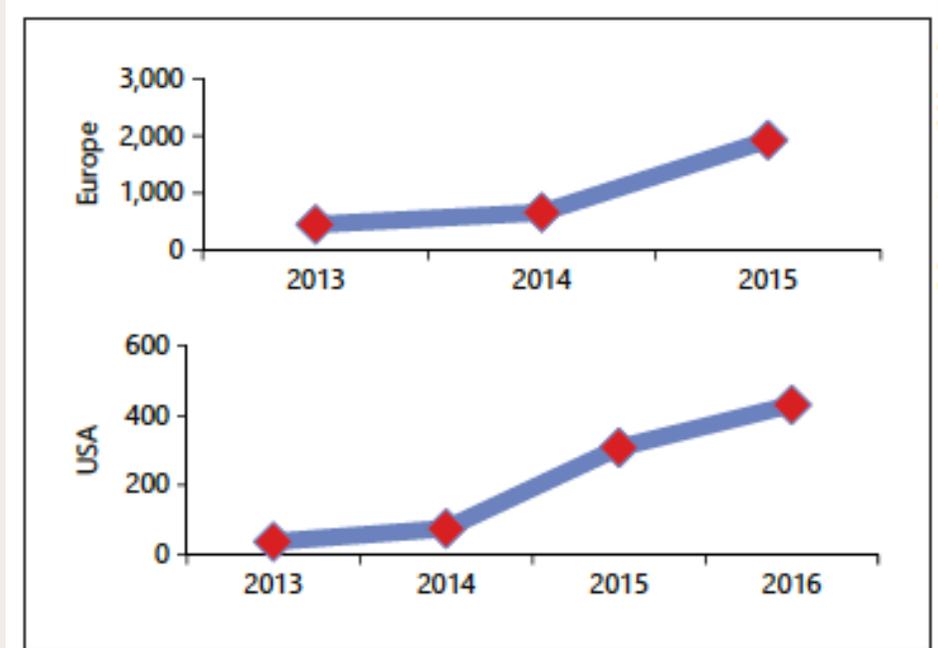


Fig. 1. The increasing number of new referrals to the participating endocrine European and US centers in the past 3 years is shown.

Comings and goings

TRANSGENDER HEALTH

The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets



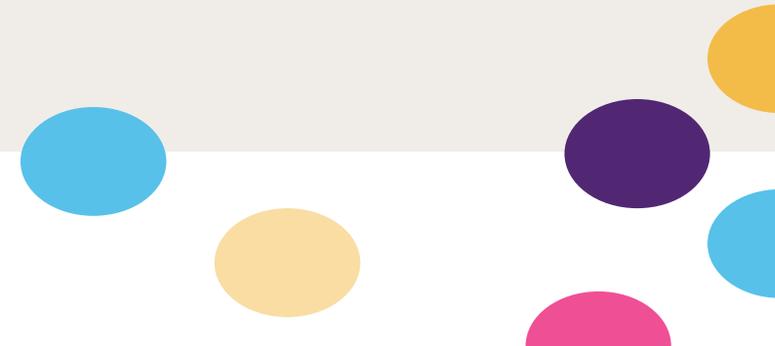
Chantal M. Wiepjes,^{1,2} Nienke M. Nota,^{1,2} Christel J. M. de Blok,^{1,2} Maartje Klaver,^{1,2} Annelou L. C. de Vries,^{2,3} S. Annelijn Wensing-Kruger,^{2,4} Renate T. de Jongh,¹ Mark-Bram Bouman,^{2,5} Thomas D. Steensma,^{2,4} Peggy Cohen-Kettenis,^{2,4} Louis J. G. Gooren,^{1,2} Baudewijntje P. C. Kreukels,^{2,4} and Martin den Heijer, MD, PhD^{1,2}

J Sex Med. 2018 Apr;15(4):582-590

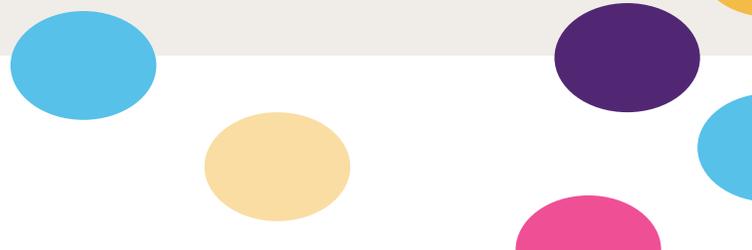
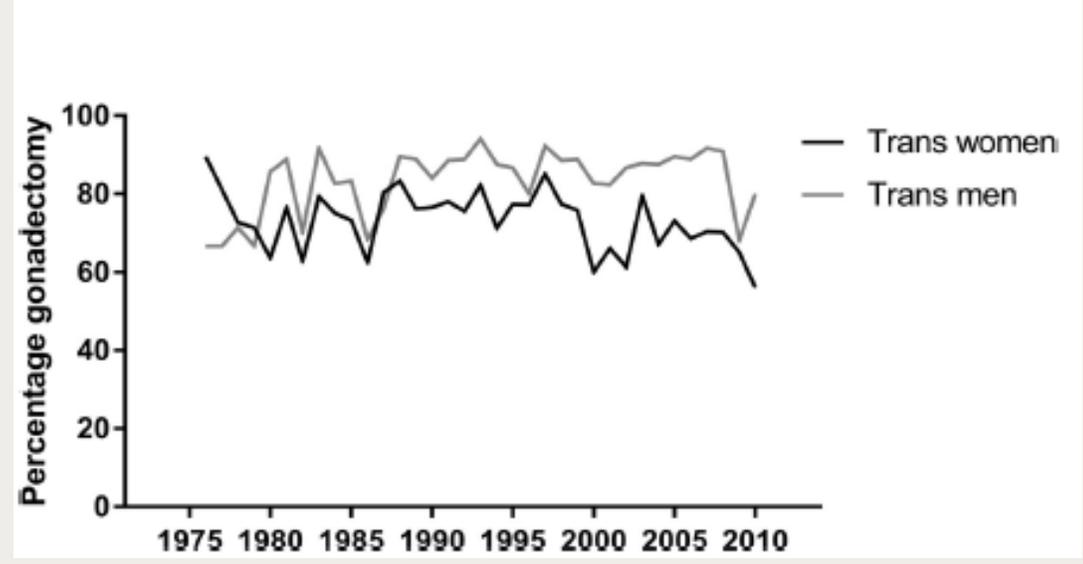
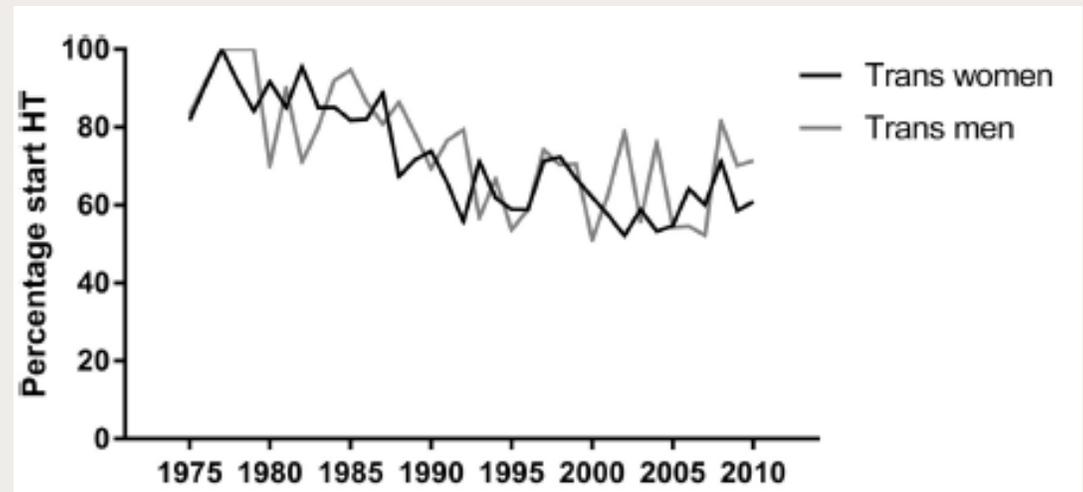
Aim: To study the current prevalence of GD, how frequently gender-affirming treatments are performed, and the number experiencing regret

Methods: Medical files of all attending from 1972 to 2015 were reviewed retrospectively 6,793 people (4,432 transwomen, 2,361 transmen)

The number/year increased 20-fold from 34 in 1980 to 686 in 2015



Comings and goings 2



Comings and goings 3

Findings: % who started GAH within 5 years after the 1st visit decreased over time, with almost **90%** in 1980 to **65%** in 2010

% who underwent gonadectomy within 5 years of GAH remained stable over time (**75%** of transwomen and **84%** of transmen)

Only **0.6%** of transwomen and **0.3%** of transmen after gonadectomy experienced regret

Conclusion: The percentage of people who regret gonadectomy remained small and did not show a tendency to increase



Thank you

UK GIDS: www.gids.nhs.uk

