The year in Endocrinology

Dorte Glintborg
Department of Endocrinology
Center of Gender Identity
Odense University Hospital, Denmark

EPATH 26-28 APRIL 2023
KILLARNEY, IRELAND

Aim of presentation

- Publications 2021-2023 within the area of endocrinology
- Relevant for health care decision making

Clinical papers

Methods

Pub med search for articles published between summer 2021-2023

Key words

- Transgender +
  - ❖ hormone treatment (636 results)
  - ❖ testosterone (291 results)
  - ❖ estrogen (147 results)
  - ❖ cardiovascular (115 results)

- Gender affirming hormone (576 results)

Gender affirming hormone treatment (GAHT)

- **Short and long term outcomes of GAHT on**
  - Mental health
  - Safety – risk of adverse effects on different organs

- **Treatment modalities (comparative, dosage, regimens)**
  - Masculinising
  - Feminising

Psychosocial Functioning in Transgender Youth after 2 Years of Hormones

Mental health 2 years after GAHT
Prospective cohort, USA

- Transgender Congruence Scale
- Beck Depression Inventory–II
- Revised Children's Manifest Anxiety Scale
- Positive Affect and Life Satisfaction measures

N=315 , aged 12-20 years
Trans M, N=190
Previous GnRH-a, N=25

CONCLUSIONS

In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.)

Chen NEJM 2022

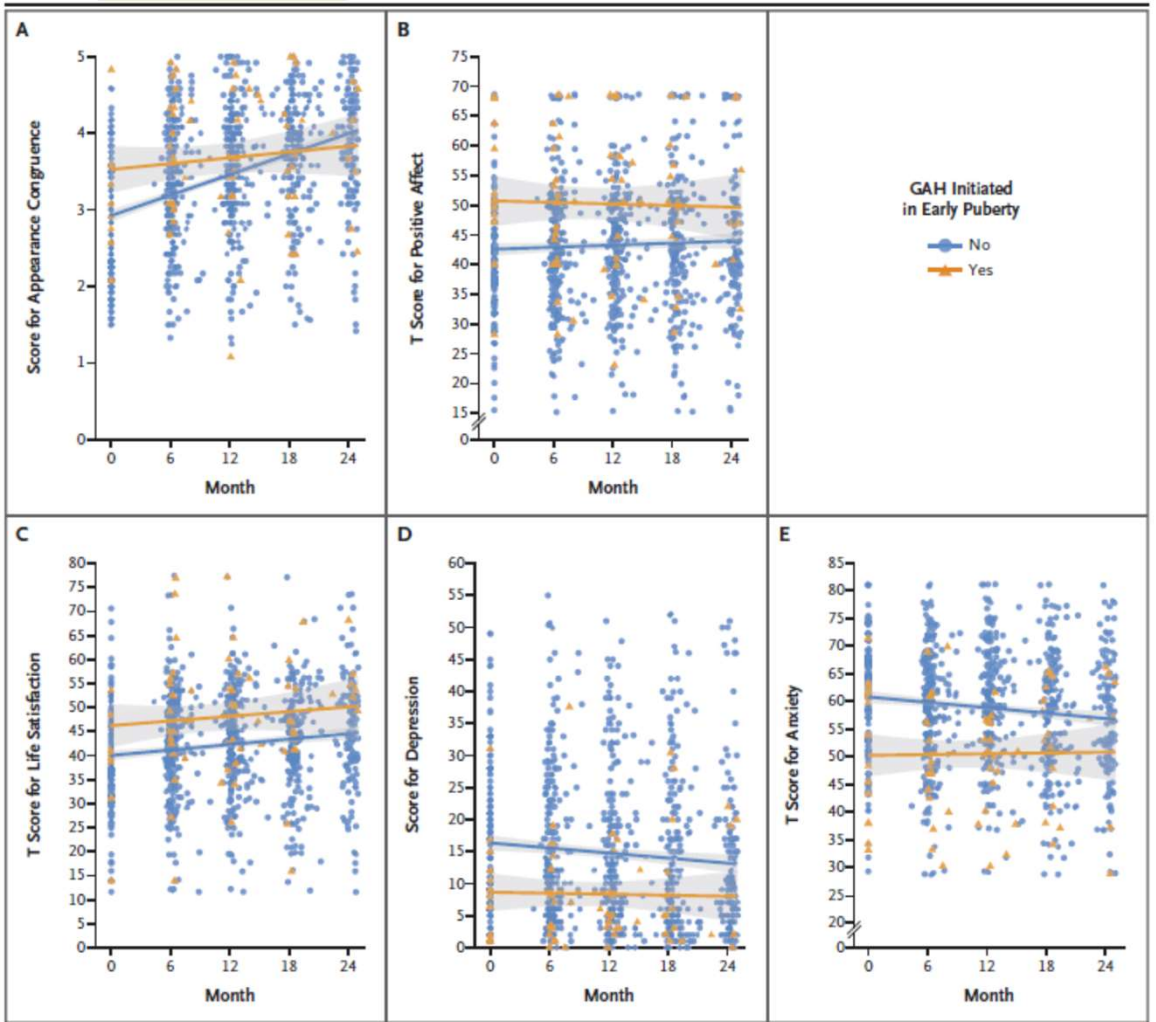


Figure 2. Psychosocial Outcomes during 2 Years of GAH.

JAMA Network | Open

Original Investigation | Pediatrics

Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care

Mental health 1 year after follow up (not all on GAHT)
Prospective cohort

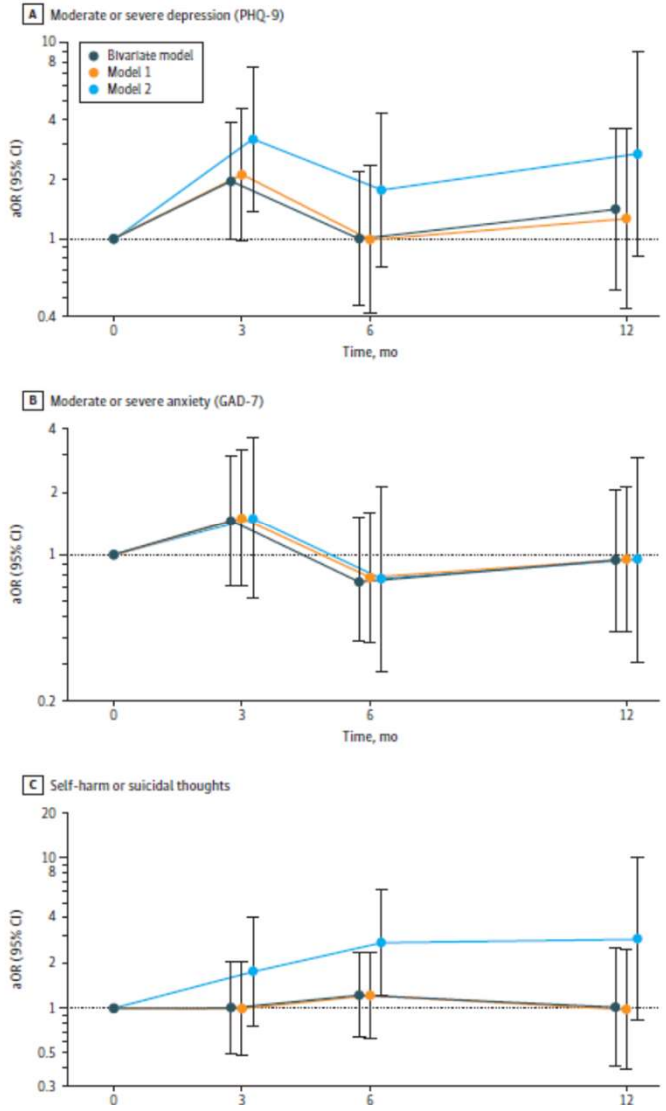
- Patient Health Questionnaire 9-item (PHQ-9)
- Generalized Anxiety Disorder 7-item (GAD-7)
- Self harm

N=104
Trans M, N=63
Previous GnRH-a, N=25
57% severe depression at baseline

CONCLUSIONS AND RELEVANCE This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months. These data add to existing evidence suggesting that gender-affirming care may be associated with improved well-being among TNB youths over a short period, which is important given mental health disparities experienced by this population, particularly the high levels of self-harm and suicide.

Tordorf JAMA 2022

Figure. Temporal Trends in Mental Health Outcomes



Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: A prospective cohort study

Mental health 18 months after GAHT
Prospective cohort, adult population

- Hospital Anxiety and Depression Scale (HADS)
- Multidimensional Scale of Perceived Social Support (MSPSS)
- The Autism Spectrum Quotient—Short Version (AQ-Short)

1271 baseline questionnaires

1 year data:
N=178, AMAB, N=95
Median age 23 years

Baseline depression 51%

GAHT reduces symptoms of depression which are predicted by having
higher levels of social support.

Although anxiety symptoms also reduce, the changes are not significant and high levels of anxiety still remain post-GAHT.

Assigned male at birth			Assigned female at birth		
n	Mean (SD)	Mean change from T0 to T1 (95% CI), *P*-value	n	Mean (SD)	Mean change from T0 to T1 (95% CI), *P*-value
95	7.03 (4.11)	−1.91 (−2.80 to − 1.01) *P* = .00	83	7.48 (3.94)	−2.21 (to 3.23 to − 1.20) *P* = .00
95	5.13 (3.92)		83	5.26 (3.52)	
95	7.54 (4.31)	−1.16 (−1.50 to 0.39) *P* = .25	83	8.69 (4.32)	−0.55 (−0.97 to 0.92) *P* = .97
95	6.98 (3.96)		83	8.66 (3.65)	

Aldridge Andrology 2021

Review

The ENIGI (European Network for the Investigation of Gender Incongruence) Study: Overview of Acquired Endocrine Knowledge and Future Perspectives

	AMAB (N = 1261)	AFAB (N = 1411)	Total (N = 2672)
Study center (%)			
Amsterdam	810 (64.2%)	873 (61.9%)	1683
Ghent	345 (27.4%)	296 (21.0%)	641
Oslo	30 (2.4%)	141 (10%)	171
Florence	67 (5.3%)	90 (6.3%)	157
Tel Aviv	9 (0.7%)	11 (0.8%)	20
Age (years)	26.6 (22.0–38.8)	22.3 (19.9–27.3)	23.9 (20.6–32.4)
Current smokers N (%)	22.5%	28.6%	25.7%
Weight (Kg)	72.0 (63.5–83.5)	67.0 (58.0–80.0)	69.0 (60.1–82.0)
Height (m)	1.78 ± 0.07	1.67 ± 0.07	1.72 ± 0.09
BMI (Kg/m^2)	22.6 (20.1–25.9)	23.7 (21.0–28.6)	23.2 (20.6–27.1)
Systolic blood pressure (mmHg)	127.0 ± 15.0	120.0 ±13.0	123.0 ± 14.0
Diastolic blood pressure (mmHg)	78.0 ± 10.0	75.0 ± 9.0	77.0 ± 10.0

Cocchetti
J Clin Medicine 2022

Long-term safety data on mortality rates, oncological risk, and cardiovascular, cerebrovascular and thromboembolic events are lacking.

Review

The ENIGI (European Network for the Investigation of Gender Incongruence) Study: Overview of Acquired Endocrine Knowledge and Future Perspectives

Cocchetti
J Clin Medicine 2022
J Sex Med 2022

	AMAB	AFAB
Biochemical monitoring	■ Appropriate hepatic and renal safety in the short-mid term ■ Increase of prolactin levels during estrogen plus CPA administration	■ Appropriate hepatic and renal safety in the short-mid term ■ Significant hematocrit increase, especially in the first three months, with serum hematocrit levels usually in the reference male range
Cardiovascular safety	■ Decrease of total cholesterol, LDL-c, HDL-c and triglycerides concentrations ■ Reduction of ATP-binding cassette transporters A1 concentrations which may influence CV risk ■ Metabolic cytokines changes (FGF-21 increase, resistin decrease), which may explain some changes in different components of the metabolic syndrome ■ Procoagulant modifications (increased levels of factor IX, XI and decreased levels of protein C)	■ Unfavorable lipid changes with an increase of total cholesterol, LDL-c and triglycerides levels and decrease of HDL-c levels ■ Metabolic cytokines changes (FGF-21 and adiponectin decrease), which may explain some changes in different components of the metabolic syndrome ■ Increase of 30-years CV risk assessed though the Framingham estimate
Bone safety	■ Increase in lumbar spine and femoral neck BMD in the mid-term ■ Preservation of volumetric bone density and geometry ■ Reduction of bone turnover markers levels	■ Increase in lumbar spine and femoral neck BMD in the mid-term ■ Reduction of bone turnover markers levels only in younger individuals (aged <50 years)
Emotional aspects and sexual health	■ Decrease in sexual desire in the first three months ■ Decrease of perceived sexual distress in the mid-term ■ No changes in sexual orientation	■ No significant changes in anger intensity ■ Increase in sexual desire in the first three months ■ Decrease of perceived sexual distress in the mid-term ■ No changes in sexual orientation

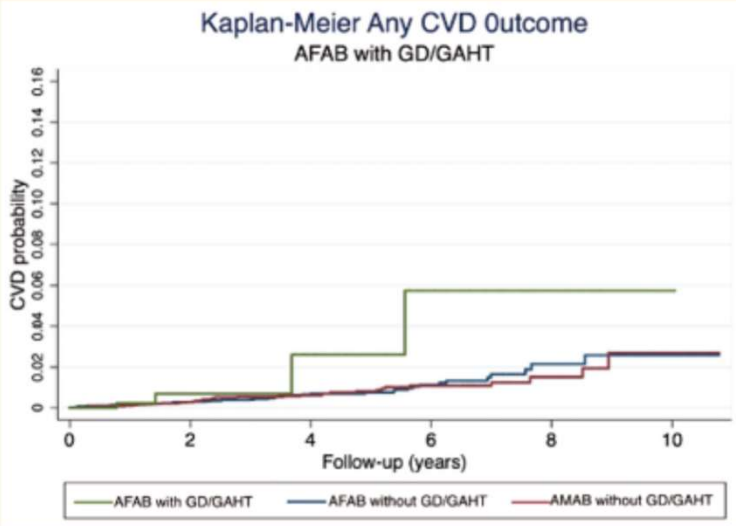
-Do transgender individuals receiving gender-affirming hormone (GAHT) treatment have a higher risk of cardiovascular disease (CVD) compared to cisgender controls?

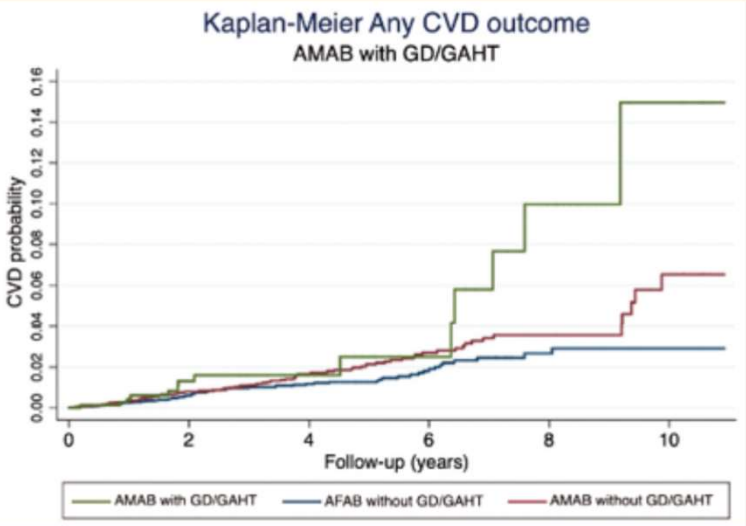
-Is there a causal association between GAHT and risk of cardiovascular disease (CVD) among transgender individuals?

Transgender individuals receiving GAHT, had higher rates of CVD events, particularly conduction disorders, compared to their cisgender counterparts.

Analysis limited to transgender individuals without GAHT yielded similar results to those with GAHT.

The incidence of CVD among transgender individuals with GAHT was low, yet increased compared to matched cisgender individuals and similar to the incidence among transgender individuals without GAHT, thus not lending support for a causal relationship between treatment and CVD outcomes.





Cardiovascular outcomes in transgender individuals in Sweden after initiation of gender-affirming hormone therapy

Swedish register based study

CVD events (ICD-10 codes of MACE)

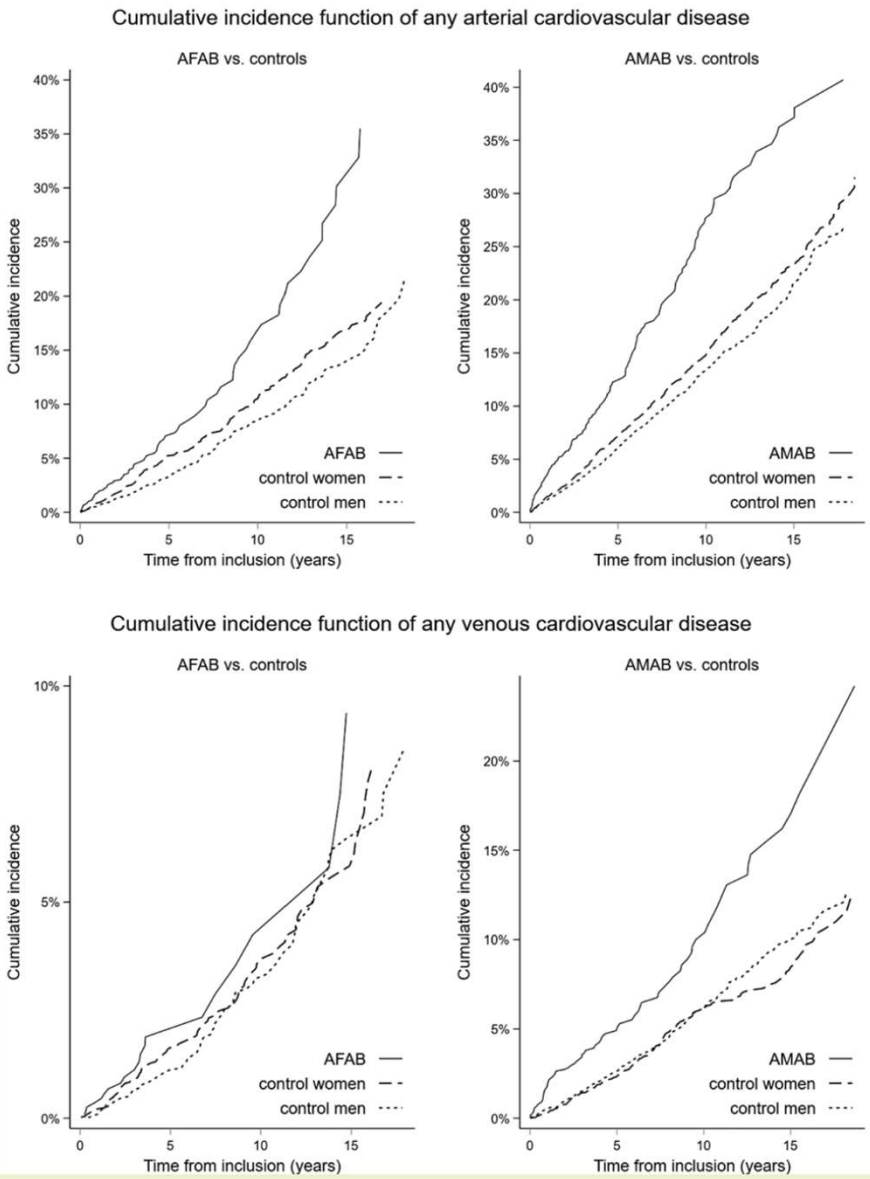
GAHT:
N= 1779 TG
AMAB, N= 847

26 years (AFAB)
31 years (AMAB)

N=17790 controls

Conduction disorders (arrythmia)

Karalexi
European Journal of Preventive Cardiology 2022



Cardiovascular risk in Danish transgender persons: a matched historical cohort study

Danish register based study

Any CVD events (ICD-10 codes of MACE, medicine use), venous disease

N= 2671 TG
AMAB, N= 1407

N=26710 controls

Gender-affirming hormone treatment (GAHT) explained part of elevated risk of CVD in transgenders AFAB, whereas GAHT did not contribute to the elevated risk of CVD in transgenders AMAB.

Glintborg
European Journal of Endocrinology 2022

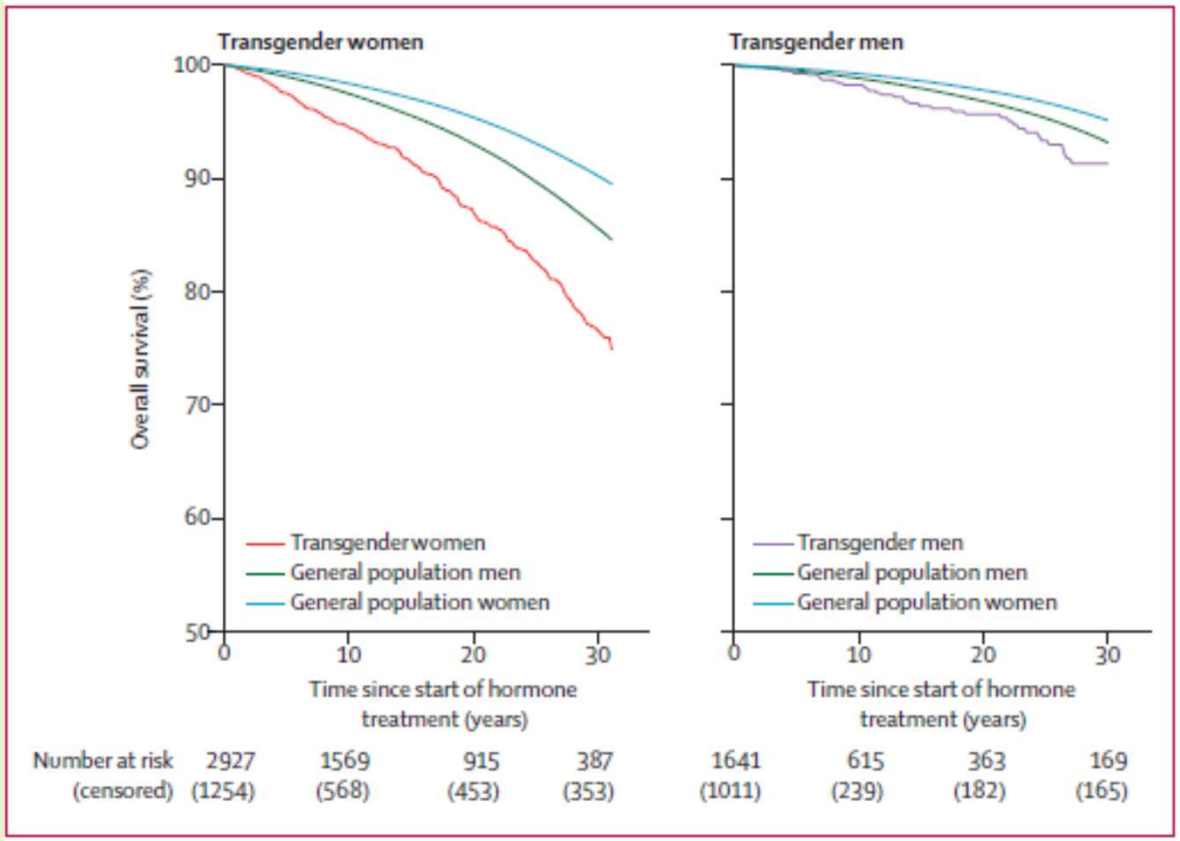
Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria

Cohort:
N= 2927 Trans W
N=1641 Trans M
Amsterdam

Results:
Increased mortality risk during GAHT

Cardiovascular disease, lung cancer, HIV-related disease, and suicide.
Non-natural causes

Conclusion: Increased mortality risk, but not specific effect of GAHT



De Blok
Lancet Diabetes Endocrinol 2021

Analysis of Mortality Among Transgender and Gender Diverse Adults in England

Cohort:
N= 1951 transW (39.9 years)
N= 1364 Trans M (29.2 years)
Dignosis codes, GPs England

Results:
Overall mortality risk:
Trans W: Higher mortality risk compared with cisgender men 1.34 (1.06-1.68) and cisgender women 1.60 (1.27-2.01)
Trans M: Higher mortality risk compared with cisgender men 1.43 (0.87-2.33) and cisgender women 1.75 (1.08-2.83)
Cancer:
Trans W: Lower cancer mortality than cisgender women 0.52 (0.32-0.83)
Trans M: Comparable cancer mortality
External causes of death:
Trans W: Increased risk of external causes of death 1.92 (1.05-3.50)
Trans M: Higher mortality from external causes of death than cisgender women 2.77 (1.15-6.65)

Conclusion: Increased mortality risk in transgender persons. These findings highlight the need to develop interventions to prevent suicide, homicide, and accidental poisonings to reduce mortality for TGD individuals.

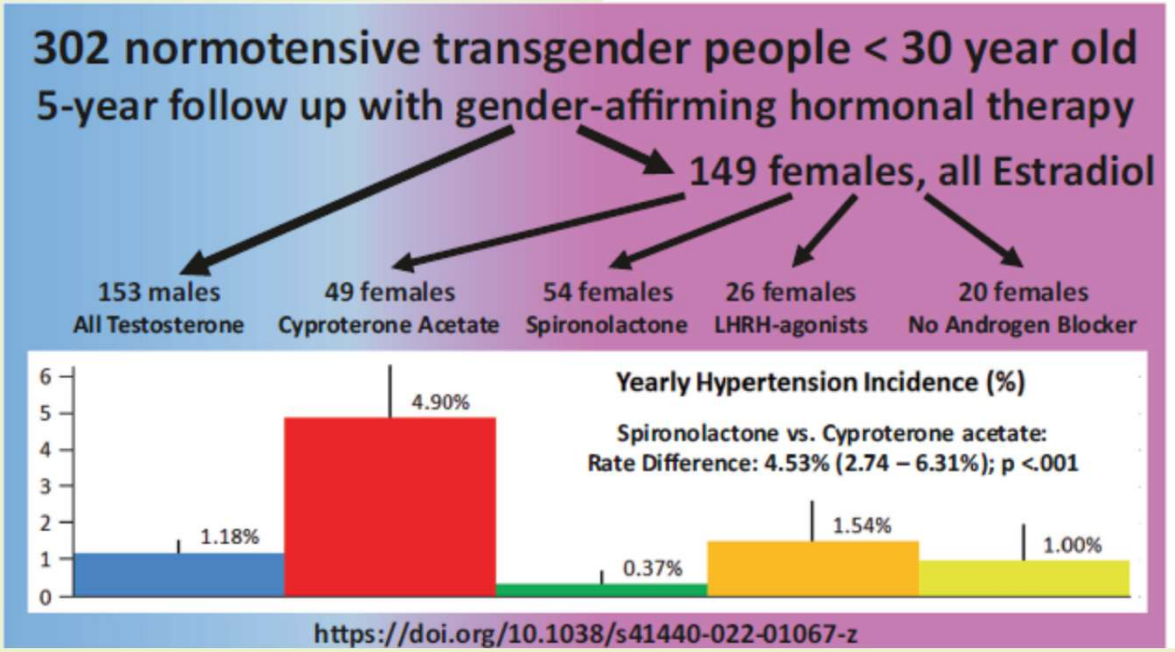
Jackson
JAMA Network 2023

Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy

Cohort:
149 trans W
153 trans M
Age < 30 year at inclusion
GAHT duration > 5 years

Results:
Highly significant increase in hypertension in trans W treated with cyproterone acetate (4.90%) vs. the rest (0.80%); the adjusted hazard-ratio was 0.227 (p=0.001)

Conclusion:
Reconsider use of cyproterone acetate



Martinez-Martin
Hypertension Research 2023

EPATH 26-28 APRIL 2023 KILLARNEY, IRELAND

Longitudinal Changes in Liver Enzyme Levels Among Transgender People Receiving Gender Affirming Hormone Therapy

Cohort:
N= 624 Trans W
N=438 Trans M
GAHT initiation and longer term use
N= 4090 cisgender M
N= 4797 cisgender W
USA

Predictors of higher liver enzymes (ALT):

BMI > 25 kg/m^2

Alcohol

Results:
Trans M: Higher alanine aminotransferase (ALT) and aspartate transaminase after GAHT

Trans W: Unchanged enzymes

Conclusion: Probably no clinical significance

Hashemi
J Sexual Medicine 2021

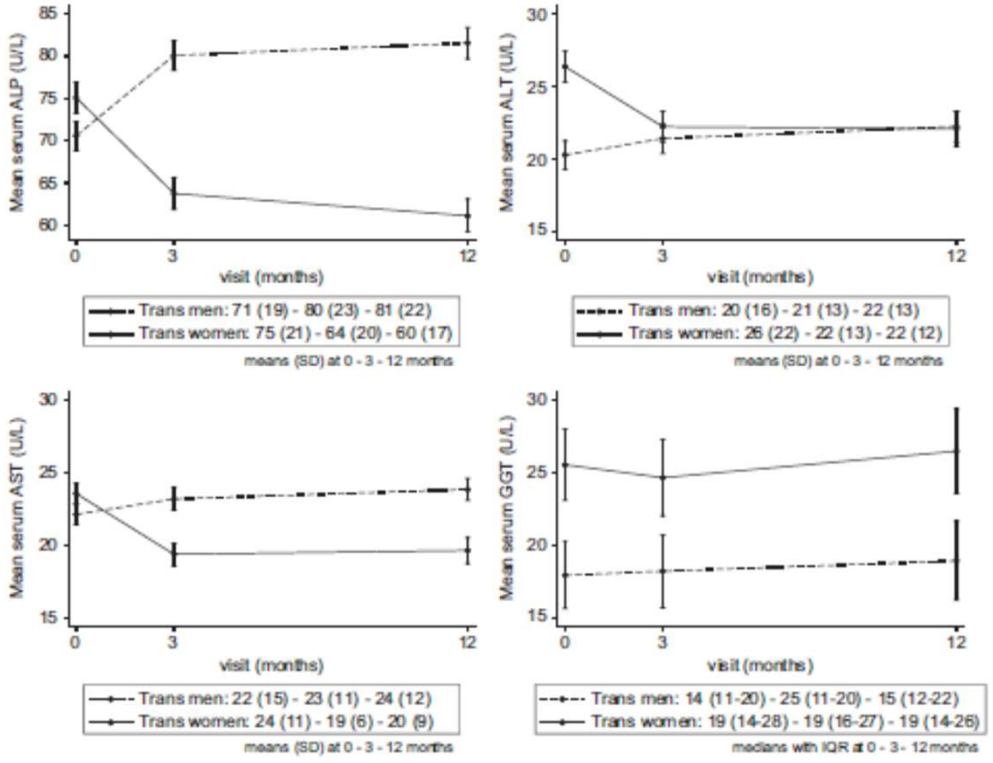
Is there a need for liver enzyme monitoring in people using gender-affirming hormone therapy?

Cohort:
N= 889 Trans W
N= 1044 Trans M
Liver injury was defined as either:
elevation of 2× upper limit of normal (ULN) of ALP, 3× ULN of ALT, or 3× ULN of AST.
ENIGI cohort (4 centers)

Results, 12 month GAHT:
TransW: 0.0%
Trans M: 0.4%

Conclusion: Probably no clinical significance, no need to measure liver enzymes

Stangl
EJE 2021



Incidence, Contributing Factors, and Implications for Clinical Management of Polycythemia in Transmasculine Patients on Testosterone

Retrospective study, USA
>12 months testosterone treatment

Cohort:
N= 511 Trans M
Median age 27 years, BMI 28 kg/m^2

Hct ≥ 50 defined polycythemia

Polycythemia
Yes N= 113
No N= 398

Conclusion: Oophorectomy important risk factor for polycythemia.

Tatarian
LGBT Health 2022

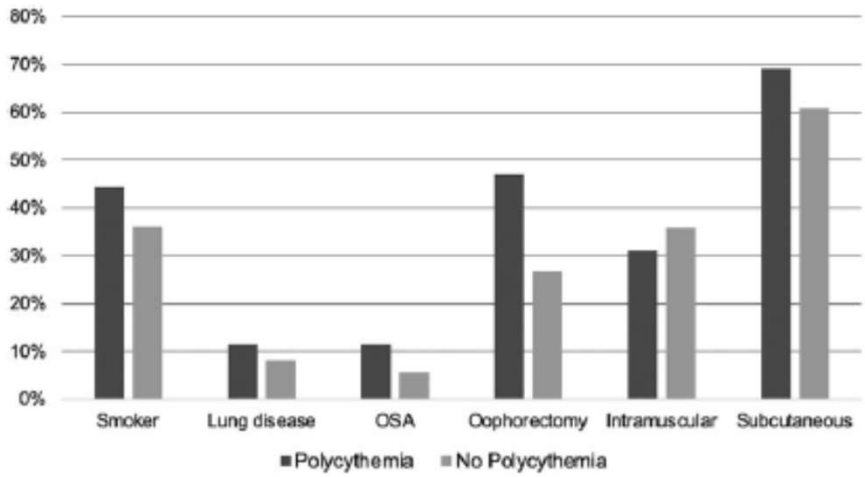


FIG. 2. Comparison of contributing factors and routes of testosterone administration between polycythemia and nonpolycythemia groups. One-hundred-thirteen patients experienced polycythemia and 398 did not. OSA, obstructive sleep apnea.

TABLE 3. ODDS RATIOS AND RELATIVE RISK FOR THE DEVELOPMENT OF POLYCYTHEMIA AMONG EACH CONTRIBUTING FACTOR

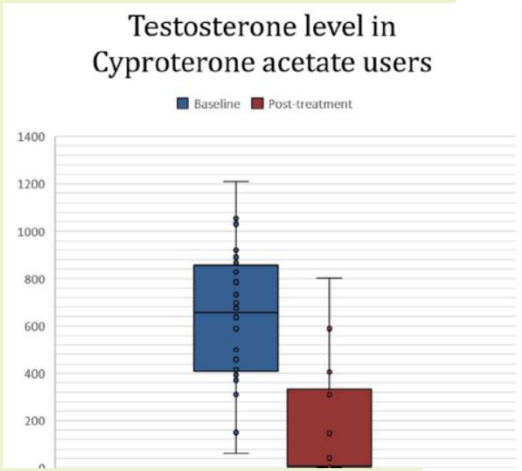
Contributing factor	*Odds ratio*	*95% CI*	*Relative risk*	*95% CI*
Age >30	**2.38**	**1.56–3.64**	**1.95**	**1.41–2.70**
BMI >30	**1.93**	**1.26–2.94**	**1.66**	**1.20–2.31**
Dose (>100 mg/week)	1.27	0.82–1.97	1.21	0.85–1.71
Nicotine dependence	1.39	0.91–2.12	1.29	0.93–1.78
Pulmonary disease	1.45	0.74–2.86	1.32	0.81–2.17
OSA	**2.14**	**1.05–4.38**	**1.73**	**1.08–2.76**
Oophorectomy	**2.39**	**1.56–3.68**	**1.93**	**1.41–2.66**

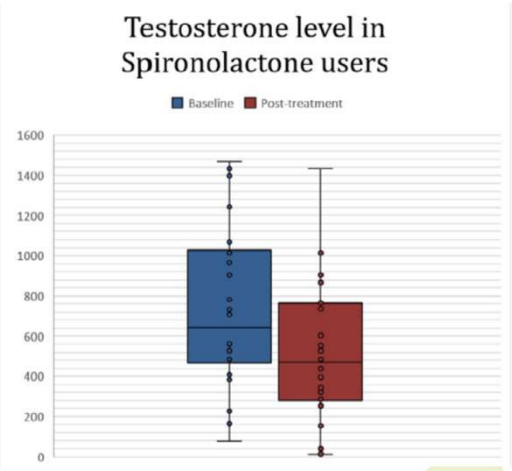
Bold indicates statistically significant values.
CI, confidence interval.

Anti-Androgenic Effects Comparison Between Cyproterone Acetate and Spironolactone in Transgender Women: A Randomized Controlled Trial

Cohort: N= 52 trans W

Design:
Oral estradiol valerate 5 mg/day +
N= 26 CPA 25 mg/day or
N= 26 spironolactone 100 mg/day





Results, 12 weeks

- Blood pressure, erection, estradiol comparable
- HDL higher in spironolactone group
- Prolactin higher in CPA group

CPA – liver injury in one person

Conclusion: CPA more efficient regarding lowering of testosterone

Burinkul
J Sexual Med 2021

EPATH 26-28 APRIL 2023 KILLARNEY, IRELAND

Effects of low-dose oral micronised progesterone on sleep, psychological distress, and breast development in transgender individuals undergoing feminising hormone therapy: a prospective controlled study

Cohort: N= 42
N= 23 micronised progesterone (100 mg oral)
N= 19 standard of care
Antiandrogen treatment: CPA, n=26, spririx n=5, orchiechtomy n=9.

Results, 3 months progesterone:

- Pittsburg sleep quality index unchanged (p=0.4)
- Kesller psychological distress scale unchanged (p=0.6)
- Tanner stage unchanged (p=0.8)

Conclusion: Significant inter-individual variation. Larger studies needed.

Table 2 Within-person 3-month change in those with added low-dose oral micronised progesterone vs controls. Mean (95% CI) are reported. *P*-value from non-parametric ANCOVA adjusted for the corresponding measure at baseline.

Parameter	Progesterone group	Control group	*P*-value
PSQI			
0 months	7.7 (6.3, 9.2)	8.4 (7.1, 9.8)	
3 months	6.9 (5.1, 8.7)	8.0 (6.7, 9.3)	0.35
K10			
0 months	24.4 (21.0, 27.8)	25.2 (22.0, 28.4)	
3 months	22.5 (19.5, 25.5)	23.8 (20.7, 27.0)	0.64
Tanner stage			
0 months	3.3 (3.1, 3.6)	3.3 (3.0, 3.7)	
3 months	3.5 (3.2, 3.7)	3.6 (3.3, 3.9)	0.42

K10, Kessler psychological distress scale; PSQI, Pittsburgh Sleep Quality Index.

Nolan
Endocrine Connection 2022

Hormone Concentrations in Transgender Women Who Self-Prescribe Gender Affirming Hormone Therapy: A Retrospective Study

Cohort: N= 527 trans W
Blood samples regarding testosterone and estrogen levels.

Results:

- Most common GAHT regimen was OCP (EE+ 2 mg CPA)
- 19% used no androgen lowering agent
- Most regimens not sufficient regarding suppression of testosterone levels.

- After gonadectomy, 21.5% used androgen lowering agents.

- 25% used recommended regimens, 5.7% had hormone levels in recommended range.

Conclusion:
Self-prescribed GAHT most often does not reach target levels of sex hormones**.**

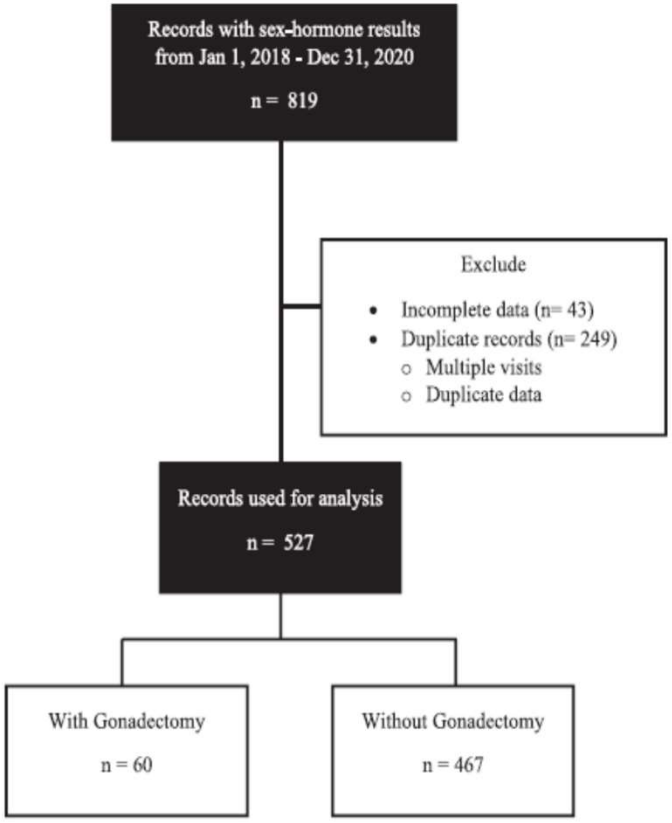


Figure 1. Inclusion flow chart.

Salakphet
Journal of Sexual Medicine 2022

Conclusion

- Evidence is growing
  - More data on larger study cohorts including national dataset
  - More long term data

- GAHT is generally safe – but:

- More studies needed
  - Mental outcomes – treatment failure, regret?
  - CVD
  - Treatment modalities – alternative options to CPA
  - Self prescribed hormones - consequenses