Transgender Bone health

June 14, 2019 Raymond Fung

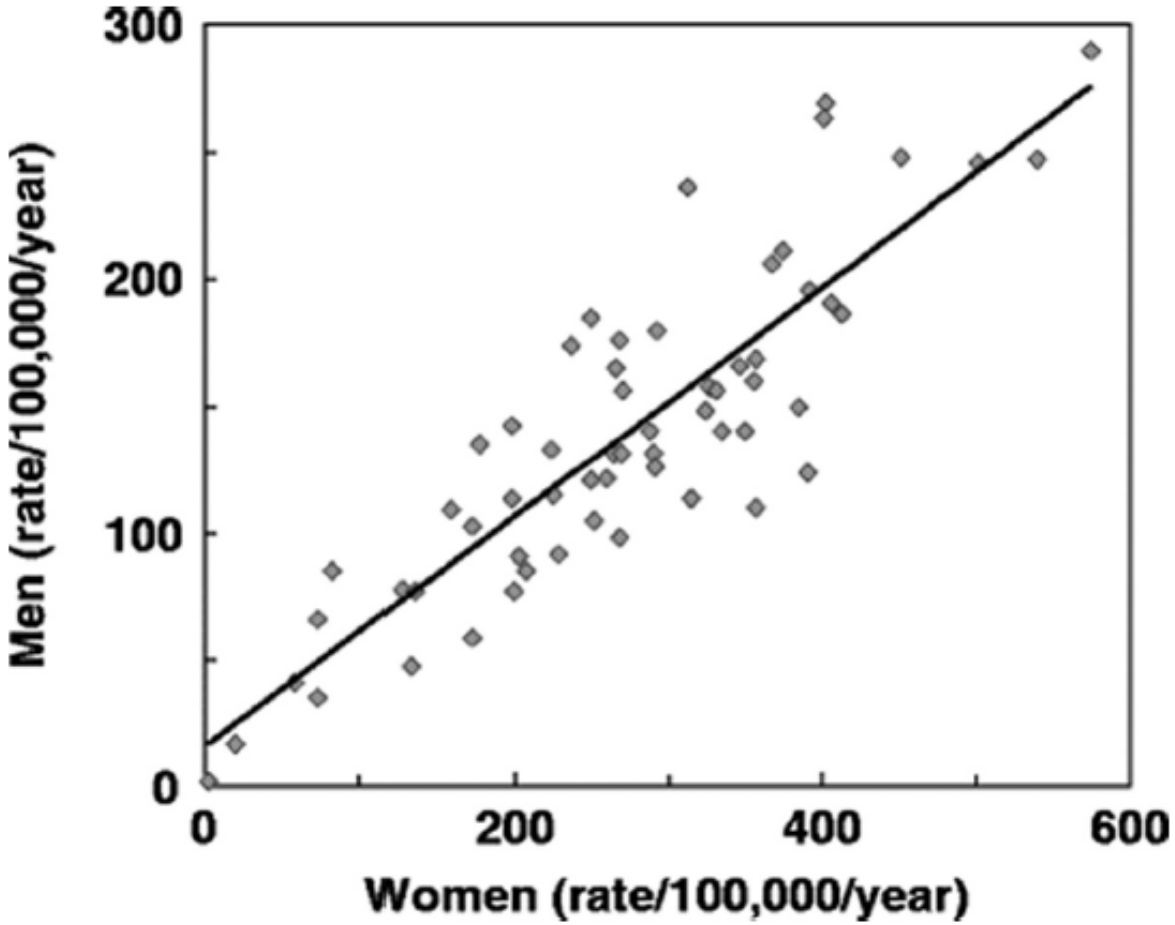
Learning Objectives

- Review role of sex steroids in bone physiology
- Speculate about the effects of transgender hormone therapy on bone health
- Review recent data on bone health in transgender people

Outline

- Sex steroids – role in bone physiology
  - Androgens vs. Estrogen
  - Peak bone mass
- Transgender hormone rx
  - Possible effects
- Effects of gonadectomy on bone
  - Our research study
- Newer data on trans hormone effects on bone

Hip Fracture rates Men vs. Women



Sex steroid actions in Male Bone, Endocrine Reviews, 2014 (Vanderschueren)

Sex steroids and bone

- Testosterone converted to:
  - DHT (5 alpha reductase)
  - 17 beta estradiol (E2) (aromatase)
- Estrogen
  - 20% from testes, 80% from peripheral tissues (trans)

Sex steroid actions in Male Bone, Endocrine Reviews, 2014 (Vanderschueren)

Male bone vs. female bone

- Bone strength = BMD + dimensions, microstructure, material properties
- Rigidity of tubular bone, increases 4th power of diameter
- Periosteal expansion during puberty/early adulthood in men
- Females – increase cortical thickness by limiting endocortical expansion
- Both central and peripheral bone sites, men have 25-33% larger cross sectional bone area than women

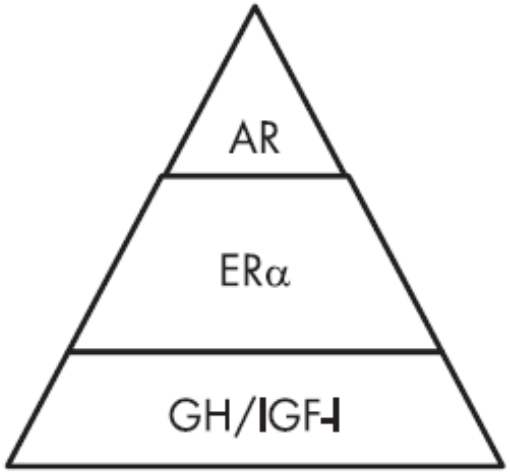
Sex steroid actions in Male Bone, Endocrine Reviews, 2014 (Vanderschueren)

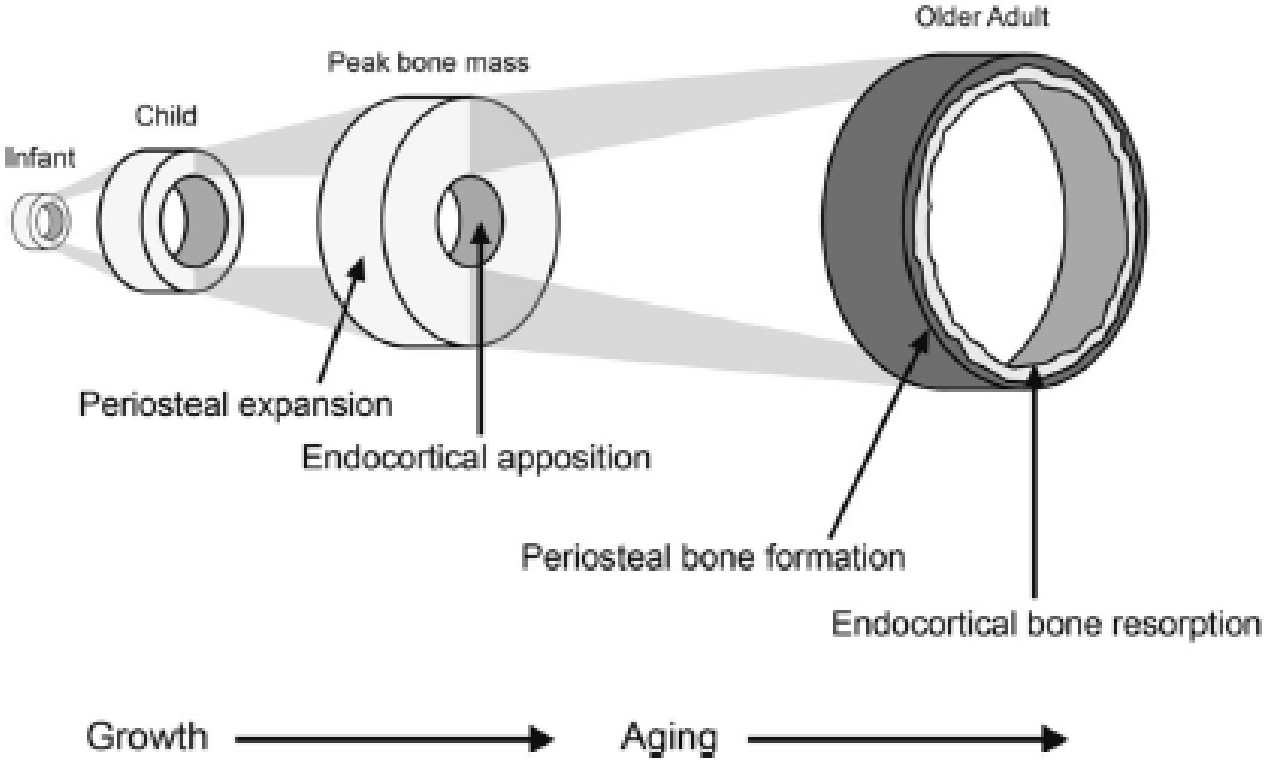
Importance of E2 in male bone

- Men ER alpha null mutation
  - Normal T, increased E2
  - Tall stature, incomplete epiphyseal closure
  - Markedly decreased BMD
  - Decreased cortical thickness due to increased endosteal expansion
  - Decreased cortical and trabecular vBMD
  - Decreased bone formation
- Men with aromatase deficiency
  - Suboptimal bone mass, cannot improve without estrogen replacement

E2 vs. T effects on bone

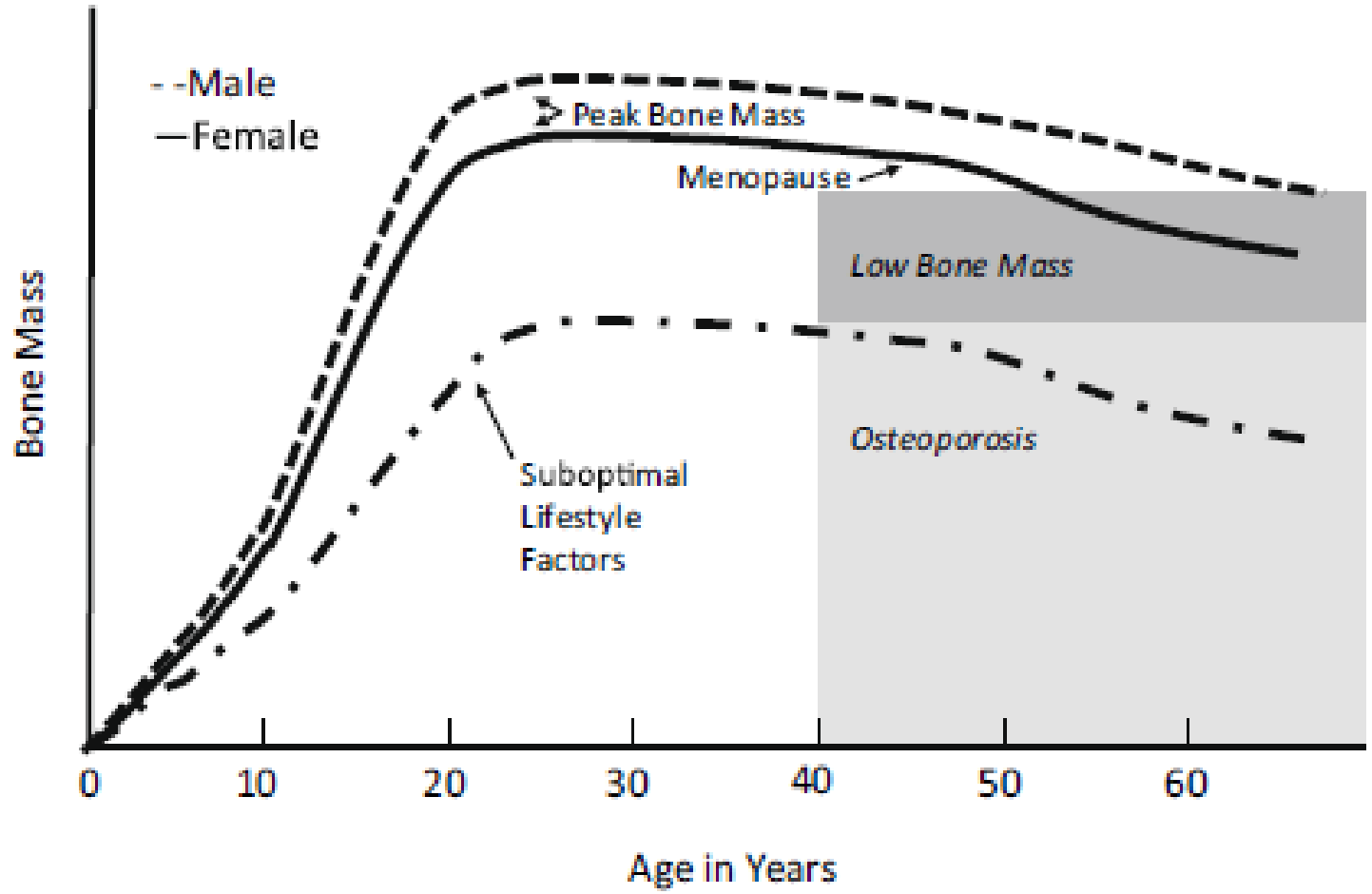
- E2 deficiency - severe consequences on bone in both genders
- Androgens – enhance bone mass in men compared to women
- XY complete androgen insensitivity
  - Normal female bone BMD
- Male ARKO identical cortical bone parameters compared to wild type female mice


AR
ERα
GH/IGF-I

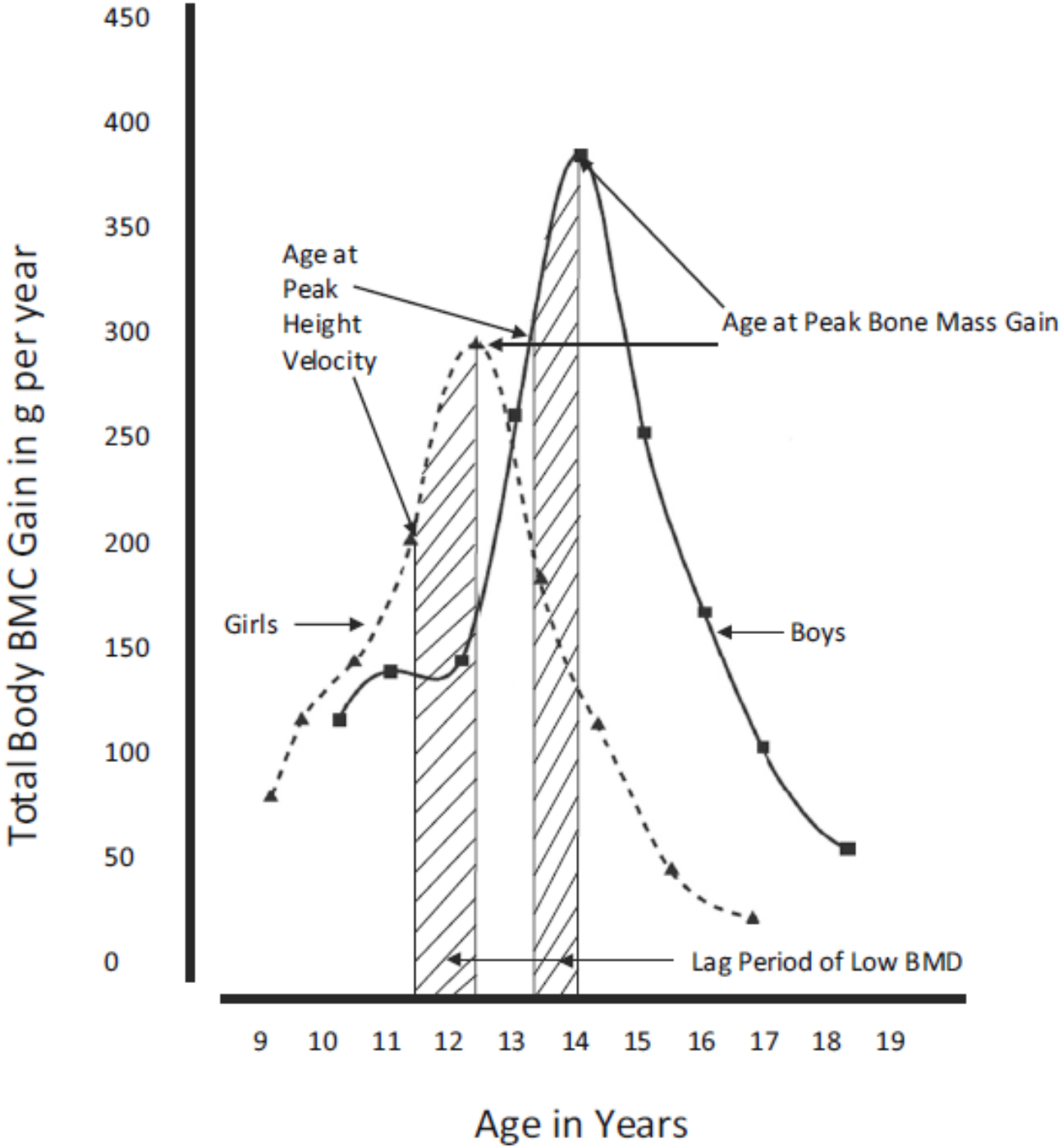

Older Adult
Peak bone mass
Child
Infant
Periosteal expansion
Endocortical apposition
Periosteal bone formation
Endocortical bone resorption
Growth
Aging


♂
♀

Peak bone mass



Peak bone mass gain



Transgender hormone Rx: Feminizing

- Give estrogen (estradiol), and block testosterone
- If given during puberty/early adulthood
  - May decrease periosteal expansion
- Adulthood – maintain bone mass
- Elderly - ? Continue estrogen vs. cis females
- ? Improved bone density
- Other factors outside of hormone:
  - Genetics
  - Nutritional
  - Physical activity
  - Others: SES, mental health, obesity, other medical conditions

Transgender hormone Rx: Masculinizing

- Give testosterone, suppress menstrual cycle
  - Conversion to estradiol
- Puberty
  - Induce periosteal expansion – increased diameter
  - Stronger bone, decreased fracture rate
- What happens in adulthood
  - Larger cortical bone size vs. control females (cross sectional)
  - Preserved BMD over 2 yrs
  - Increased muscle mass may help induce these cortical bone changes
- Older transmales
  - ? Maintenance
- Other factors: nutrition, physical activity, mental health, stress, SES

Caenegem, E. T'Sjoen, G. Bone in trans persons. Current opinion in endocrinology, 2015

Transcare during puberty

- Pt presents during puberty
- First step – GnRH agonist therapy to hold puberty
- Earliest start Tanner stage 2
- Lag time before cross sex hormones are given
- Official recommendation – age 16
- Crucial time for bone mass accrual
- How does this affect BMD
- Is there catch up after cross sex hormones are given?

Puberty suppression and BMD

- 19 transmales, age 15.0 (+/-2) for 1.5 years
- 15 transfemales, age 14.9 for 1.3 years
- Decrease in area BMD z scores, and bone mineral apparent density z scores
- No change in BMD
- Reassessed at age 22 – incomplete catch up
- Mean age start sex hormone rx 16.6

Klink, D et al. Bone mass in young adulthood following GnRH treatment and cross sex hormone treatment in adolescents with gender dysphoria. JCEM 2015

BMD and puberty suppression

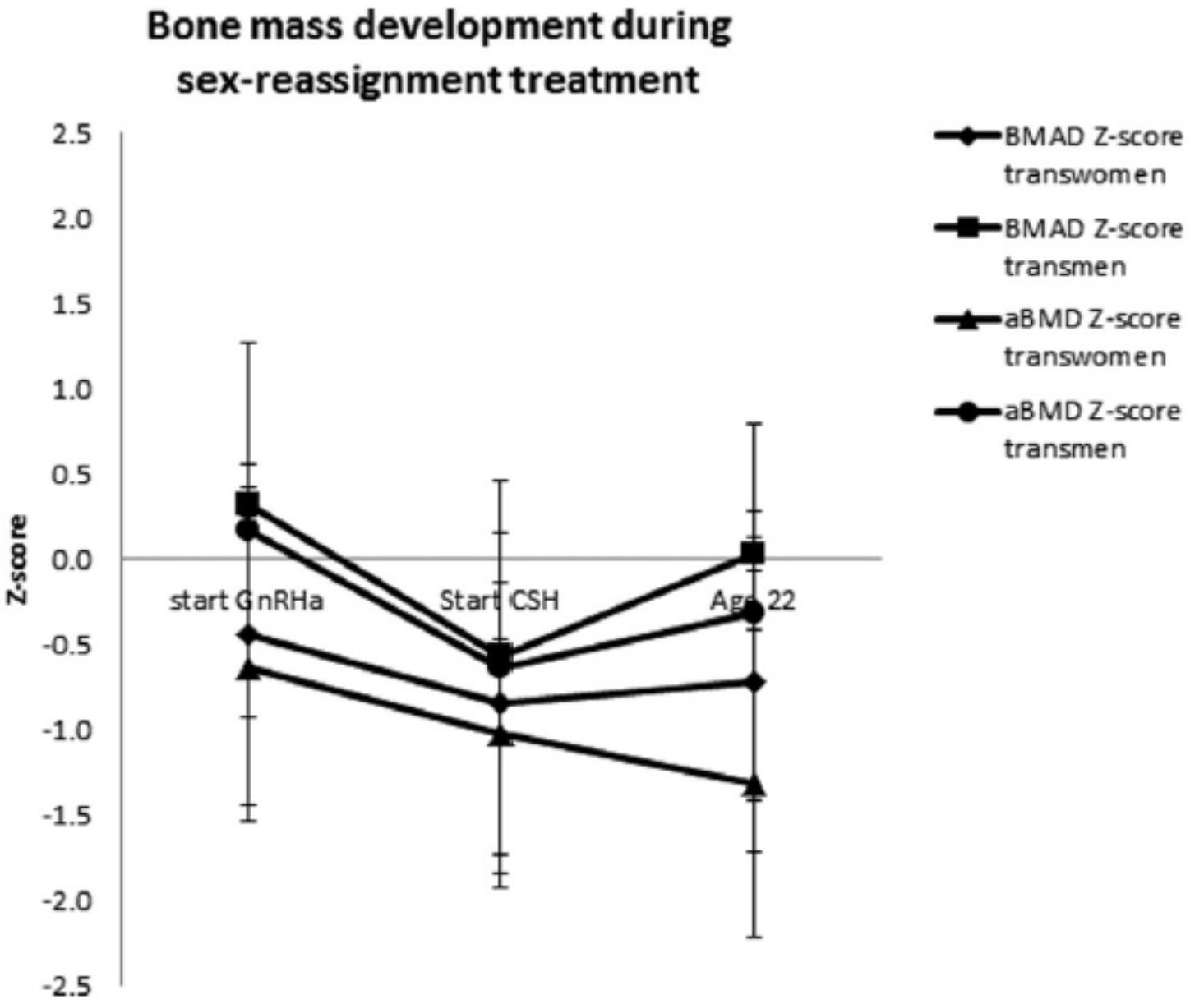


Figure 1. Longitudinal *z*-score (mean ± SD) development of the LS from start medical treatment until the age of 22 years in transmen and transwomen.

	Start GnRHa	(n)	Start CSH	(n)	Age 22 y	(n)
Transwomen						
LS						
BMAD, g/cm^3	0.22 ± 0.03	11	0.22 ± 0.02	13	0.23 ± 0.03	13
BMAD *z* score	−0.44 ± 1.10	12	−0.90 ± 0.80	14	−0.78 ± 1.03	14
Range	—		—		−2.76–1.18	14
aBMD, g/cm^2	0.84 ± 0.13	12	0.84 ± 0.11	15	0.93 ± 0.10	15
aBMD *z* score	−0.77 ± 0.89	12	−1.01 ± 0.98	13	−1.36 ± 0.83	13
Range	—		—		−3.1–0.30	13
T-score	—		—		−1.5 ± 1.10	15
Range	—	—			−3.1–0.40	15
FN						
BMAD, g/cm^3	0.28 ± 0.04	12	0.26 ± 0.04	14	0.28 ± 0.05	14
BMAD *z* score	−0.93 ± 1.22	11	−1.57 ± 1.74	10	—	—
aBMD, g/cm^2	0.88 ± 0.12	14	0.87 ± 0.08	15	0.94 ± 0.11	15
aBMD *z* score	−0.66 ± 0.77	7	−0.95 ± 0.63	11	−0.69 ± 0.74	11
Range	—		—		−2.0–0.5	11
T-score	—		—		−0.75 ± 0.78	15
Range	—		—		−2.0–0.10	15

Transmen						
LS						
BMAD, g/cm^3	0.25 ± 0.03	18	0.24 ± 0.02	19	0.25 ± 0.28	19
BMAD *z* score	0.28 ± 0.90	18	−0.50 ± 0.81	19	−0.033 ± 0.95	19
Range	—		—		−1.8–2.03	19
aBMD, g/cm^2	0.95 ± 0.12	18	0.91 ± 0.10	19	0.99 ± 0.13	19
aBMD *z* score	0.17 ± 1.18	18	−0.72 ± 0.99	19	−0.33 ± 1.12	19
Range	—		—		−2.3–2.5	19
T-score	—		—		−0.43 ± 1.2	19
Range	—		—		−2.5–0.8	19
FN						
BMAD, g/cm^3	0.32 ± 0.04	18	0.31 ± 0.04	19	0.33 ± 0.05	19
BMAD *z* score	0.01 ± 0.70	18	−0.28 ± 0.74	18	—	—
aBMD, g/cm^2	0.92 ± 0.10	18	0.88 ± 0.09	19	0.95 ± 0.10	19
aBMD *z* score	0.36 ± 0.88	13	−0.35 ± 0.79	16	−0.35 ± 0.74	16
Range	—		—		−1.80–0.80	
T-score	—		—		0.005 ± 0.87	19
Range	—		—		−1.90–1.10	19

Summary

- Transfemale –have decreased aBMD z scores compared with pretreatment level at age 22
- Transmales – trend for decrease in z scores at age 22
- Absolute bone mass stable/slight decrease with GnRH monotherapy followed by increase after start of cross sex hormone therapy
- Used natal sex as reference for aBMD z scores

Limitations

- Small numbers
- BMD at age 22 –short duration
- Compared to sex assigned at birth
- Short duration of GnRH, and started fairly late (age 15) – so difficult to know effect if started earlier
- No long term fracture data

Bone Health post gonadectomy

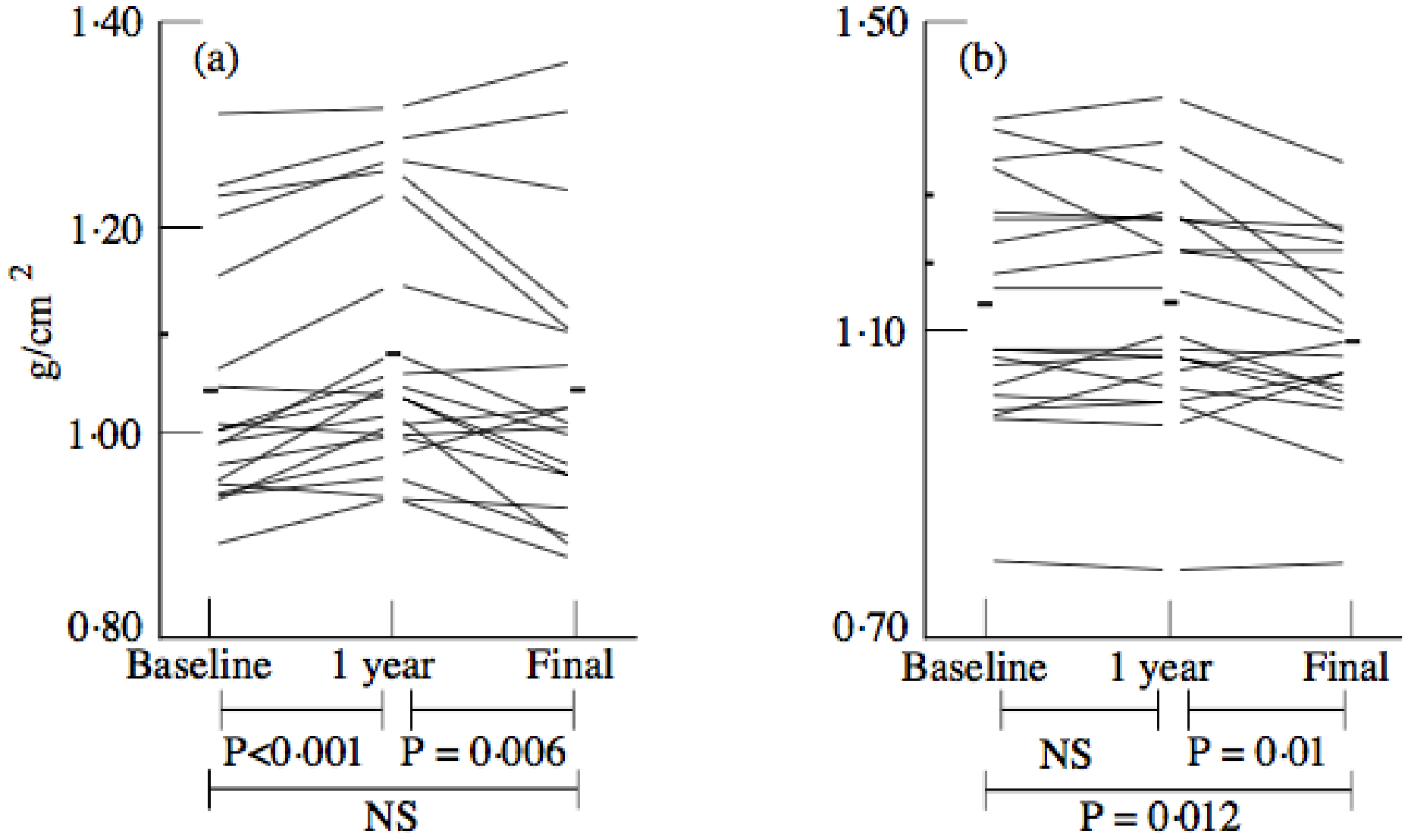
- Estrogen +/- testosterone plays important role in maintenance of bone health
- Many trans pts, post gonadectomy, have high LH/FSH levels, even though they are staying on same amount of estrogen/ testosterone
- Does this really affect their bone health?

Case

- 28 year old transman
  - Testosterone for 5 years, 100mg IM weekly
  - LH/FSH levels 5-7 range prior to surgery
  - Post oophorectomy LH 33, FSH 51
  - Total testosterone level day 3 post injection, 39 (normal 8-29), LH 20, FSH 34
  - Is he at risk for bone loss?

1998 Dutch BMD study

- Long-term follow-up of bone mineral density in transsexuals treated with cross-sex hormones
  - Van Kesteren et al, Clinical Endocrinology, 1998
- 20 trans women, 19 trans men
- BMD done baseline, 1 year after hormone therapy, and 28-63 months after
- Trans men: final measurements done 11-39 months after gonadectomy
- Trans women: final measurements done 12-44 months after gonadectomy


1·40
1·20
1·00
0·80
g/cm 2
(a)
Baseline
1 year
Final
P<0·001
P = 0·006
NS
1·50
1·10
0·70
(b)
Baseline
1 year
Final
NS
P = 0·01
P = 0·012

Study results

- LH level correlated with BMD at final measurements
- Trans men: decrease in BMD correlated to higher LH, and interpreted as inadequate testosterone to maintain bone density
- Small study
- Different estrogen/testosterone regimens

Study Design

- Trans patients planning on gonadectomy in next 12 months, age 20 and above
- Baseline BMD and hormone levels within 12months prior to surgery
- Compare to follow up BMD and hormone levels at least 1 year post surgery
- BMD done at WCH (compare both M and F reference ranges)
- Subset: bone markers pre and post as well

Exclusion

- Concomittant medications affecting BMD
  - Bisphosphonates, denosumab
  - Systemic glucocorticoid therapy
  - Chemotherapy
- Medical conditions significantly affecting BMD
  - Rheumatoid arthritis
  - Hyperthyroidism
  - Hyperparathyroidism
  - Neurologic disease causing paralysis
  - Multiple myeloma

Outcome measures

- Change in BMD between baseline and post surgery
- Change in gonadotropin and sex hormone levels between baseline and post surgery, and if these are correlated to BMD
- Change in bone turnover markers at baseline and post surgery, and if these are correlated with BMD

Target Sample Size

- 110 trans men and 110 trans women
- Allowing for 10% drop out rate

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Newer Data

http://www.exactdrive.com/news/steps-to-implement-a-data-strategy-into-your-programmatic-media-buys

Meta-analysis on bone health in transgender individuals

- Search up to April 2015, studies on bone health in transgender individuals receiving sex steroids
- adolescents and adult, transwomen (estrogen, antiandrogens) and transmen (testosterone)
- Baseline BMD, to post therapy BMD, or compared trans individuals to a reference group
- Random effects model used to pool weighted mean differences

Singh-Ospina, Naykky et al. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. JCEM Nov 2017

Results

- 391 studies – included 13
- 392 transwomen (9 studies), and 247 transmen (8 studies)
- 12 studies evaluated change in BMD over time, and on evaluated fracture rates, all observation
- 11 – before and after treatment comparisons of the same patients; 2 compared trans individuals to controls

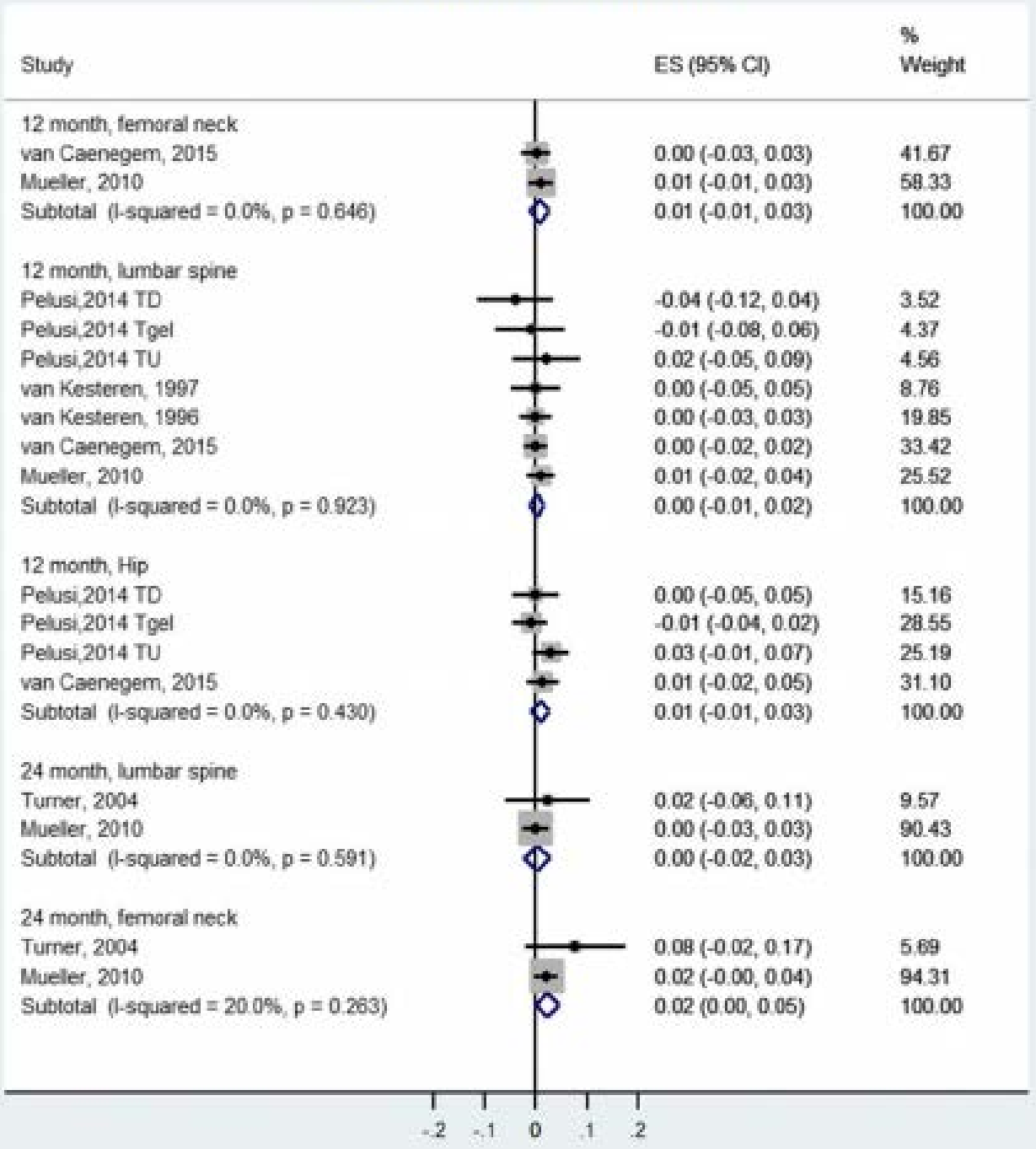
Results

- Mean age ranged from 19 to 43 years
- Outcome assessments were performed at 12, 24 months for majority of studies
- Risk of bias – moderate
- Cohorts represented totality of practice as opposed to selected cases

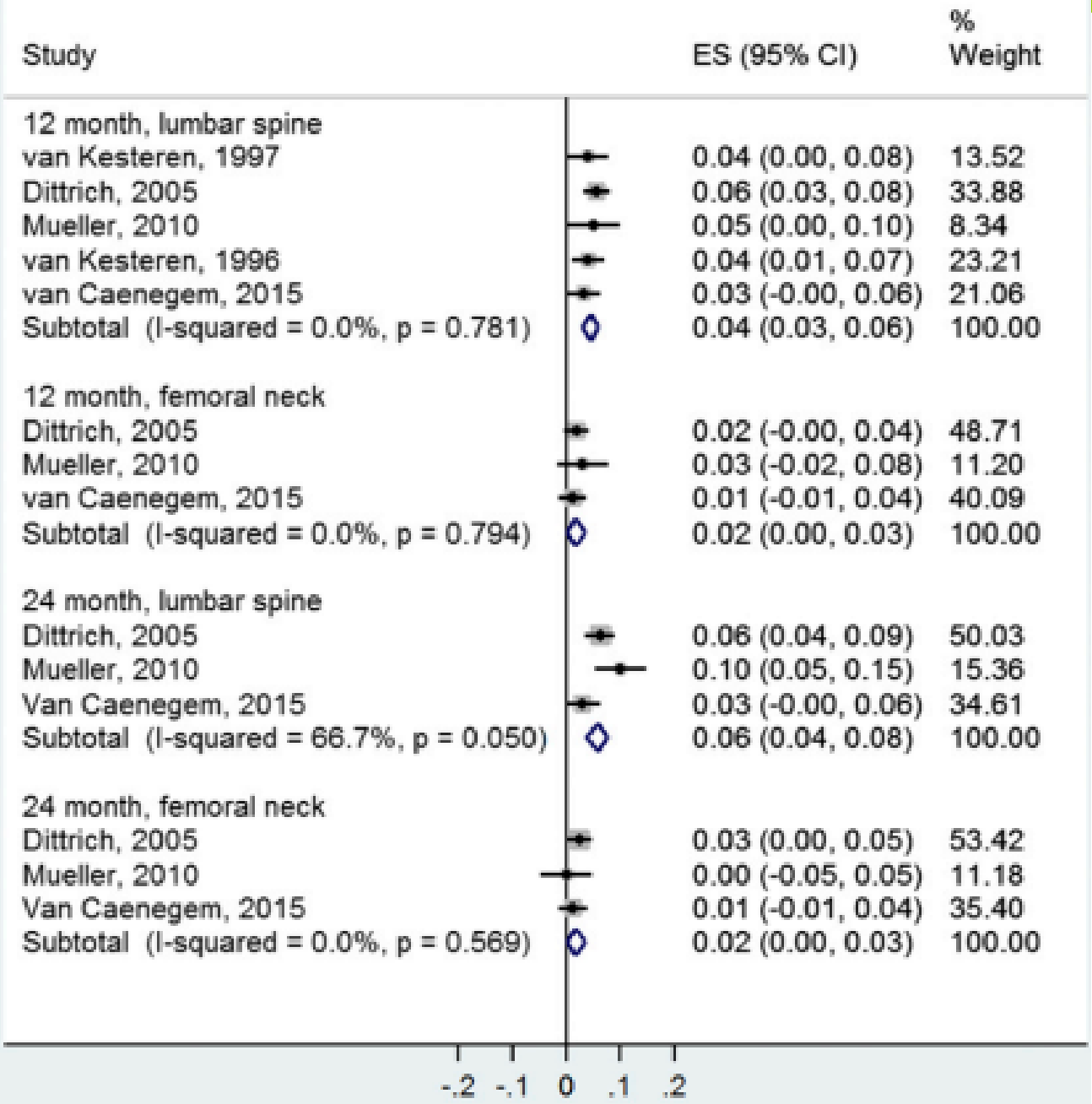
Results

- Transmen – no significant changes in BMD in LS, fem neck, total hip BMD at 12 and 24 months
- Transwomen – significant increase
  - At lumbar spine
    - 12 months: 0.04 g/cm2 (0.03-0.06)
    - 24 months: 0.06 g/cm2 (0.04-0.08)
  - Fem neck – not significant
- Transwomen compared to control group (sex at birth) – not statistically significant different

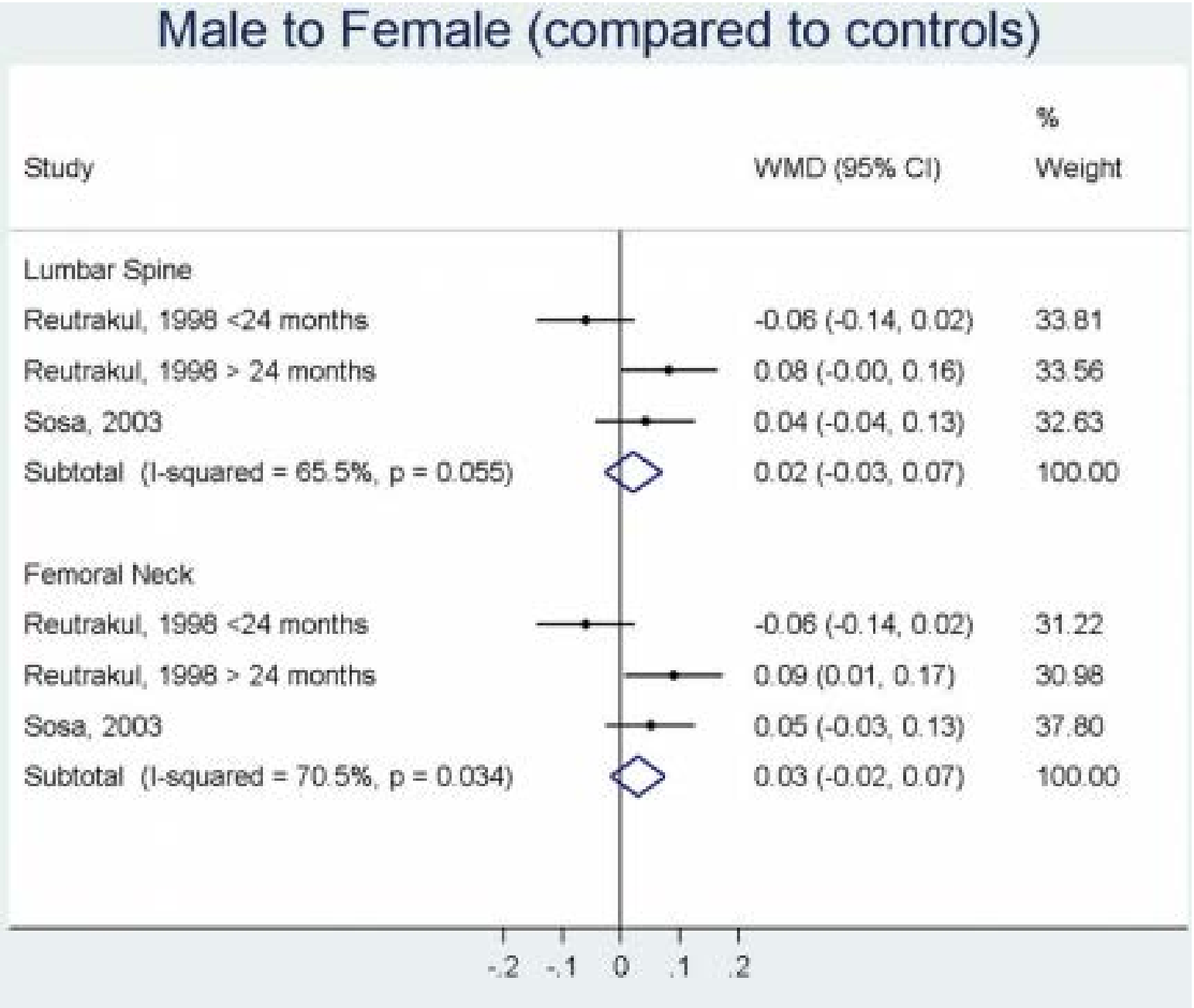
Female to Male



Male to Female



Male to Female (compared to controls)



Results

- One study looked at fracture rates in 53 transwomen and 53 transmen over 1 year with no fractures in either group

Summary

- Majority of studies – looked at effects of sex steroids on BMD in young individuals
- Transmen – no significant change at 12-24 months
- Transwomen – increase in BMD at lumbar spine at 12, 24 months, no change in fem neck/hip
- Long term effects, fracture rates unknown

Longitudinal 10 year study

- Retrospective data, Netherlands, since 1998 -2016
- BMD at start of HxT, 2, 5, 10yrs post
- gonadectomy could be obtained after 1-1.5 years of hormone therapy
- Transwomen – oral or transdermal estrogen, anti-androgen
- Transmen – oral, transderma, or IM testosterone

Wiepjes, C et al. Bone Safety During the First Ten Years of Gender-Affirming Hormonal Treatment in Transwomen and Transmen. *J Bone Mineral Research, 2018*

BMD

- Obtained before start of HT (1 yr prior, 4 mon after)
- 2 yr (1-3yr), 5 yr (3-7.5yr), 10 yr (7.5-12yr)
- DXA Hologic Delphi, updated in 2004, replaced by Hologic Discovery A in 2011, phantom calibration allowed for comparison of BMD values with difference of < 1.0%
- T and Z scores were calculated based on birth-sex reference range population (NHANES)

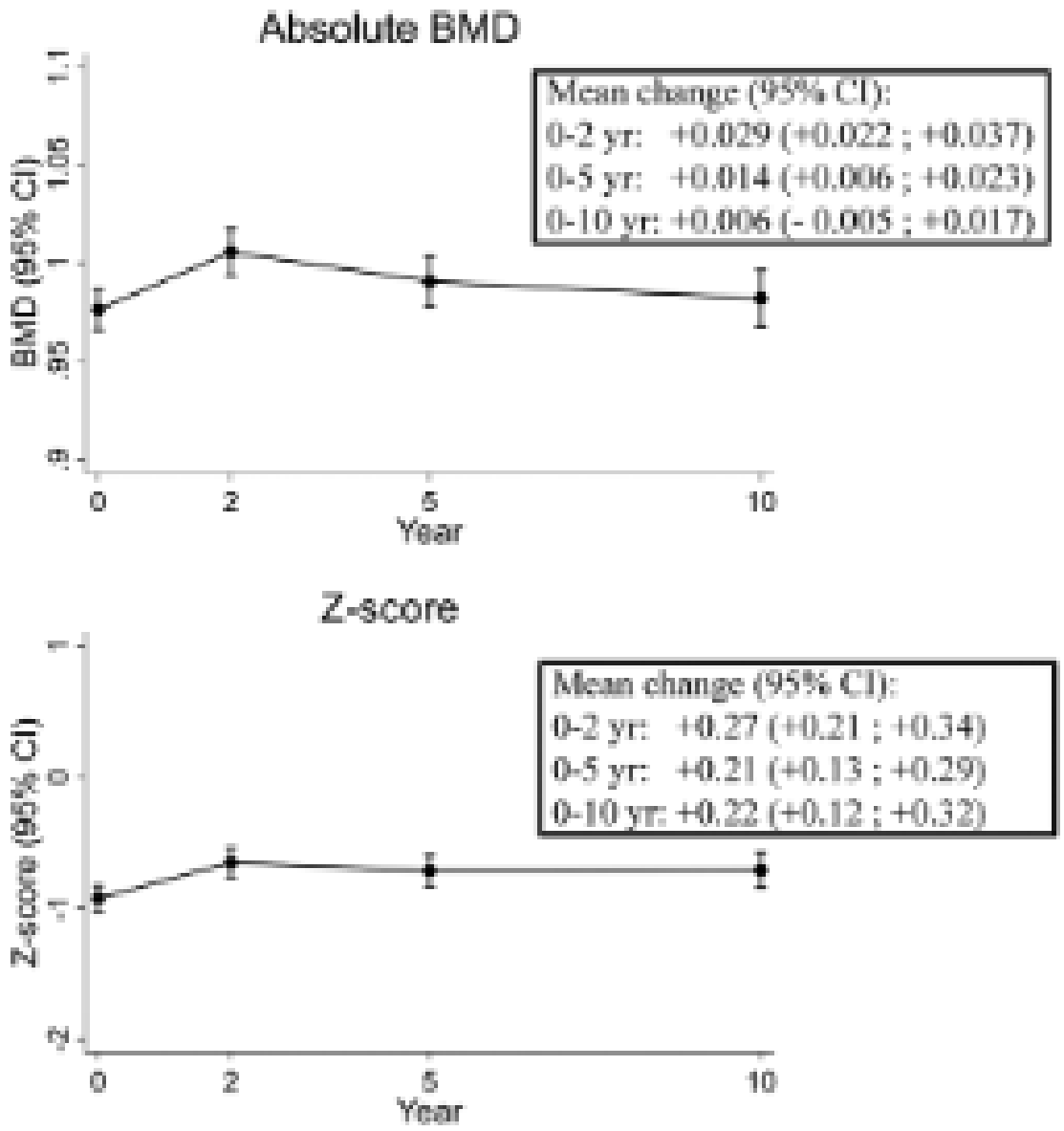
Results: cohort

- 711 transwomen
  - 2 years: 234 (33%)
  - 5 years: 174 (24%)
  - 10 years: 102 (14%)
- 543 transmen
  - 2 years: 236 (43%)
  - 5 years: 95 (17%)
  - 10 years: 70 (13%)

Baseline characteristics	Transwomen		Transmen	
Age (years), median (IQR)	35 (26–46)		25 (21–34)	
Ethnicity, white (%)	97.2		95.2	
BMI (kg/m^2), mean ± SD	23.7 (4.3)		25.6 (5.7)	
Smoking, yes (%)	34.9		39.5	
Bone mineral density	Male reference	Female reference	Male reference	Female reference
Lumbar spine, mean ± SD				
Absolute BMD (g/cm^2)	0.976 ± 0.140		1.030 ± 0.127	
T-score	−1.07 ± 1.27	−0.67 ± 1.27	−0.61 ± 1.14	−0.20 ± 1.14
Z-score	−0.93 ± 1.32	−0.31 ± 1.39	−0.54 ± 1.15	+0.01 ± 1.14
Total hip, mean ± SD				
Absolute BMD (g/cm^2)	0.928 ± 0.136		0.948 ± 0.118	
T-score	−0.72 ± 0.89	−0.13 ± 1.09	−0.61 ± 0.75	+0.01 ± 0.92
Z-score	−0.58 ± 0.92	+0.07 ± 1.16	−0.55 ± 0.76	+0.07 ± 0.93
Femoral neck, mean ± SD				
Absolute BMD (g/cm^2)	0.789 ± 0.129		0.838 ± 0.118	
T-score	−1.06 ± 0.93	−0.56 ± 1.14	−0.72 ± 0.83	−0.14 ± 1.02
Z-score	−0.73 ± 0.94	−0.25 ± 1.16	−0.59 ± 0.85	−0.05 ± 1.02
Osteoporosis (%)	14.2	5.8	5.2	2.4
Low bone density (%)	21.9	9.4	10.3	4.3

Baseline characteristics	Transwomen		Transmen	
Laboratory measurements[a]	Baseline	During HT	Baseline	During HT
Estradiol (pmol/L), median (IQR)	95 (68–124)	235 (160–338)	185 (59–390)	159 (113–220)
Testosterone (nmol/L), median (IQR)	20 (16–25)	1.1 (0.7–1.3)	1.3 (1.2–1.7)	26 (18–38)
LH (U/L), median (IQR)	3.4 (2.3–4.6)	1.2 (0.1–6.2)	4.2 (2.4–7.1)	3.3 (0.7–8.8)
25(OH)D (nmol/L), median (IQR)	42 (26–58)	53 (35–72)	50 (30–73)	57 (40–78)
Calcium (mmol/L), mean ± SD	2.36 (0.08)	2.32 (0.08)	2.34 (0.08)	2.36 (0.08)
Creatinine (μmol/L), mean ± SD	76 (11)	72 (11)	66 (10)	78 (11)
AF (U/L), mean ± SD	71 (19)	67 (23)	70 (22)	78 (21)
SHBG (nmol/L), median (IQR)	35 (26–46)	43 (29–59)	51 (31–81)	28 (20–36)

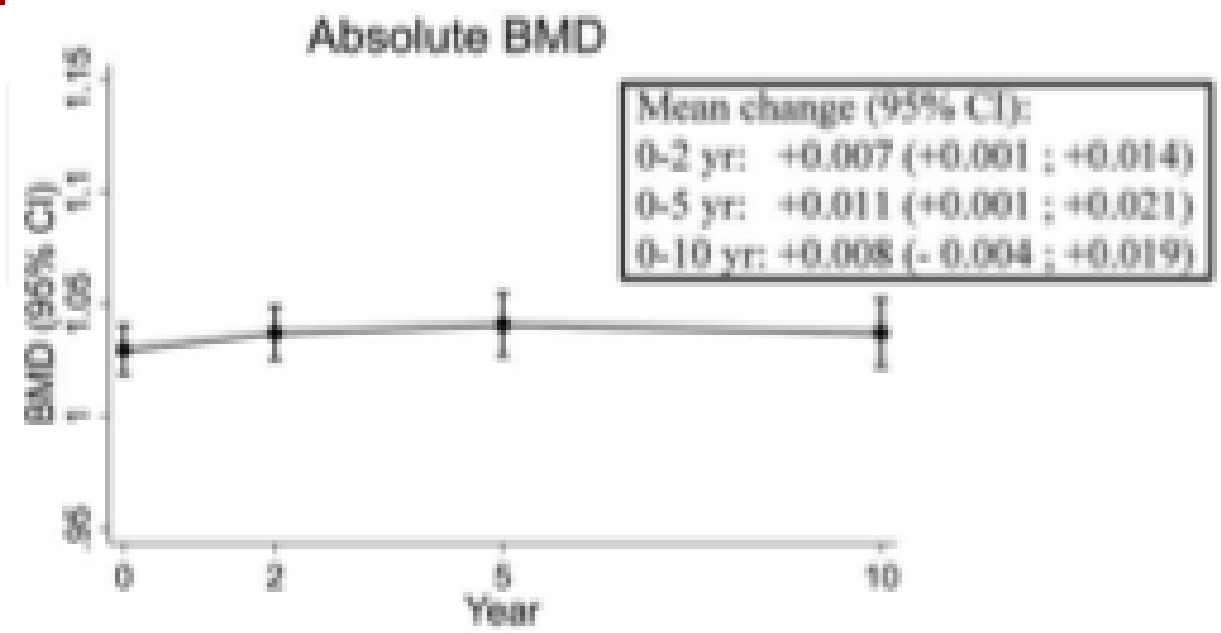
Transwomen

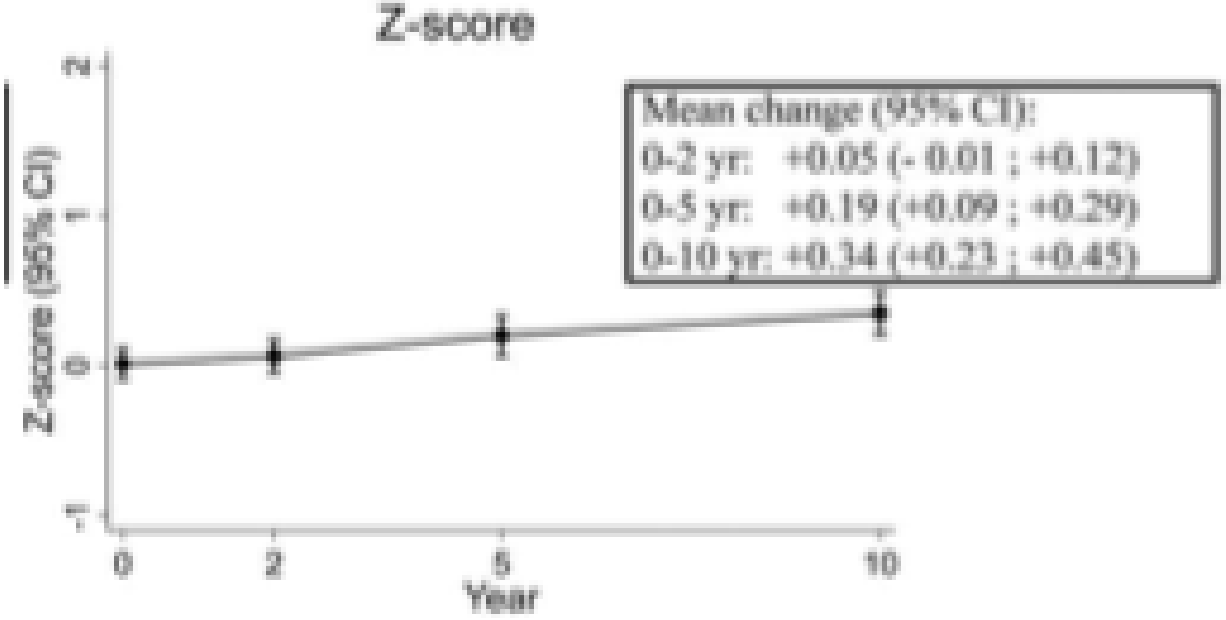

Absolute BMD
Mean change (95% CI):
0-2 yr: +0.029 (+0.022 ; +0.037)
0-5 yr: +0.014 (+0.006 ; +0.023)
0-10 yr: +0.006 (- 0.005 ; +0.017)
BMD (95% CI)
.9
.95
1
1.05
1.1
0
2
5
10
Year
Z-score
Mean change (95% CI):
0-2 yr: +0.27 (+0.21 ; +0.34)
0-5 yr: +0.21 (+0.13 ; +0.29)
0-10 yr: +0.22 (+0.12 ; +0.32)
Z-score (95% CI)
-.2
-.1
0
1
0
2
5
10
Year

Transwomen- LS

- At 10 yrs compared to baseline
  - BMD +0.006g/cm^2 (-0.005 to +0.017) –same
  - Z score: +0.22 (0.12-0.32) - increased
- Stratified age groups (<30, 30-40, >40) – no difference
- Tertile estradiol levels:
  - Highest tertile: + 0.044g/cm^2 (0.025 – 0.063)
  - Lowest tertile : -0.026g/cm^2 (-0.044 to -0.009)
- Multivariate analysis: no diff found in age, testosterone, LH; higher estradiol tertile associated with larger increase in LS BMD than lower

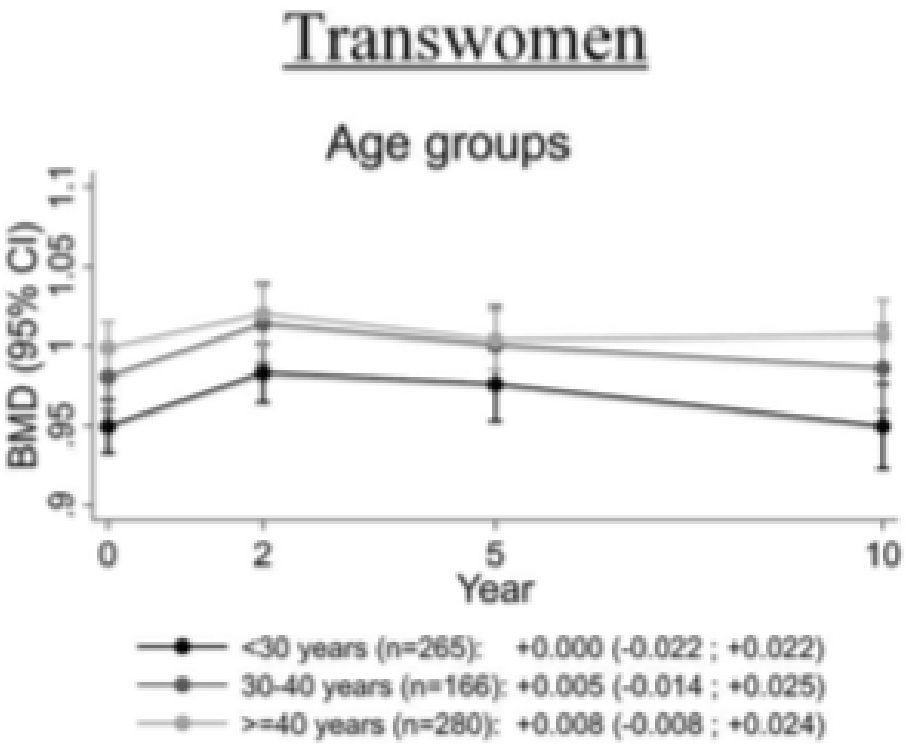
Transmen

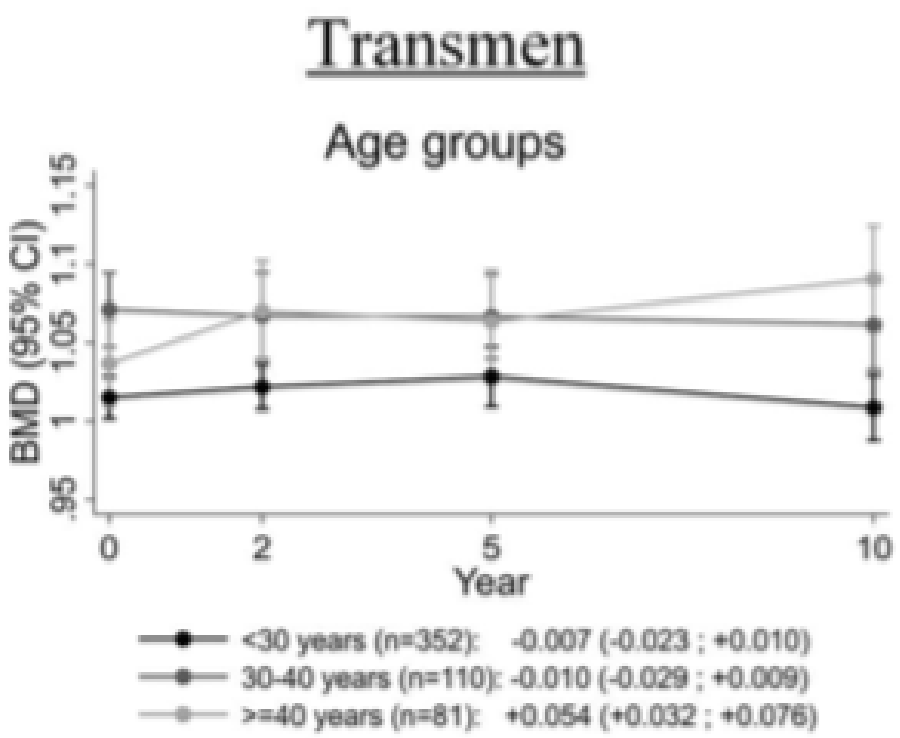

Absolute BMD
Mean change (95% CI):
0-2 yr: +0.007 (+0.001 ; +0.014)
0-5 yr: +0.011 (+0.001 ; +0.021)
0-10 yr: +0.008 (- 0.004 ; +0.019)
BMD (95% CI)
.95
1
1.05
1.1
1.15
0
2
5
10
Year

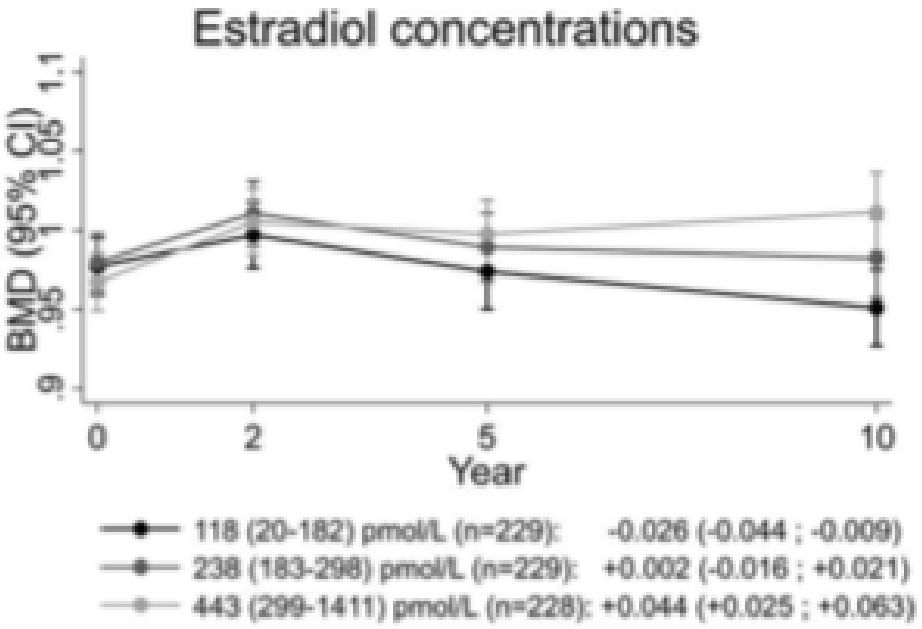

Z-score
Mean change (95% CI):
0-2 yr: +0.05 (- 0.01 ; +0.12)
0-5 yr: +0.19 (+0.09 ; +0.29)
0-10 yr: +0.34 (+0.23 ; +0.45)
Z-score (95% CI)
-1
0
1
2
0
2
5
10
Year

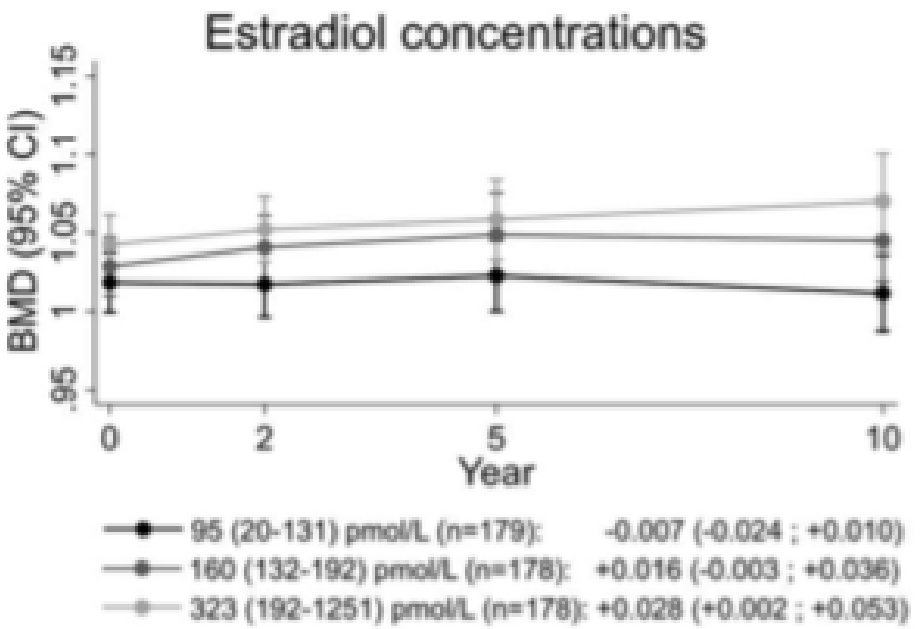
Transmen - LS

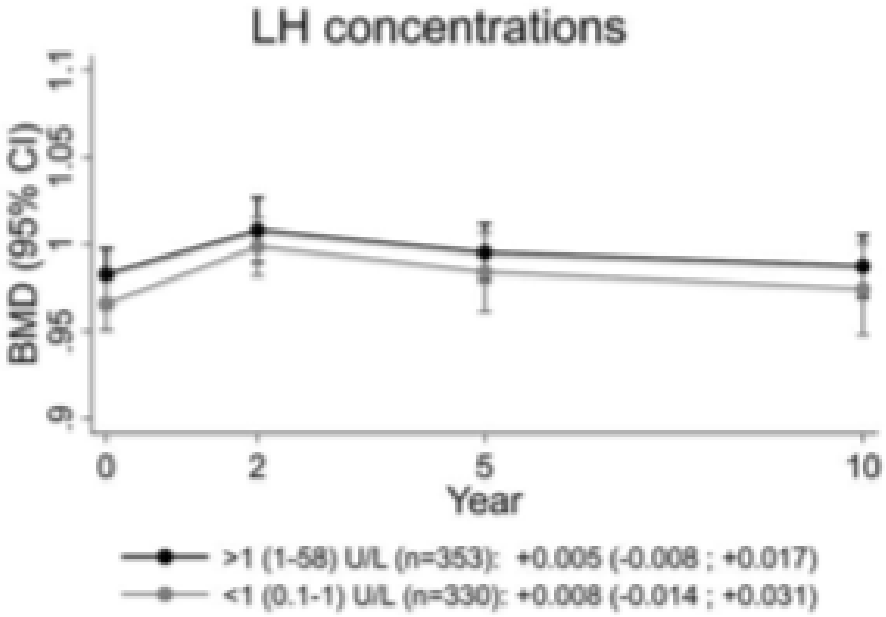
- At 10 years compared to baseline
  - BMD +0.008g/cm^2 (-0.004 to +0.019) -same
  - Z score: +0.34 (+0.23 to +0.45) – increased
- Age >40 yrs
  - BMD increased +0.054g/cm^2 (0.032 to 0.076) compared with no change in younger age groups
- Estradiol Tertiles
  - Highest estradiol tertile increased BMD, no change in lower tertiles
- Testosterone – not associated with change in LS BMD
- Suppressed LH (<1) associated with increase in LS BMD, no change in those with higher LH
- Lowest baseline tertile BMD – had increased BMD, other tertiles did not

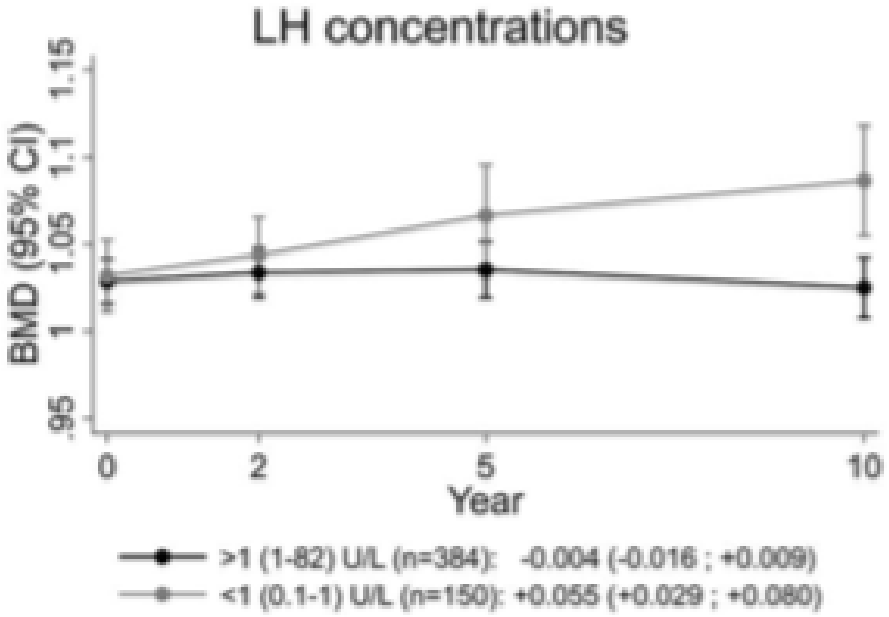

Transwomen
Age groups
BMD (95% CI)
.9
.95
1
1.05
1.1
0
2
5
10
Year
<30 years (n=265): +0.000 (-0.022 ; +0.022)
30-40 years (n=166): +0.005 (-0.014 ; +0.025)
>=40 years (n=280): +0.008 (-0.008 ; +0.024)


Transmen
Age groups
BMD (95% CI)
.95
1
1.05
1.1
1.15
0
2
5
10
Year
<30 years (n=352): -0.007 (-0.023 ; +0.010)
30-40 years (n=110): -0.010 (-0.029 ; +0.009)
>=40 years (n=81): +0.054 (+0.032 ; +0.076)


Estradiol concentrations
BMD (95% CI)
.9
.95
1
1.05
1.1
0
2
5
10
Year
118 (20-182) pmol/L (n=229): -0.026 (-0.044 ; -0.009)
238 (183-298) pmol/L (n=229): +0.002 (-0.016 ; +0.021)
443 (299-1411) pmol/L (n=228): +0.044 (+0.025 ; +0.063)


Estradiol concentrations
BMD (95% CI)
.95
1
1.05
1.1
1.15
0
2
5
10
Year
95 (20-131) pmol/L (n=179): -0.007 (-0.024 ; +0.010)
160 (132-192) pmol/L (n=178): +0.016 (-0.003 ; +0.036)
323 (192-1251) pmol/L (n=178): +0.028 (+0.002 ; +0.053)


LH concentrations
BMD (95% CI)
.9
.95
1
1.05
1.1
0
2
5
10
Year
>1 (1-58) U/L (n=353): +0.005 (-0.008 ; +0.017)
<1 (0.1-1) U/L (n=330): +0.008 (-0.014 ; +0.031)

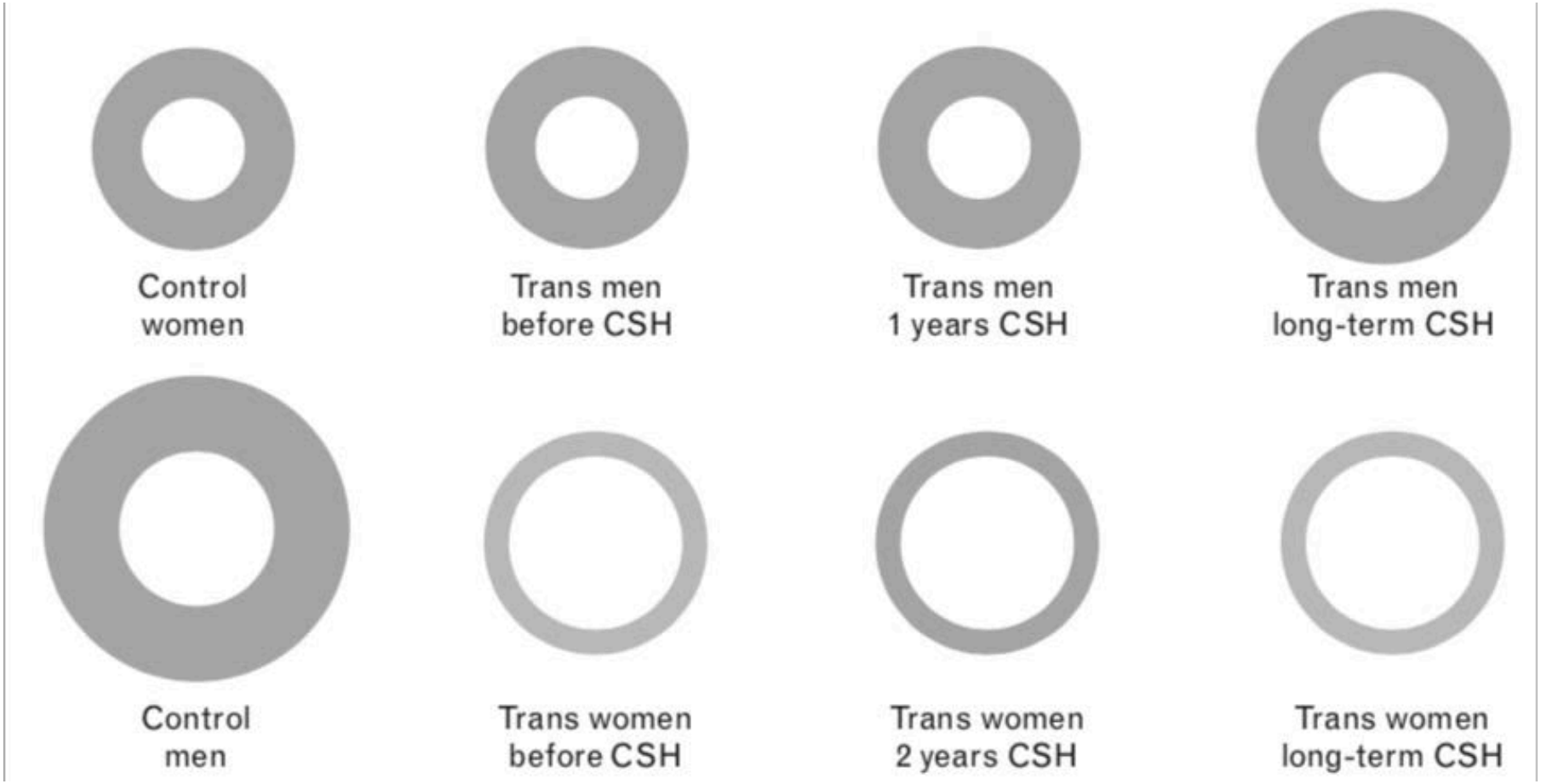

LH concentrations
BMD (95% CI)
.95
1
1.05
1.1
1.15
0
2
5
10
Year
>1 (1-82) U/L (n=384): -0.004 (-0.016 ; +0.009)
<1 (0.1-1) U/L (n=150): +0.055 (+0.029 ; +0.080)

Discussion

- Lumbar spine Z scores increased in both transmen and transwomen during 10 yrs of HxT
- Used comparison to sex assigned at birth (most had attained peak bone mass at baseline prior to start of hormone therapy)
- Natural course of BMD is to decreased after attaining peak bone mass
- However, BMD did not change over 10 yrs, so Z scores increased
- Likely indicates no negative influence of hormone therapy on BMD
- Low BMD found in transwomen at baseline
  - Consistent with previous studies
  - Lower 25 OH vit D, lower muscle mass than control cis men, ? Decreased physical activity

Discussion

- Highest increase in BMD was found in those age 50 and older
- May be explained by higher sex hormone levels in persons on HxT compared with age matched cisgender persons
- Cis-women would be peri/postmenopausal while transmen at same started testosterone



Overview of bone geometry – Trans men and women

Caenegem, E. T'Sjoen, G. Bone in trans persons. Current opinion in endocrinology, 2015

Questions left unanswered

- Long term, fracture data
- Pediatric/adolescent data
- New normative data for transgender individuals that relate to fracture risk

BEYOND THE BREAK

- This webinar will be archived within 1-3 business days.
- Find all our archived sessions at http://osteostrategy.on.ca/btb-main
- If you haven't done so already, please complete an evaluation survey at https://www.surveymonkey.com/r/btbwebinar
- If you have questions about Beyond the Break, please contact Kevin at kng@osteoporosis.ca

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