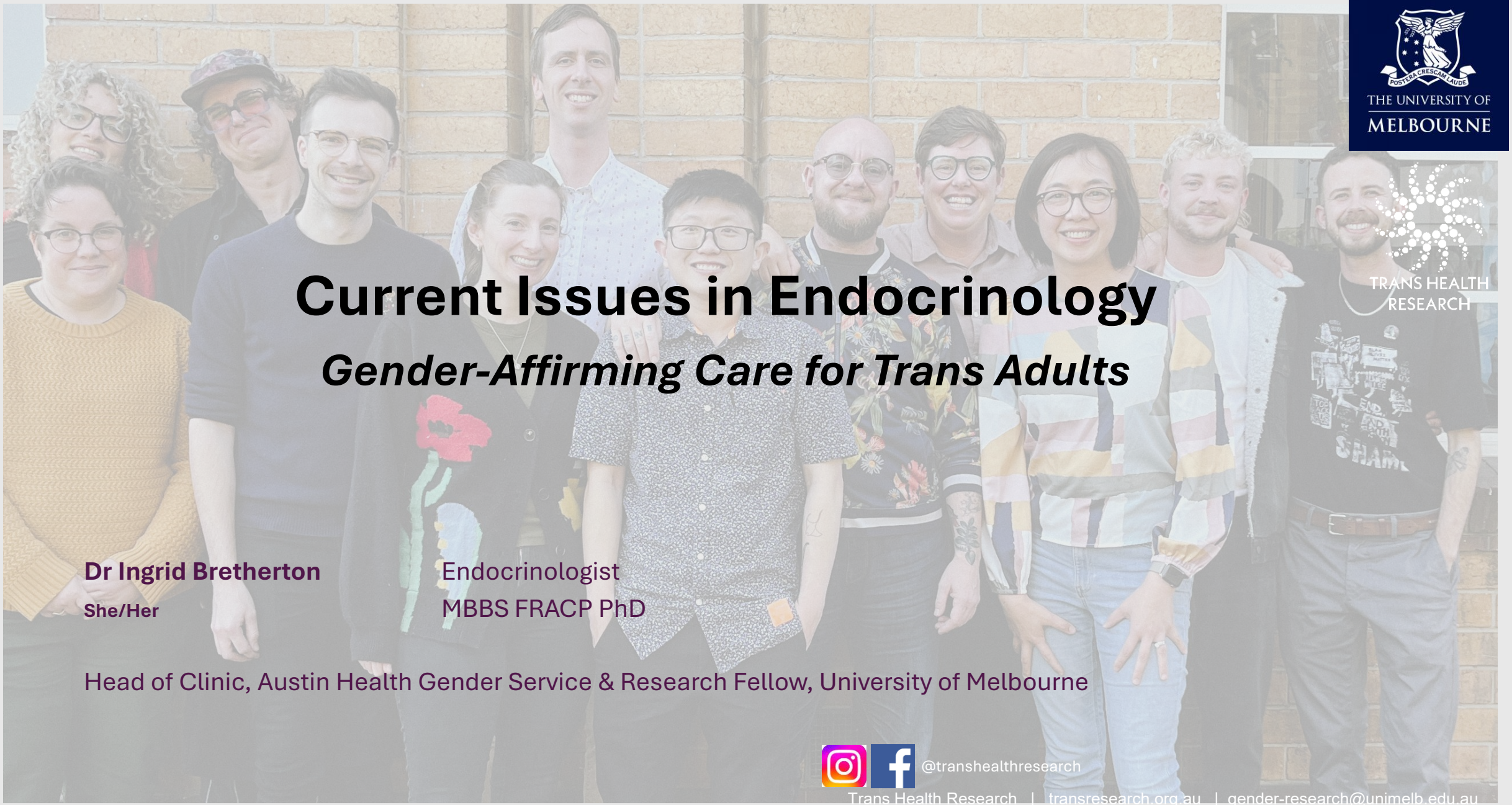


# Current Issues in Endocrinology

## *Gender-Affirming Care for Trans Adults*


**Dr Ingrid Bretherton**
**She/Her**

Endocrinologist
MBBS FRACP PhD

Head of Clinic, Austin Health Gender Service & Research Fellow, University of Melbourne

# Acknowledgment of Country

I acknowledge the **Kaurna people** as the Traditional Custodians of the land on which we meet and the **Wurundjeri people of the Kulin Nation**, on whose lands I live and work.

I pay my respects to their Elders past, present, and emerging.

I also acknowledge the gender diverse Aboriginal people including Sistergirls, Brotherboys and trans mob.

**Disclosure of  interest**: I have no disclosures

# Setting the scene

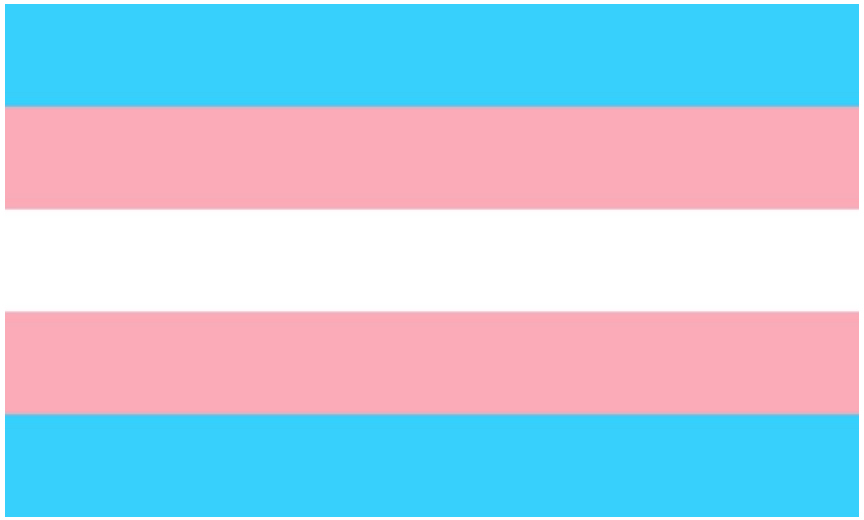
- **GAHT is safe, effective, often life-saving**
  - Reduced gender dysphoria and improved emotional well-being & social functioning[1], Decreased depression and suicidality[2]
- **But not without risk**
  - Sex hormone receptors act across metabolism, bone, cardiovascular system, brain, and reproductive tissues → endocrine monitoring is essential[3,4]
- **Evidence gaps remain**
  - Reliance on low–moderate quality data (small sample size, lack of controls, retrospective cohorts, heterogeneous regimens)


*1. Skewis F, Bretherton I et al Front Endocrinol. 2021*
*2. Nolan BJ et al. JAMA 2023*
*3. Hembree WC, et al.. J Clin Endocrinol Metab. 2017*
*4. Coleman E, et al. WPATH SOC Version 8. Int J Transgend Health. 2022*

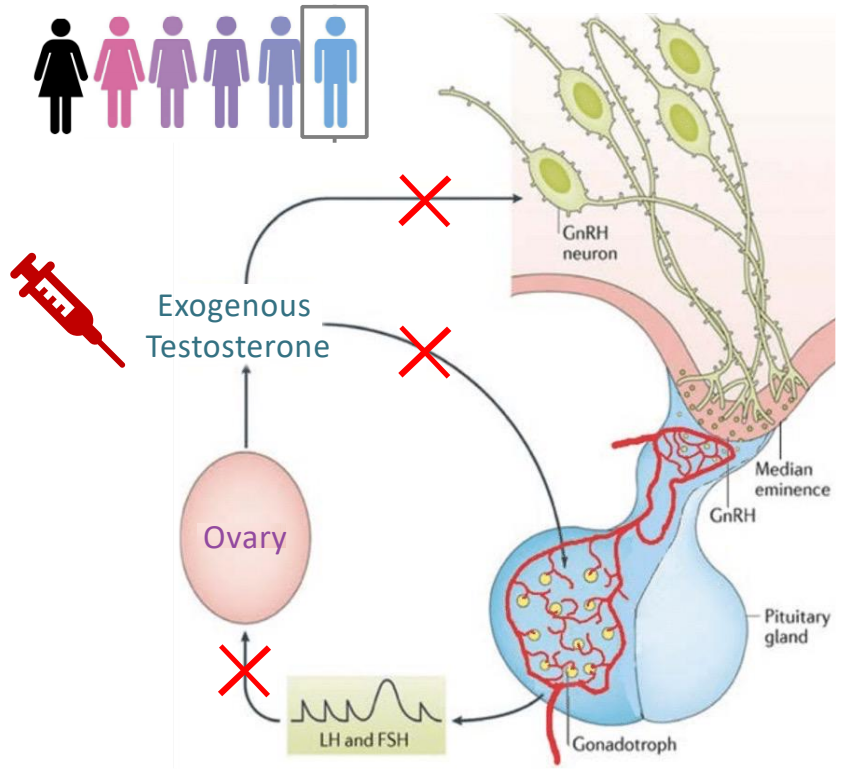
# Presentation overview

GAHT and:

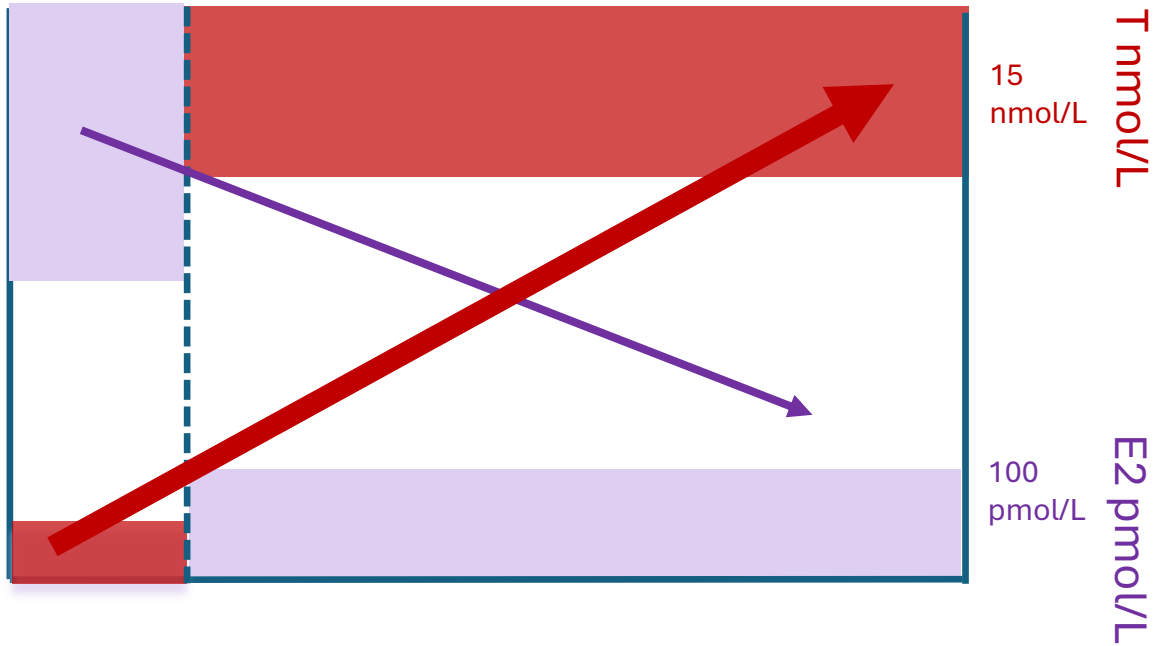
- Bone health
- Metabolic health
- Reproductive health
- Summary
- Conclusions



# Biochemical targets for masculinisation

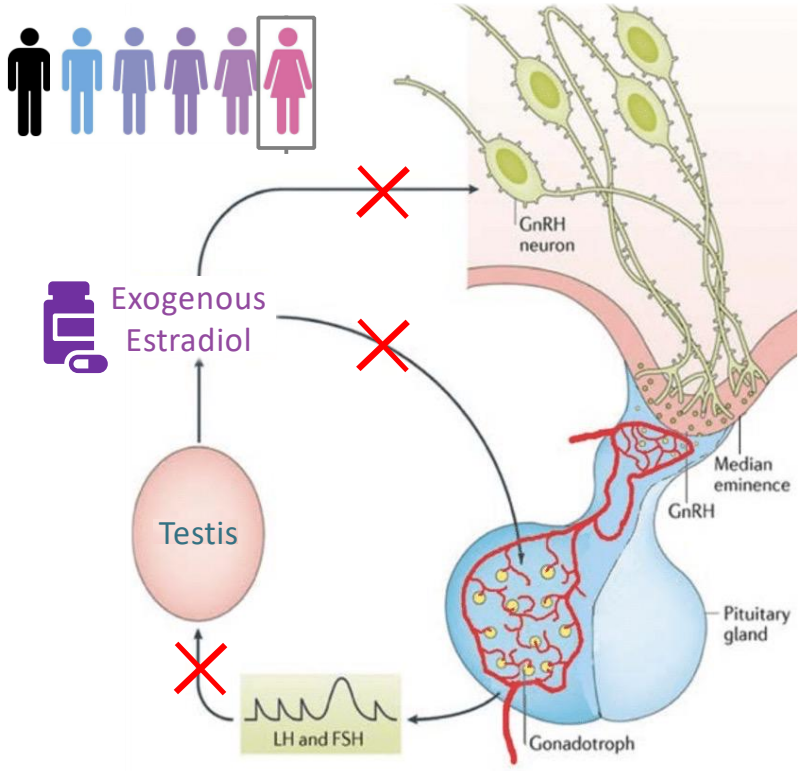


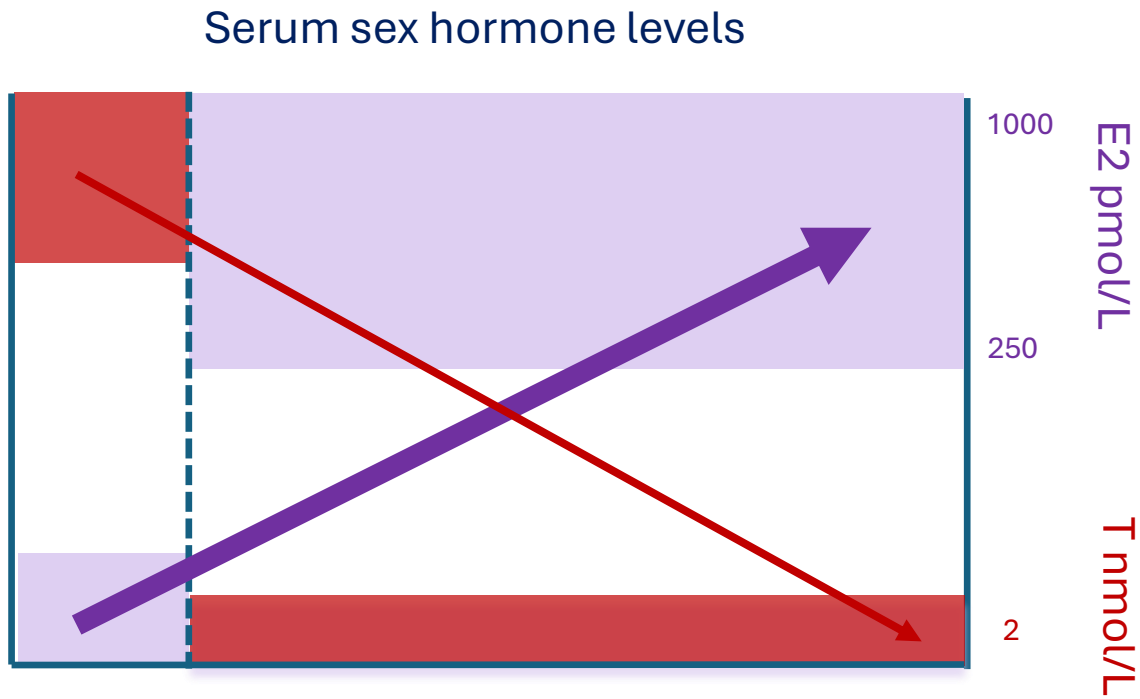

Serum sex hormone levels




- Cis male reference range T
- Reduced E2 synthesis (sits above cis male)

# Biochemical targets for feminisation*




- Cis female T (add AA if testes are intact)
- Cis female reference range E2

***Not all about numbers:** Bloods to support safety, but clinical outcomes as primary measures of efficacy

# Biochemical targets- gender non-binary

- **May not fit conventional ‘targets’**
  - Highly individualized
  - May desire full, partial, subtle or selective* changes
- **Avoid hormone blockade alone**
  - ↓ BMD, ↓ Lean mass, ↑ Fat mass, Metab dysfunc
- **Monitoring & Safety**
  - Similar principles as binary trans adults

*UCSF Gender Affirming Health Program. (n.d.). Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. Retrieved from https://transcare.ucsf.edu/guidelines*

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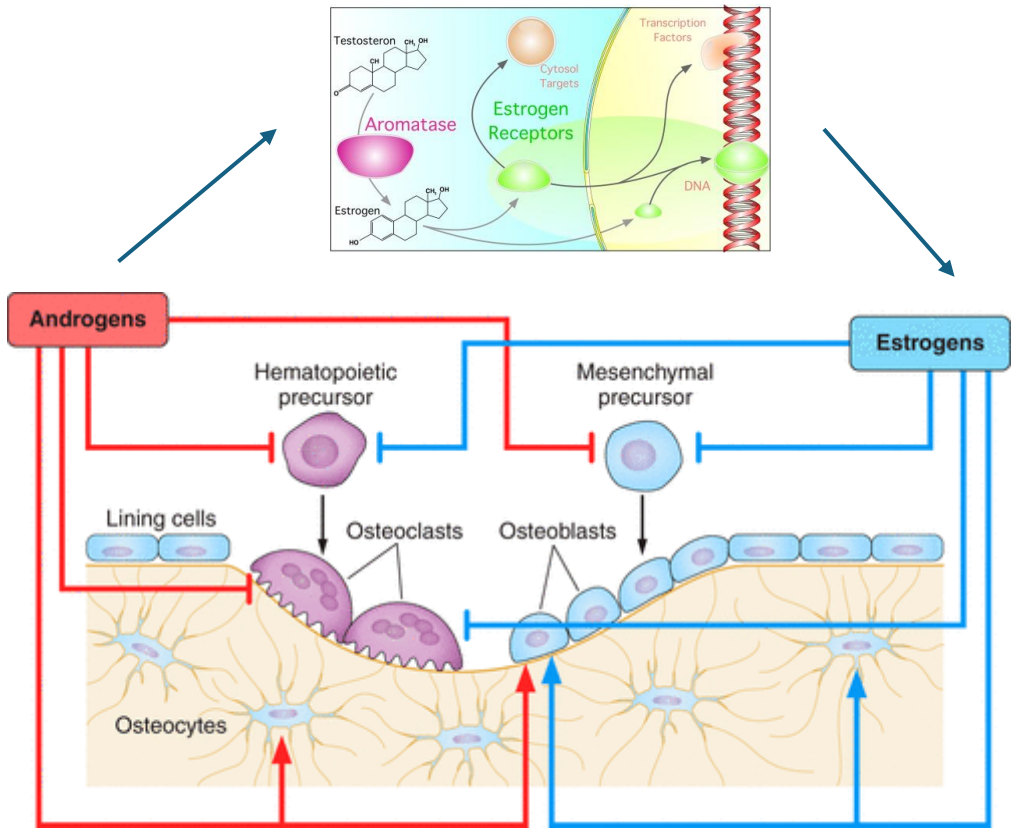
# *Bone Health*

# Sex hormone regulation of bone

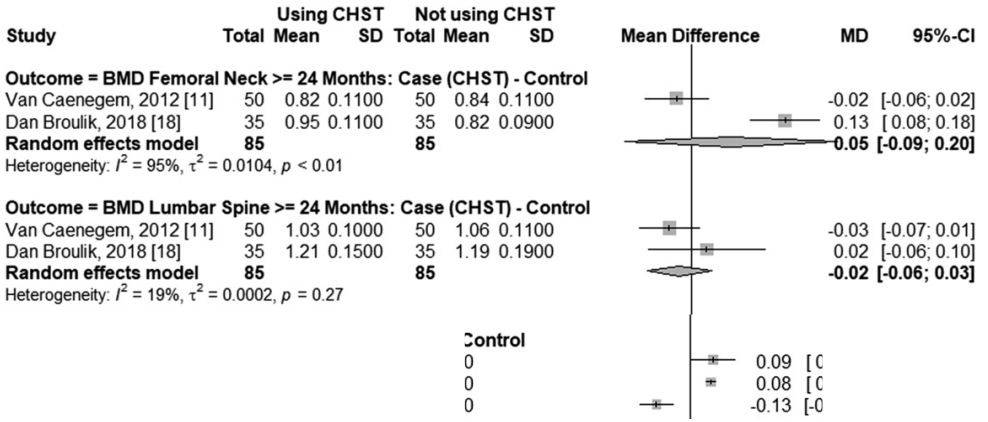
- **Testosterone (T)**
  - Promotes **periosteal apposition** → increases bone size and strength.
  - Slightly inhibits bone remodeling, mostly indirectly.
- **Estradiol (E2)**
  - Controls the birth rate of remodeling units.
  - Modulates volume of bone resorbed and formed.
  - **Key regulator of bone remodeling**
- **Aromatization T -> E2**
  - In cis men, **T is partially converted to E2** via aromatase.



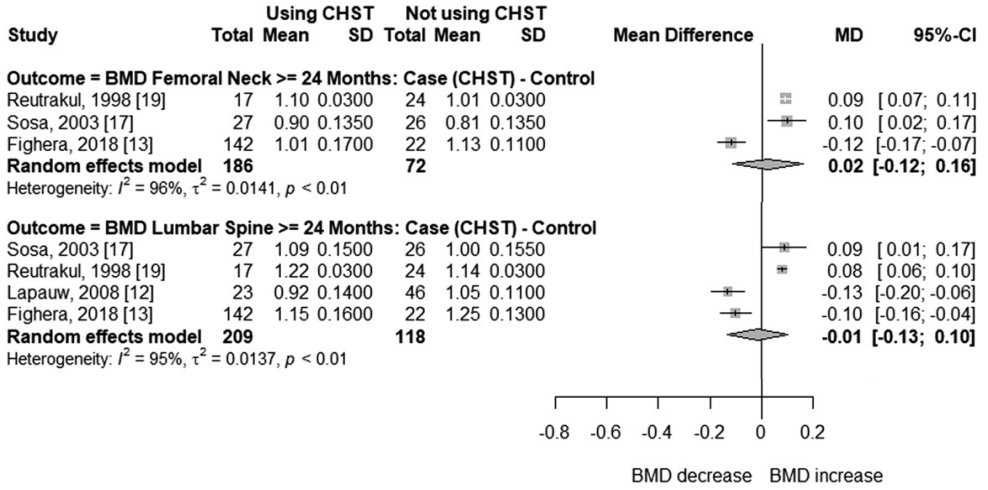

*Falahati-Nini A, et al. Relative contributions of testosterone and estrogen in regulating bone resorption.... J Clin Invest. 2000;106(12):1553–1560.*
*Leblanc ES, et al. J Steroid Biochem Mol Biol. 2017;171:205–213.*
*Image: Almeida M et al. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. Physiological Reviews. 2016*

# Areal BMD (DXA) Data is Inconsistent

## Masculinising Hormones




## Feminising Hormones



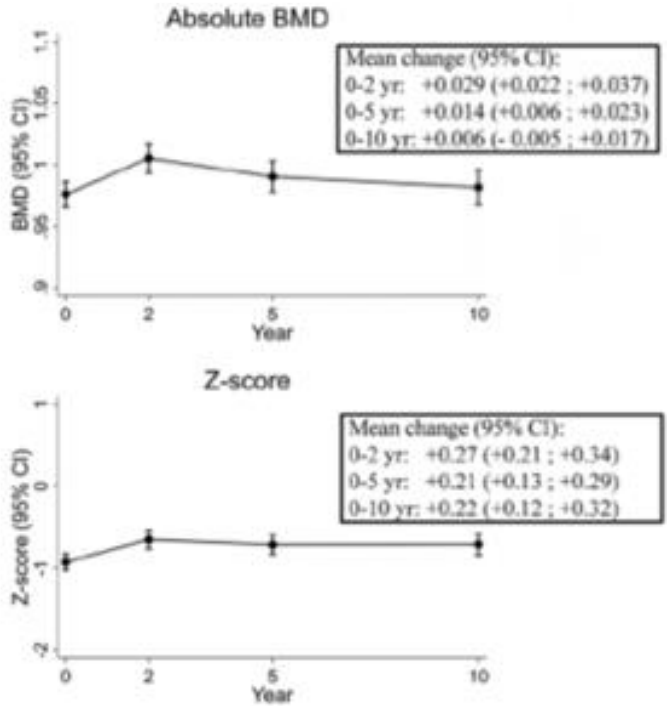

POSSIBLE REASONS

- Body composition changes
- Variable formations
- Insufficient dosing
- Known baseline differences

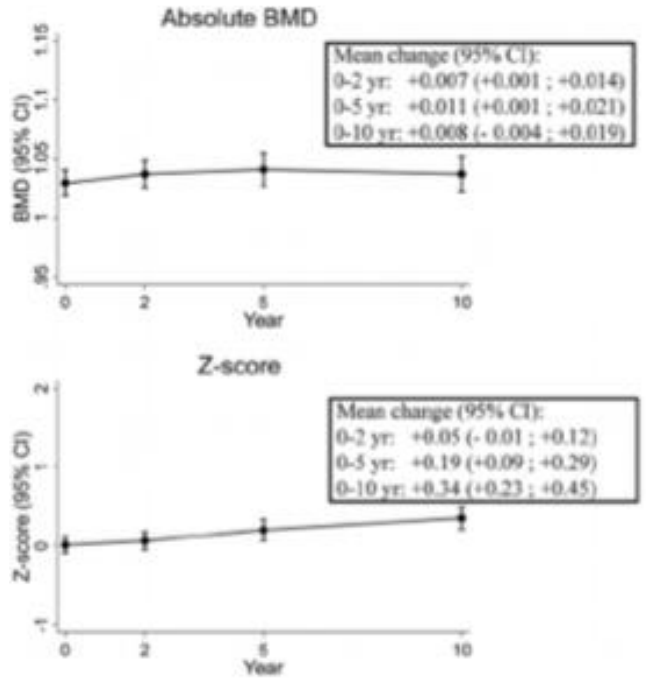
*Fighera et al. Bone Mass Effects of Cross-Sex Hormone Therapy in Transgender People: Updated Systematic Review and Meta-Analysis. J Endo Soc 2019*

# Areal BMD (DXA) Stable Over Time

## Feminising Hormones




## Masc Hormones

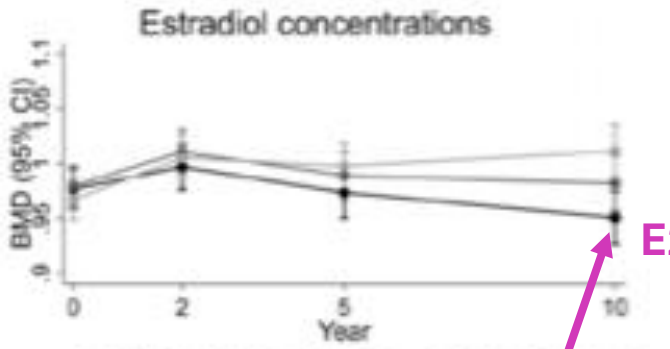



*Absolute BMD and Z scores over 10 years of fem and masc GAHT*

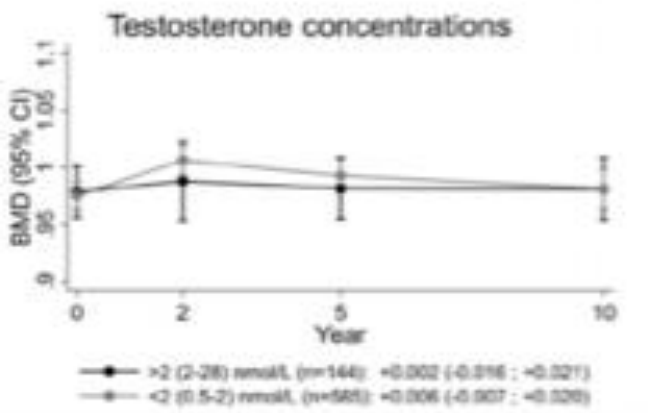
*Wiepjes et al. Bone Safety During the First Ten Years of Gender-Affirming Hormonal Treatment in Transwomen and Transmen. JBMR 2019*

# Lower E2 Concentrations = Lower BMD

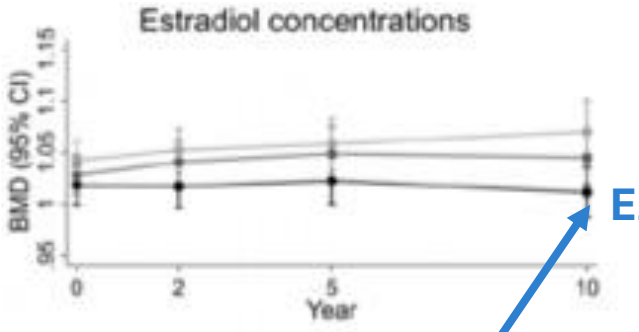
## Feminising Hormones




E2 < 182 pmol/L

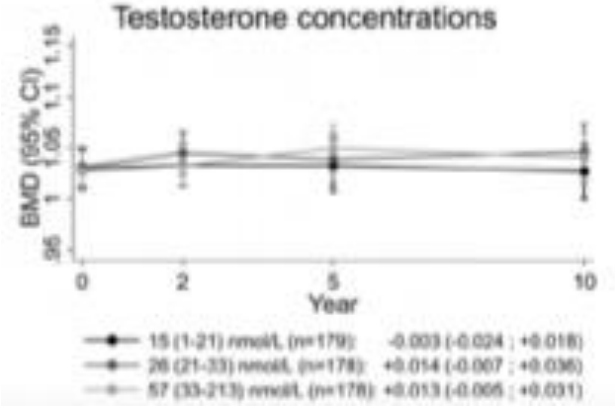



## Masculinising Hormones




E2 < 131 pmol/L

Lowest tertile E2



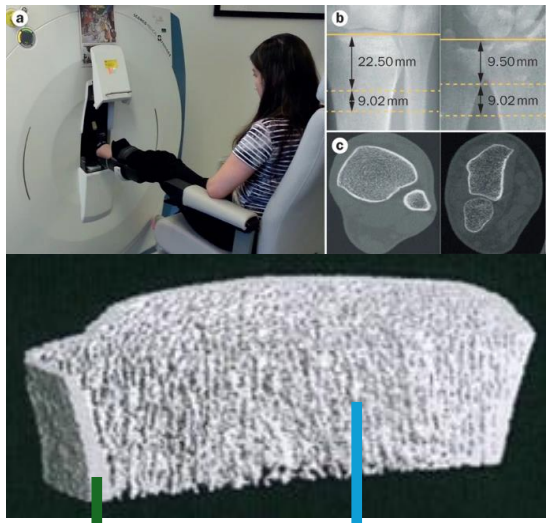



*Wiepjes et al. Bone Safety During the First Ten Years of Gender-Affirming Hormonal Treatment in Transwomen and Transmen. JBMR 2019*

# Bone: Volumetric Density (3D) ↓ in trans women

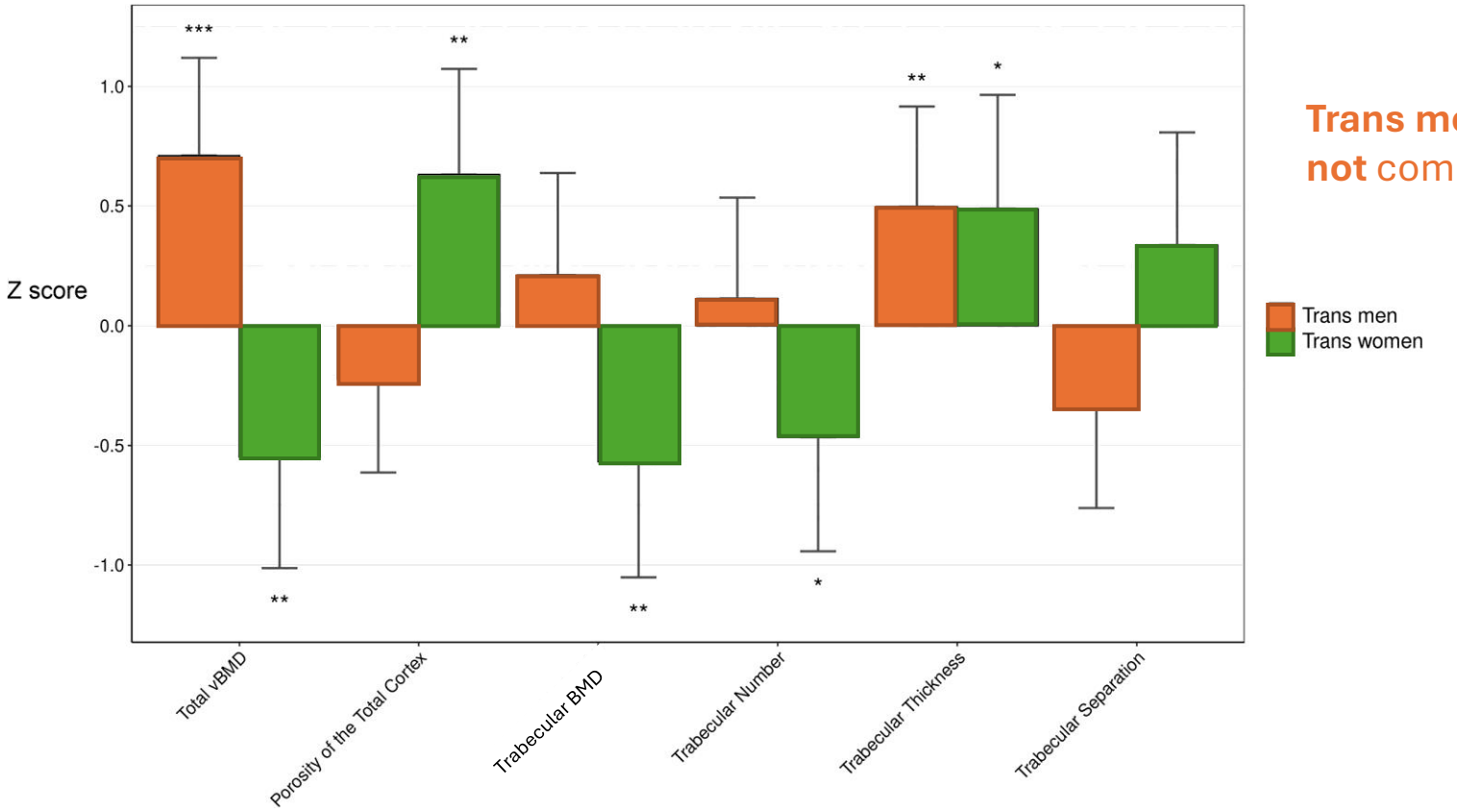
*Cross-Sectional Study*

41 **trans men** vs 71 cis female controls
40 **trans women** vs 51 cis male controls




Cortex (outer)

Trabecular (inner)




**Trans men**: Bone structure **not** compromised



*Bretherton et al. Bone Microarchitecture in Transgender Adults: A Cross-Sectional Study. J Bone Miner Res 2022;37:643-648*

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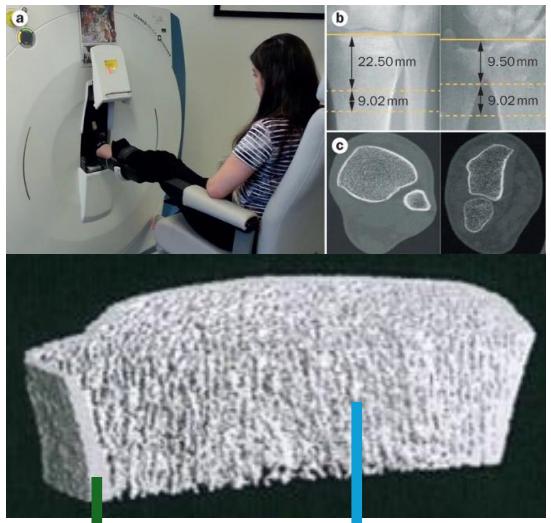
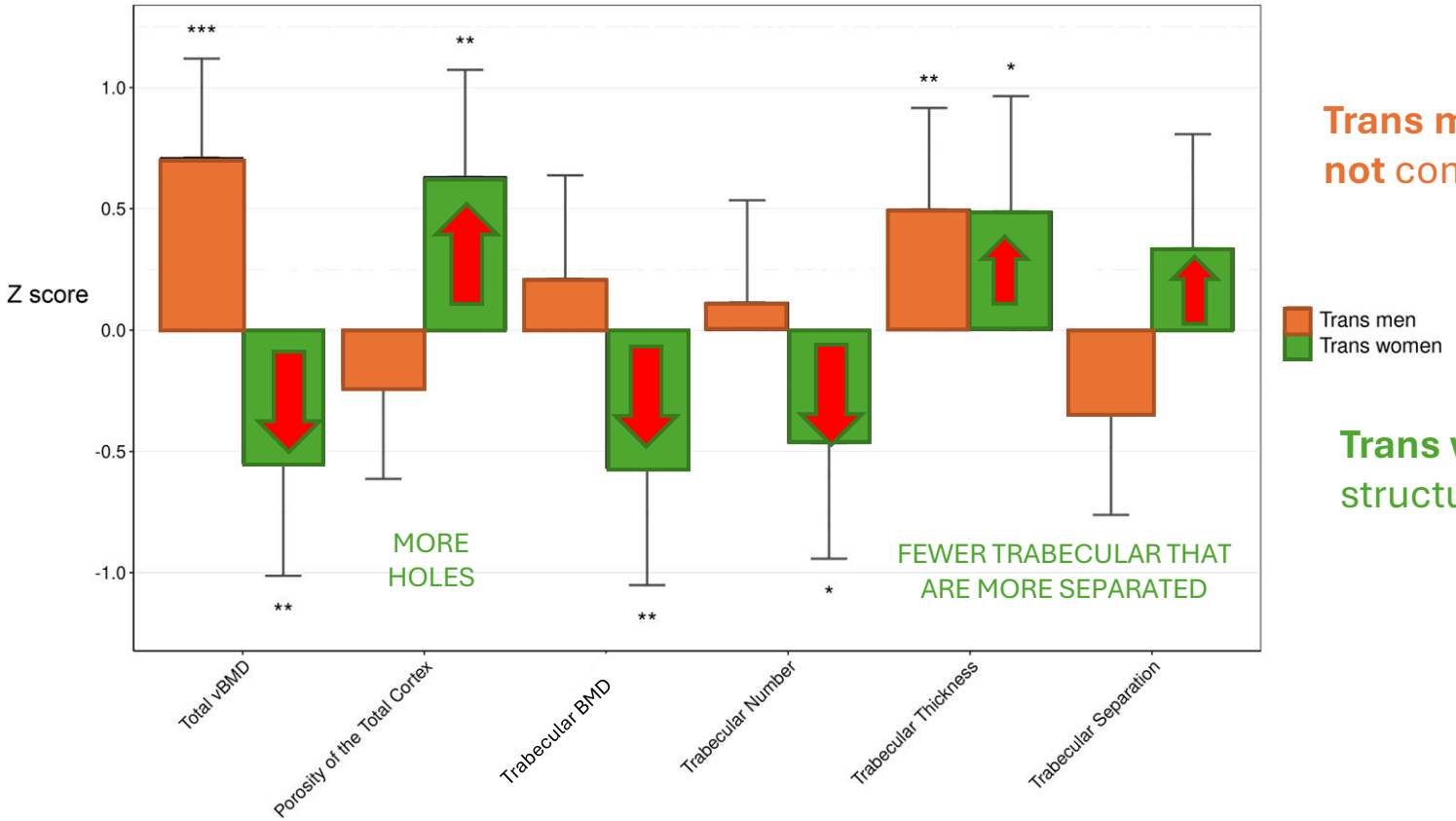



Cortex (outer)

Trabecular (inner)



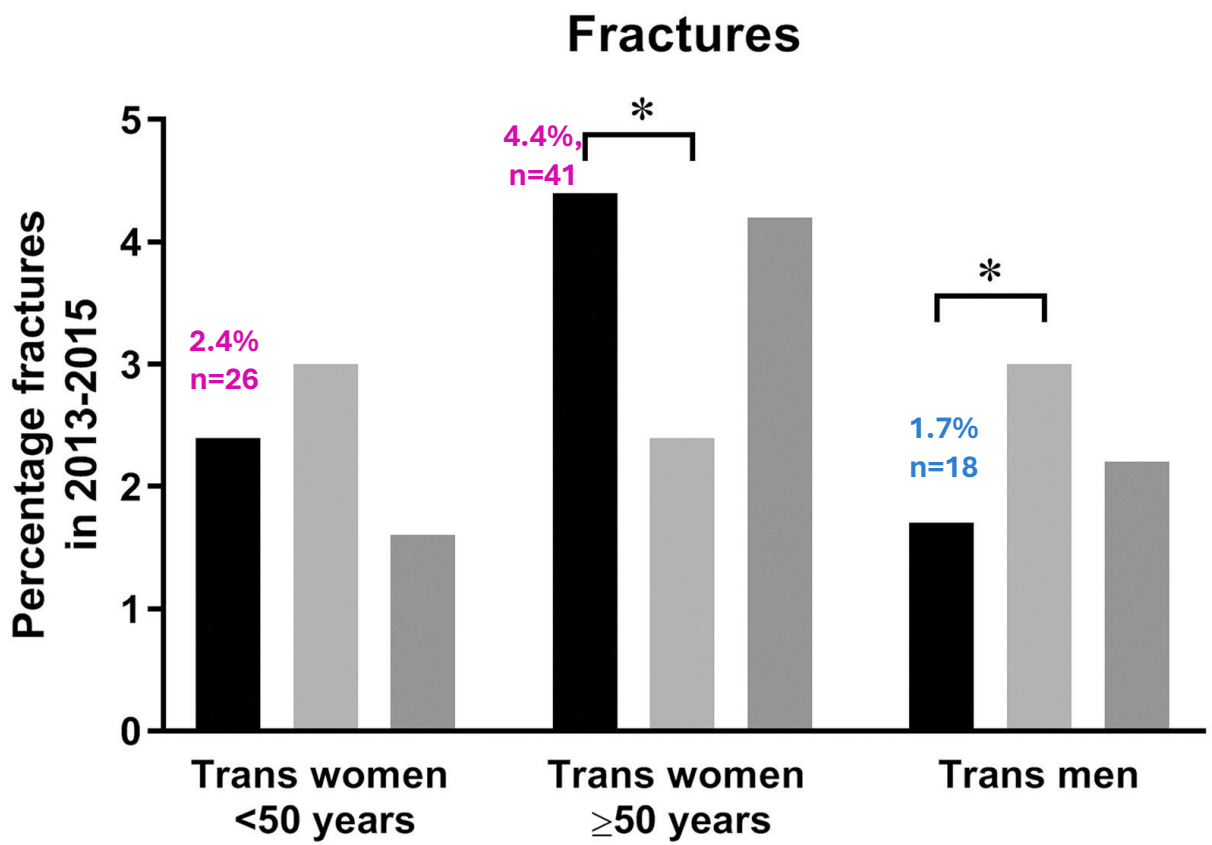

**Trans men:** Bone structure **not** compromised

**Trans women:** Bone structure compromised



*Bretherton et al. Bone Microarchitecture in Transgender Adults: A Cross-Sectional Study. J Bone Miner Res 2022;37:643-648*

# Fracture risk higher in older trans women




Trans people
Control men
Control women

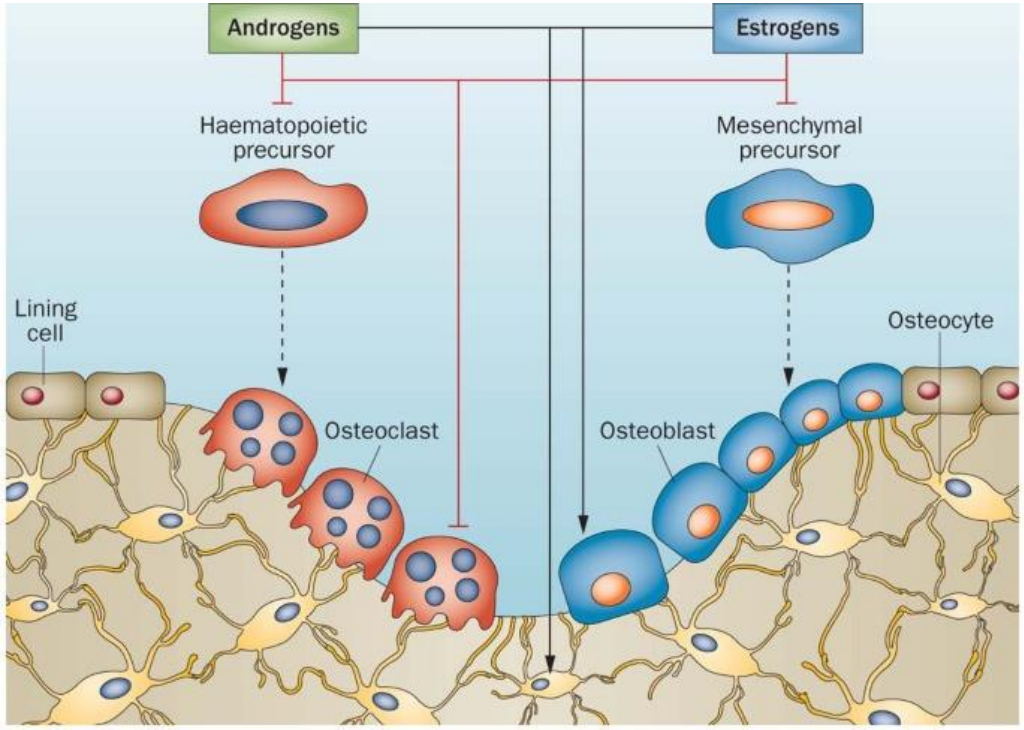
- *Dutch study: 2,023 trans individuals; 1089 < 50 years of age Rx GAHT median of 8 yrs, 934 individuals age 50+ Rx GAHT median of 19 yrs*
- Trans men had reduced risk of cf cis men
- Trans women > 50 years higher number fractures cf cis men, similar rates to menopausal cis women

*Wiepjes et al. Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. JBMR 2019*

# Anabolic effect of E2

- **Transgender mouse high E2 conc:**
  - Increased cortical bone stiffness and strength at the femoral mid-diaphysis.
  - Enhanced endocortical bone formation, indicating an anabolic effect on bone tissue.

- **Suggest high-dose E2 -> anabolic effects on bone**




**Venkatesh VS, Davey RA, et al.** *High circulating concentrations of estradiol are anabolic for bone mass and strength in an adult male-to-female transgender mouse model.* **Bone.** 2024

# Bone Health in Trans Adults- Summary

| | Masculinising Hormone Therapy  | Feminising Hormone Therapy  |
|---|---|---|
| **DXA (aBMD)** | ↓/↑ | ↓/↑ |
| **Bone morphology (vBMD)** | ↑ | ↓ |
| *Total vBMD* | ↑ | ↓ |
| *Cortical porosity* | ↓ | ↑ |
| *Trabec BV/TV, number, sep* | ↑ | ↓ |
| **Fracture risk** | -/↓<br>Reduced risk fractures cf cis men | -/↑<br>> 50 years fracture risk = menopausal cis women/ higher cf cis men |

# Practical Approach: Bone Health Monitoring

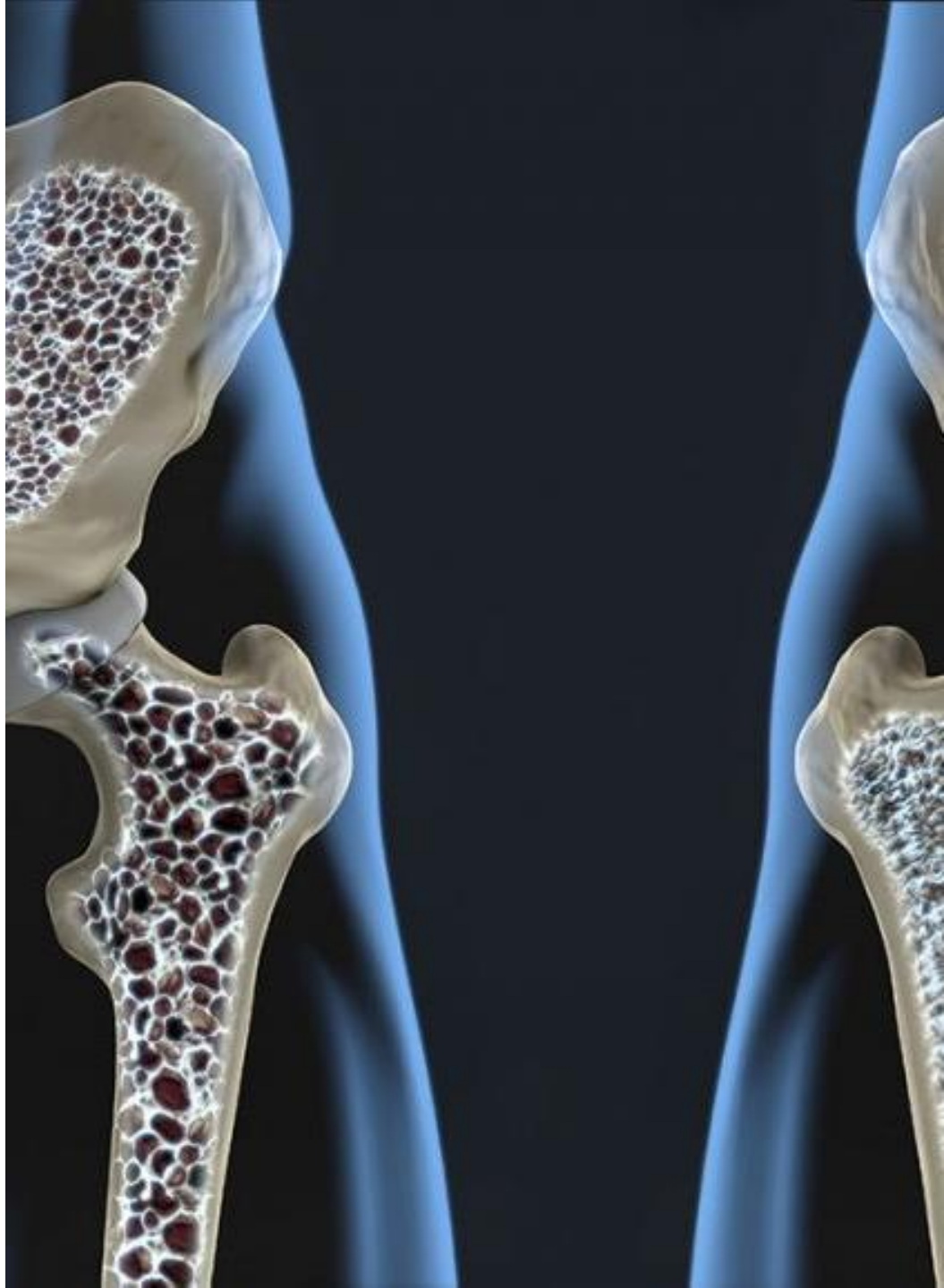
**General**

- Encourage smoking/vaping cessation, adequate dietary calcium (>1000 mg/day) and vitamin D supplementation*, regular weight-bearing activities*
- **Masculinising hormone therapy**: No specific bone-related advice
- **Feminising hormone therapy**: Aim for estradiol >182 pmol/L*.

**Monitoring**

- Annual vitamin D
- DXA scan only if additional risk factors present:
    - Prior GnRHa use without timely GAHT initiation.
    - Androgen blockers with low/no estrogen.
    - Prior gonadectomy with poor GAHT adherence.
- Affirmed gender rather than sex assigned at birth as ref
- Serial DXA scans are more informative than a single timepoint for monitoring bone health trends.

*No trans-specific guidelines exist; recommendations are **adapted from cisgender guidelines** and limited trans health data.



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# Metabolic Health

# Trans adult have higher overall mortality

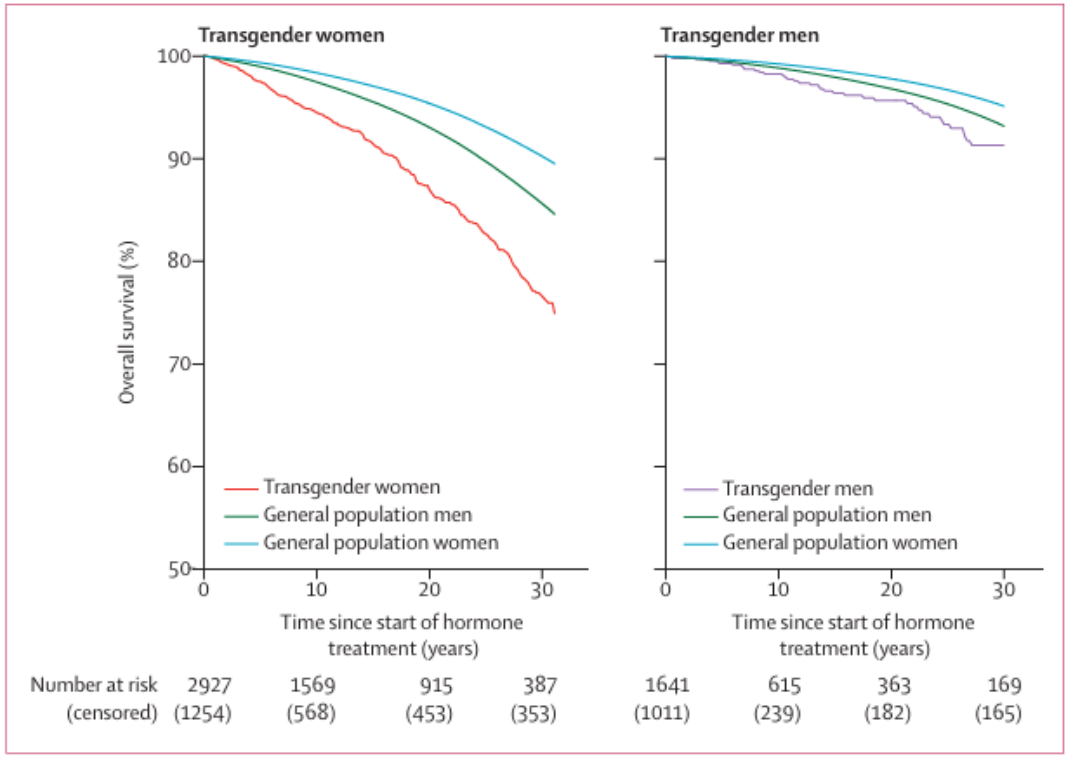



*Figure 2:* **Cumulative survival in transgender women and transgender men during follow-up**

- Trans adults on GAHT ~ **two-fold higher mortality rate**
- 2021 n=4568 Dutch trans people over five decades

*De Blok et al. Mortality trends over five decades in adult transgender people receiving hormone treatment. Lancet Diabetes Endocrinol. 2021.*

# Trans women have higher CVS mortality

- Trans men
  - **No significant increase in mortality from CVS disease** including MI (cf pop men or women)
  - Higher risk of death from non-natural causes (cf women)

- Trans women
- **Higher risk of death**
  - **Due to CVS disease**, HIV-related disease, lung cancer and suicide
  - Death from CVS disease
    - Death from myocardial infarction risk similar to men, but 2.6 times higher than women

| | Transgender women | | | Transgender men | | |
|---|---|---|---|---|---|---|
| | Number who died (n) | SMR compared with general population men | SMR compared with general population women | Number who died (n) | SMR compared with general population women | SMR compared with general population men |
| Overall* | 241 | 1·6 (1·4–1·9) | 2·4 (2·1–2·7) | 34 | 1·6 (1·1–2·1) | 1·1 (0·8–1·5) |
| Cardiovascular disease | 50 | 1·4 (1·0–1·8) | 2·6 (1·9–3·4) | <10 | 1·6 (0·5–3·2) | 0·8 (0·3–1·6) |
| Myocardial infarction | 17 | 1·1 (0·7–1·7) | 3·0 (1·7–4·5) | <10 | 1·0 (0·0–3·7) | 0·4 (0·0–1·4) |
| Thromboembolism | NA | NA | NA | NA | NA | NA |
| Other | 33 | 1·5 (1·1–2·1) | 2·5 (1·7–3·4) | <10 | 1·8 (0·5–4·0) | 1·1 (0·3–2·3) |
| Cancer | 76 | 1·3 (1·0–1·6) | 1·6 (1·3–2·0) | <10 | 0·8 (0·4–1·4) | 0·8 (0·4–1·4) |
| Lung cancer | 34 | 2·0 (1·4–2·8) | 3·1 (2·1–4·2) | <10 | 1·1 (0·2–2·7) | 1·0 (0·2–2·3) |
| Cancer of digestive tract | 17 | 1·0 (0·6–1·5) | 1·5 (0·9–2·4) | <10 | 0·4 (0·0–1·6) | 0·3 (0·0–1·0) |
| Other | 25 | 1·1 (0·7–1·6) | 1·0 (0·6–1·4) | <10 | 0·8 (0·3–1·6) | 1·1 (0·4–2·2) |
| Infection | 13 | 5·4 (2·9–8·7) | 8·7 (4·7–14·1) | NA | NA | NA |
| HIV | <10 | 14·7 (1·8–40·9) | 47·6 (5·8–132·6) | NA | NA | NA |
| Other | <10 | 4·8 (2·4–8·0) | 7·6 (3·8–12·7) | NA | NA | NA |
| Non-natural cause | 32 | 2·7 (1·8–3·7) | 6·1 (4·2–8·4) | <10 | 3·3 (1·2–6·4) | 1·3 (0·5–2·5) |
| Suicide | 18 | 3·1 (1·8–4·7) | 6·8 (4·1–10·3) | <10 | 2·8 (0·6–6·8) | 1·2 (0·3–3·0) |
| Other | <14 | 2·3 (1·2–3·6) | 5·2 (2·9–8·4) | <10 | 4·0 (0·8–9·7) | 1·3 (0·3–3·2) |
| Other | 70 | 1·9 (1·5–2·3) | 2·7 (2·1–3·4) | 14 | 2·8 (1·6–4·5) | 1·9 (1·0–3·0) |

Data are absolute values or standardised mortality ratio (95% CI). N indicates the number of patients who started hormone therapy who died. Absolute numbers of people who died are only presented if the number exceeds ten cases to guarantee patient anonymity. SMR=standardised mortality ratio. NA=not applicable (no deaths in the population). HIV=human immunodeficiency virus. *Overall mortality risk for the period that cause-specific death data were available (1996–2018).

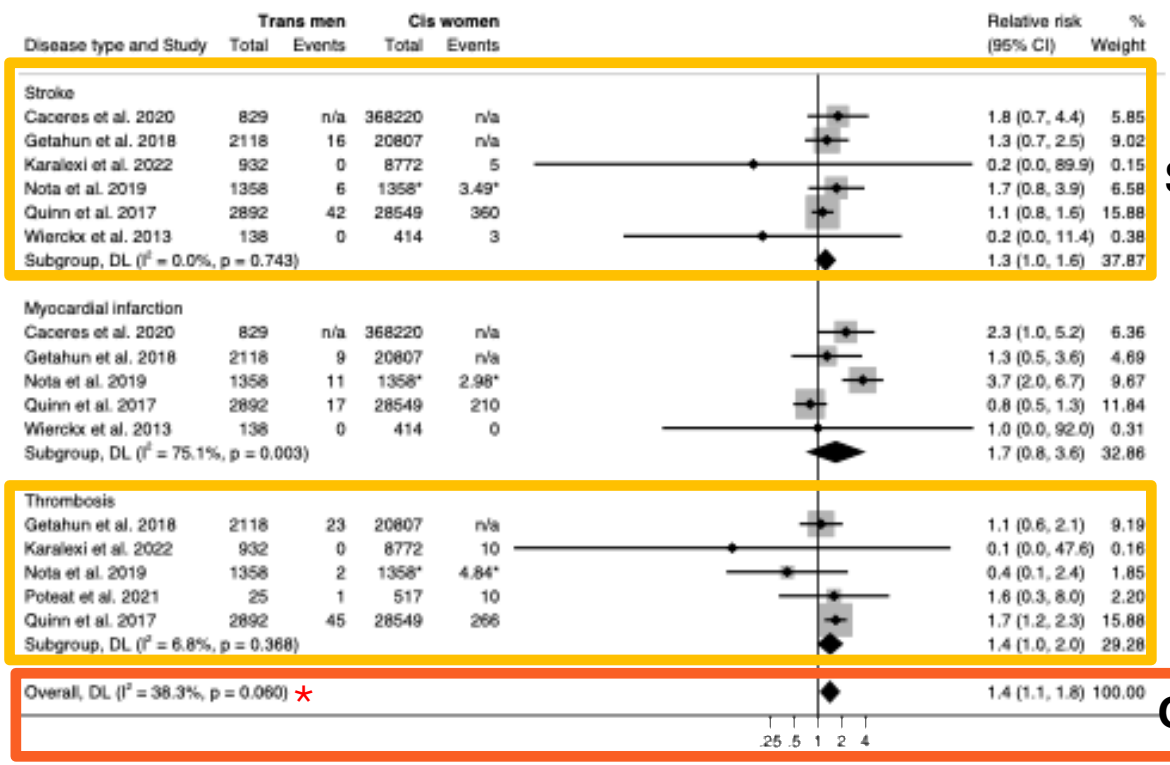
***Table 3:*** **Cause-specific standardised mortality ratios in transgender women and transgender men compared with general population men and general population women**



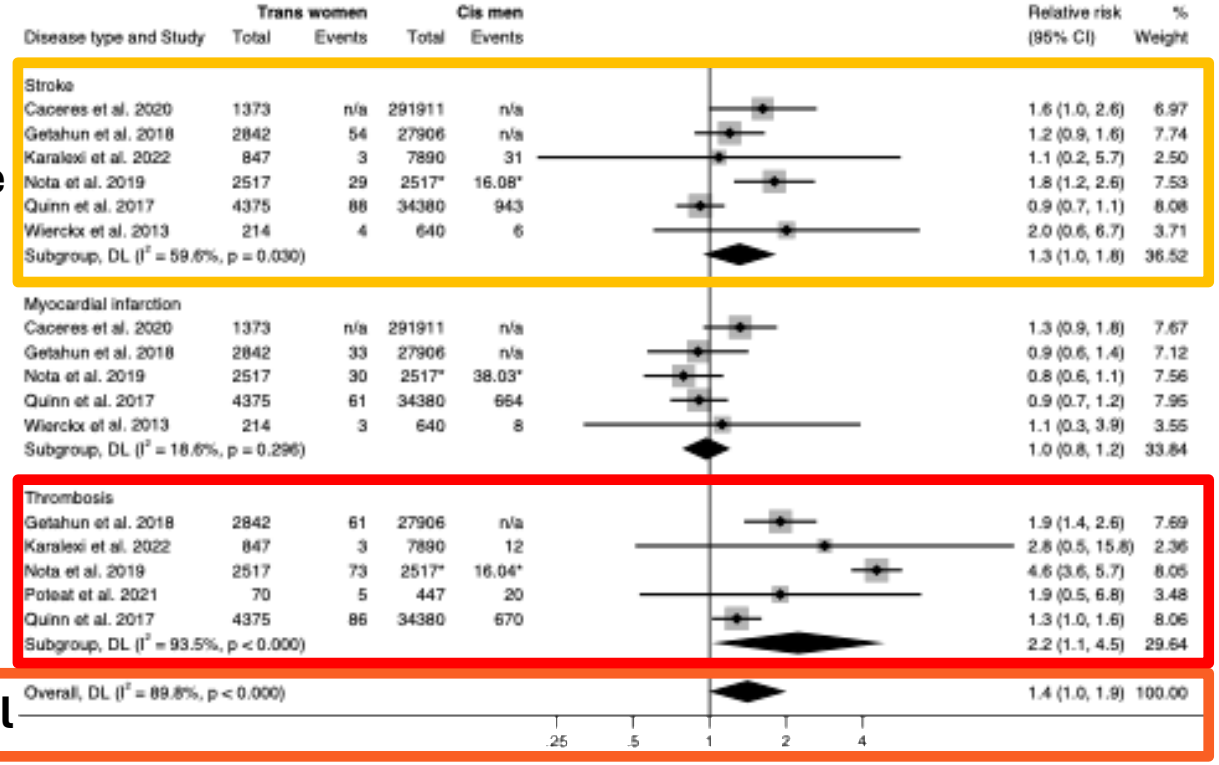
*1. De Blok CJ et al. Mortality trends over five decades in adult transgender people receiving hormone theory. Lancet Diab Endoc 2021*

# Trans Adults have Higher CVS risk

## Masc Hormones




## Fem Hormones




**Stroke**

**MI**

**VTE**

**Overall**

- *Feminising HT included older formulations no longer used such as EE and CEE*

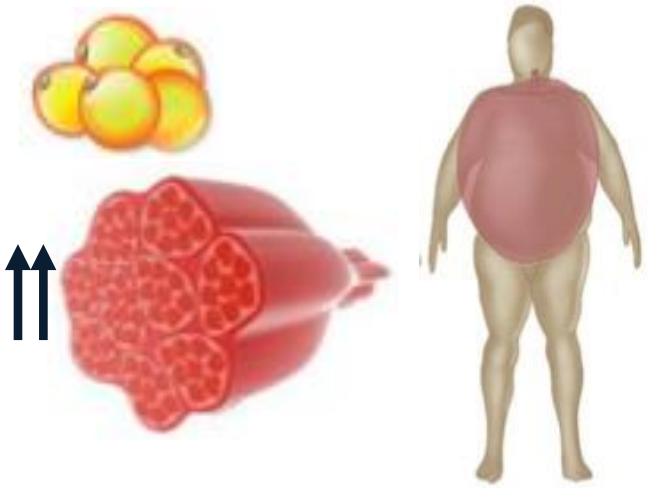


*Zijverden et al. CVS disease in transgender people: a systematic review and meta-analysis. EJE 2024*

# Body Composition Changes are Dramatic

- Cross sectional study: 84 trans individuals (GAHT min 12 months) cf 78 age cf controls
- Body composition scanning via DXA

## Masc Hormones



- Similar overall fat
- Higher android fat
- Higher lean mass (+7.8kg)

## Fem Hormones

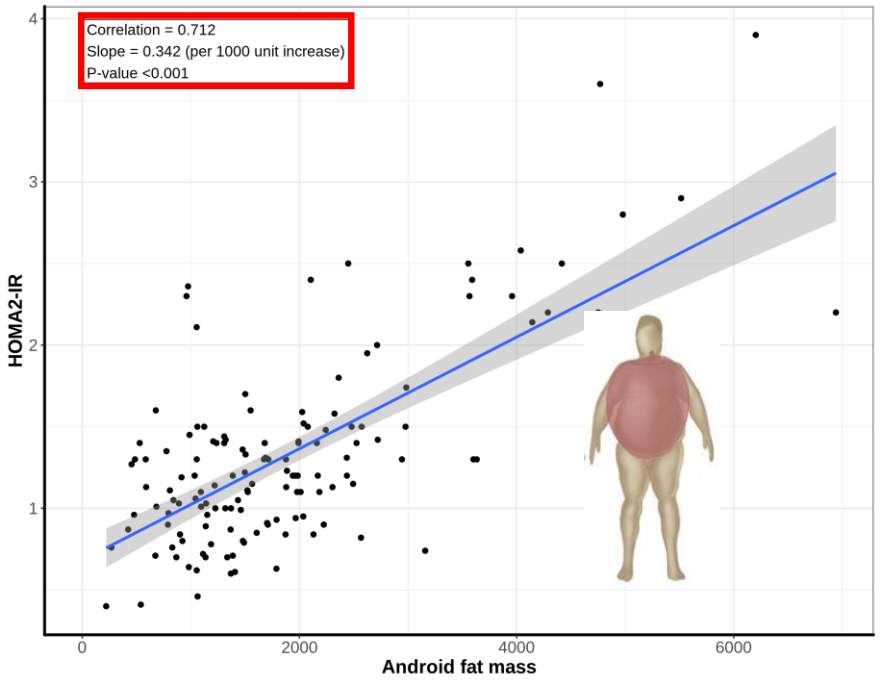
- Higher overall fat (+9.8kg)
- Higher gynoid fat
- Lower lean mass (-6.9kg)

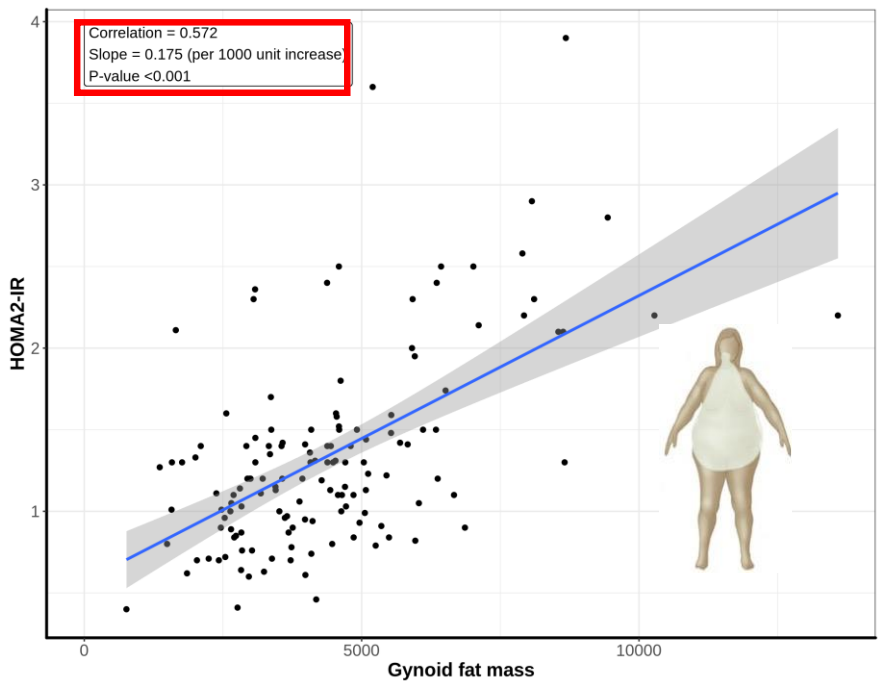


*Bretherton I, Cheung A. Insulin resistance in transgender individuals correlates with android fat mass. Ther Adv Endocrinol Metab. 2021*

# Insulin Resistance Higher in Trans women

- Fasting glucose, and c-peptide -> calculation of (HOMA2-IR), validated surrogate marker of IR
- IR sig correlated with android fat mass- therefore hypothesised trans men would have IR
  - Trans men-insulin resistance not higher
  - Trans women higher insulin resistance 1.6 (1.3–1.9), $p < 0.001$)



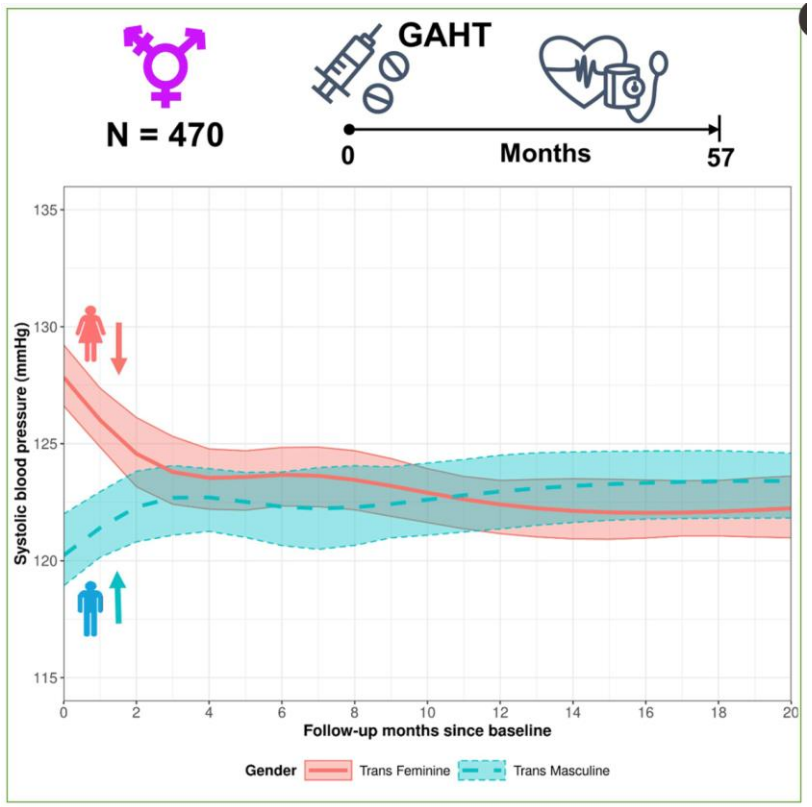




*Bretherton I, Cheung A. Insulin resistance in transgender individuals correlates with android fat mass. Ther Adv Endocrinol Metab. 2021*

# Blood pressure and Lipids

- Masculinising hormones
  - Blood pressure
    - Minimal change, slight increase in some studies[1]
  - Lipids
    - Two large cohort studies[2,3]: ↑ LDL, ↓ HDL, variab TG

- Feminising hormones
  - Bloods pressure
    - Minimal change, slight decrease in some studies[1]
  - Lipids
    - Meta-analysis of 29 studies (n=323)[4:] ↓ LDL, ↑ HDL, ↑ TG (especially oral)





1. *Glintborg D et al Diabetologia 2024 2. Wieckz K et al.. J Sex Med Aug 2014 3. van Velzen DM et al. J Clin Endocrinol Metab 2019*
2. *4. Maraka S et al. J Clin Endocrinol Metab 2017 5. Figure: Banks K, Hypertension. 2021 Jun;77(6):2066-2074.*

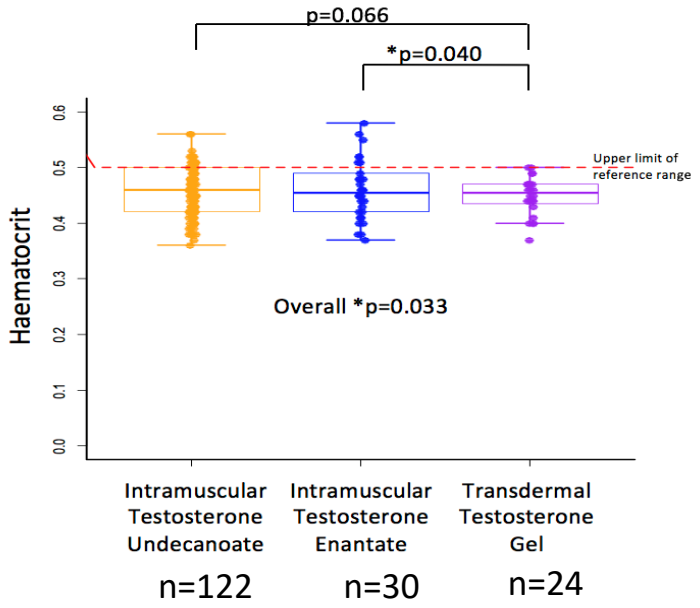
# Thrombotic Risk

## Masculinising hormones

- Polycythaemia associated with IM > transdermal T
  - 1 in 4 on IM T testosterone enanthate, 1 in 6 on IM T undecanoate, None on transdermal T[1]

## Feminising hormones

- Modern E2 lower VTE risk, similar to cis women Rx E2[2,3]
- 2019 meta-analysis: risk 0-2% (cf ~6% VTE risk for those on 100mcg EE)[2]
- Transdermal preparations preferred*
  - *2020: trans women on E2 hypercoagulable GCA similar to cis women irrespective of route[3]




Polycythaemia With Different Formulations of Testosterone


1. *Nolan B, Cheung AS. Prevalence of polycythaemia with different formulations of testosterone therapy in transmasculine individuals. IMJ 2020*
2. *Nolan B, Cheung AS. Estradiol Therapy in the Perioperative Period: Implications for Transgender People Undergoing Feminizing Hormone Therapy Yale J Biol Med. 2020*
3. *Khan J et al. Venous Thrombotic Risk in Transgender Women Undergoing Estrogen Therapy: A Systematic Review and Metanalysis. Clin Chem. 2019*
4. *Lim H, Cheung AS. Global Coagulation Assays in Transgender Women on Oral and Transdermal Estradiol Therapy. JCEM 2020*

# Metabolic Health in Trans Adults- Summary

| | Masculinising Hormone Therapy  | Feminising Hormone Therapy  |
|---|---|---|
| **Overall** | ↑ | ↑ |
| **VTE** | -/↑ | ↑↑ |
| **Stroke** | -/↑ | -/↑ |
| **Myocardial infarction** | -/↑<br>Similar to cis men, higher to cis women | -/↑<br>Higher than cis women, Similar to cis men |
| **Fat mass** | - | ↑↑ |
| **Lean mass** | ↑↑ | ↓↓ |
| **Insulin resistance** | - | ↑ |
| **Lipids** | ↑ TC, LDL, and TG, lower HDL | - / (↑TG at 24 months) |
| **Bloods pressure** | - | - |

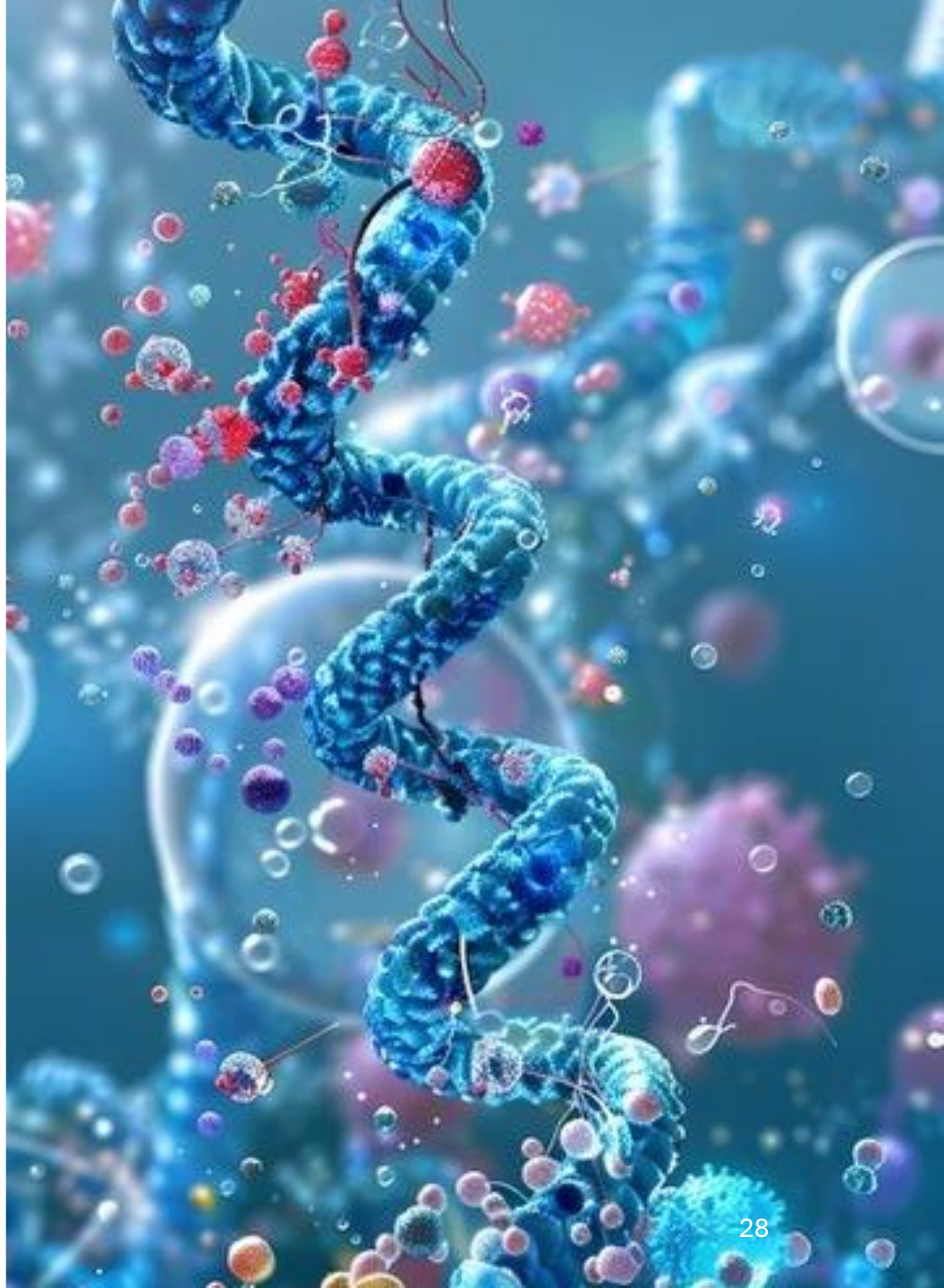
# Practical Approach: Metabolic Health Monitoring

**General**

- Encourage smoking/vaping cessation, healthy eating, regular exercise
- Address minority stress, socioeconomic factors, mental health barriers to accessing healthcare and monitoring
- Masculinising hormone therapy:
    - Opt for transdermal T if polycythaemia present
- Feminising hormone therapy:
    - Avoid ethinyl estradiol
    - Choose transdermal estrogen if at higher risk VTE (Age > 45 years, prior VTE, smoker, high BMI
    - Consider spironolactone as choice of androgen blockers in trans women if blood pressure elevated

**Monitoring**

- Baseline and then at least annual metabolic screen (FBE, EUC, CMP, LFT, fasting glucose, HbA1c, lipids)
- Annual blood pressure and weight



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# Reproductive Health

# Reproductive Health- Masculinising hormones

- **Fertility preservation**
  - GAHT suppresses gonadal function (? reversible) → oocyte cryopres always discussed, rarely done

- **Contraception**
  - Progestins preferred: Drospirenone (Slinda), levonorgestrel IUD (Mirena/ Kyleena), Implanon NXT, MPA (Depot Provera)
  - Other:  barrier method

- **Menstrual management:**
  - Amenorrhea in ~85% by 6 months. More likely with higher T levels
  - Progestins (listed above + norethisterone aka Primolut)
  - Hysterectomy ideally with ovaries left in situ

# Reproductive Health- Masculinising hormones

- **Pregnancy**
  - Pause T and allow levels to drift to baseline, min 3 months at baseline before TTC
  - Recommence following delivery/ breast-chest feeding completed

- **Commonly co-occuring during reproductive years**
  - *PMDD* → symptoms often improve on testosterone therapy
  - *Endometriosis / Adenomyosis* → often improves but may require adjunctive RX (progestogens)
  - *PCOS* → metabolic monitoring; fertility considerations remain

- **Menopause**
  - If on standard dose T: usually uneventful if on adequate T. Topical vaginal E2 PRN
  - If on low dose T- can add Slinda, levonorgestrel IUD for BTB. Can add MHT

# Reproductive Health- Feminising hormones

- **Fertility preservation**
  - GAHT suppresses gonadal function (? reversible) → sperm cryopres
  - Suggest sexual health screen at same time

- **Contraception**
  - Azoospermia not guaranteed, contraception recommended

- **Sexual function**
  - Less T suppression / add back T if gonadectomy
  - Prometrium (anecdotal)
  - Consider non hormonal factors (psychological, CVS risk factors). PDE5

# Reproductive Health- Feminising hormones

- **Prometrium**
  - Anecdotally helps with sleep, libido, breasts, mood
  - One study no effects, another improved breast outcomes (Amsterdam study n=90, 30% increase with 3D scanning)

- **Lactation induction**
  - High dose domperidone and estradiol + progesterone for breast priming, followed by withdrawal and regular breast pumping. Breast pumping/feeding plus low-dose maintenance. galactagogue

- **Age of ‘natural’ menopause**
  - Given poorer bone health in age >50 years suggest lifelong E2

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# Summary and Key Points

# Summary

**Bone health:**

- Trans men favourable bone health data
- Trans women: ↓ volumetric BMD, ↑ fracture risk >50 yrs
- DXA for monitoring in those at higher risk (affirmed gender for DXA reference)

**Metabolic health:**

- 2× higher overall mortality and higher CVS risk
- Trans women:
  - ↑ CV mortality, MI risk 2.6× cis women, insulin resistance, ↑ triglycerides (oral > transdermal)
  - VTE risk in modern oestrogen safer, VTE rates similar to cis women
- Trans men:
  - ↑ lipids
  - Polycythaemia risk: IM testosterone ↑ risk cf transdermal

**Reproductive health:**

- Trans men: Fertility, contraception, menstrual management (Progestins useful)
- Trans women: sexual function changes; possible emerging Prometrium data

# Conclusions

- Gender affirming care are essential, and life saving
- Some risk, small in comparison to benefit
- Unclear exact contribution of GAHT
    - Bone and metabolic health risks vary with hormone regimen, age, baseline health, and lifestyle
    - Bone data showing lower BMD in trans women more consistent with insufficiency dosing/ other RF
    - Modern regimens likely much more favourable on CVS risk including VTE
    - Minority stress adds additional burden → ↑ CVS & metabolic risk
- Screening, monitoring and aggressive optimisation of risk factors
- Significant research gaps remain

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# Thank you


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# Other Common Issues

# Common issues- masculinsing hormones

- **Acne**
  - 80% in first year often chest and back, often dissipates after 12 months
  - Benzoyl peroxide, topical retinoids, clindamycin/tretinoin gel (Acnatac), oral tetracyclines, isotretinoin

- **Hair thinning**
  - *Topical /PO/SL Minoxidil (0.25–2.5 mg/day)*, SE: dose-dependent hypertrichosis, low BP
  - *5-α reductase inhibitors*– reduce DHT, SE: may blunt masculinisation
  - *Other:* Hair transplant , PRP injections, microneedling, low-level laser therapy, stem cells therapies


- **Polycythaemia risk**
  - RFs: IM T, Smoking, OSA, Polycythaemia vera(rare)
  - Monitor Sx, aim hct 0.5 or below, consider T gel, venesection

- **Common comorbidities**
  - *Hypermobility Syndromes* → joint pain and instability; require tailored physical therapy but anecdotally improves
  - *POTS*→ anecdotally most report improved cardiovascular tolerance
  - *CFS/ME* → monitor closely but anecdotally improves

# Common issues feminizing hormones

- **Migraine with aura**
  - Transdermal E2 preferred, patches ideal

- **Hair thinning (pre-existing)**
  - Optimize estrogen + anti-androgen therapy
  - *5α-reductase inhibitors, minoxidil (*caution as SE dose-dependent hypertrichosis)


- **Prolactin**
  - Pituitary lactotroph cells have E2 + P4 receptors. E2 and CPA increase PRL- rarely clinically significant
  - Indications for treating prolactinoma: >10mm size, galactorrhea. Avoid checking PRL unless symptoms

# Monitoring Recommendations

## Initial GAHT (first year)

- **Review:** 3 monthly until stable.
- **Check:**
  - Symptoms and side effects.
  - Blood pressure, weight/BMI.
  - Serum estradiol or testosterone (timed to regimen).
  - FBE, renal/liver function, lipids/glucose if relevant.
- **Adjust dose** to achieve target hormone range, minimise risks.

## Long-term (after stable dosing)

- **Review:** 6-12 monthly (or more often if risk factors).
- **Check:**
  - Same as above but add metabolic screen (glucose, HBA1c, lipids, vitamin D)

- **Bone Health**: **DEXA scan only** if additional risk factors for osteoporosis are present
- **Sexual Health:** Screening as indicated by sexual practices and risk profile (STIs, HIV, etc.)
- **Cancer Screening:** Based on **age and organs present**: cervix, prostate, breast/chest, bowel.
- **Cervical Screening:** Every **5 years** for anyone with a cervix, ages **25–74 years**.
- **Breast / Chest Screening:**
  - Mammogram every **2 years** for oncec ≥5 years of feminising hormones, ages **50–69 years**
  - **Chest examination:** Every **2 years** for those **50–69 years** post-top surgery with residual breast tissue.