Belgian Menopause Society 23 November 2024

Sex steroid levels in menopause: what can we measure and how? Treatment targets?

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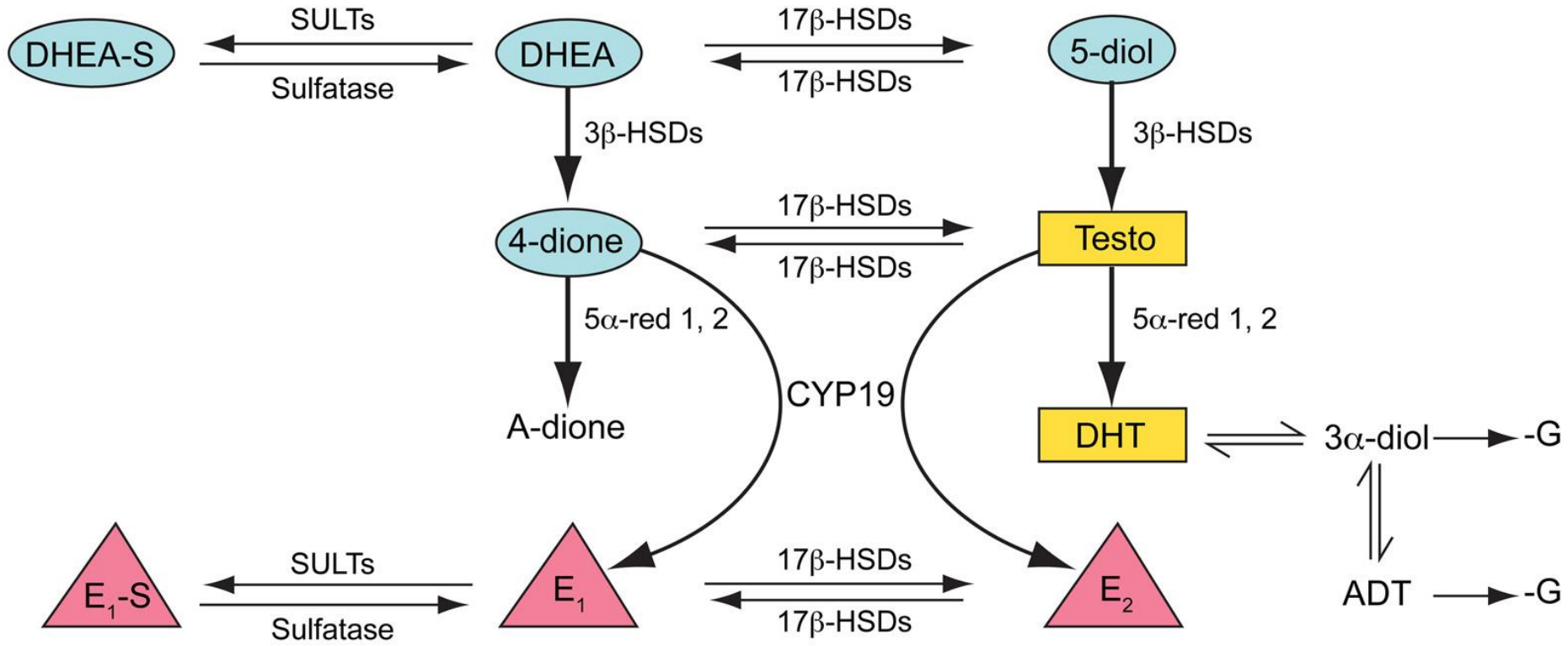
No disclosures

Sex steroid levels after menopause

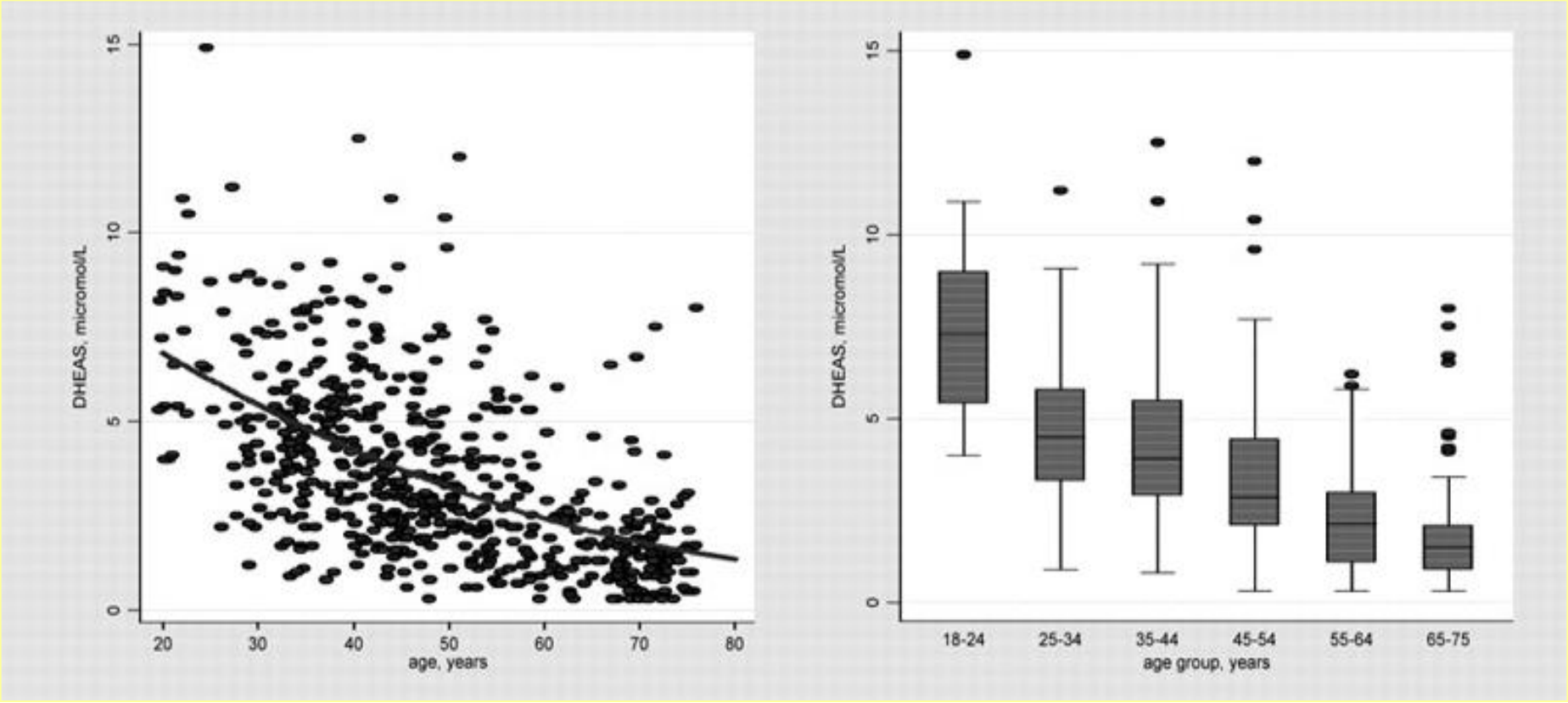
- Analytical aspects
- Endogenous estrogens after menopause
  - and menopausal symptoms
  - and cardiovascular health
  - and breast
  - and bone
- Estrogen therapy
- Endogenous and exogenous testosterone

Sources of estrogens after menopause



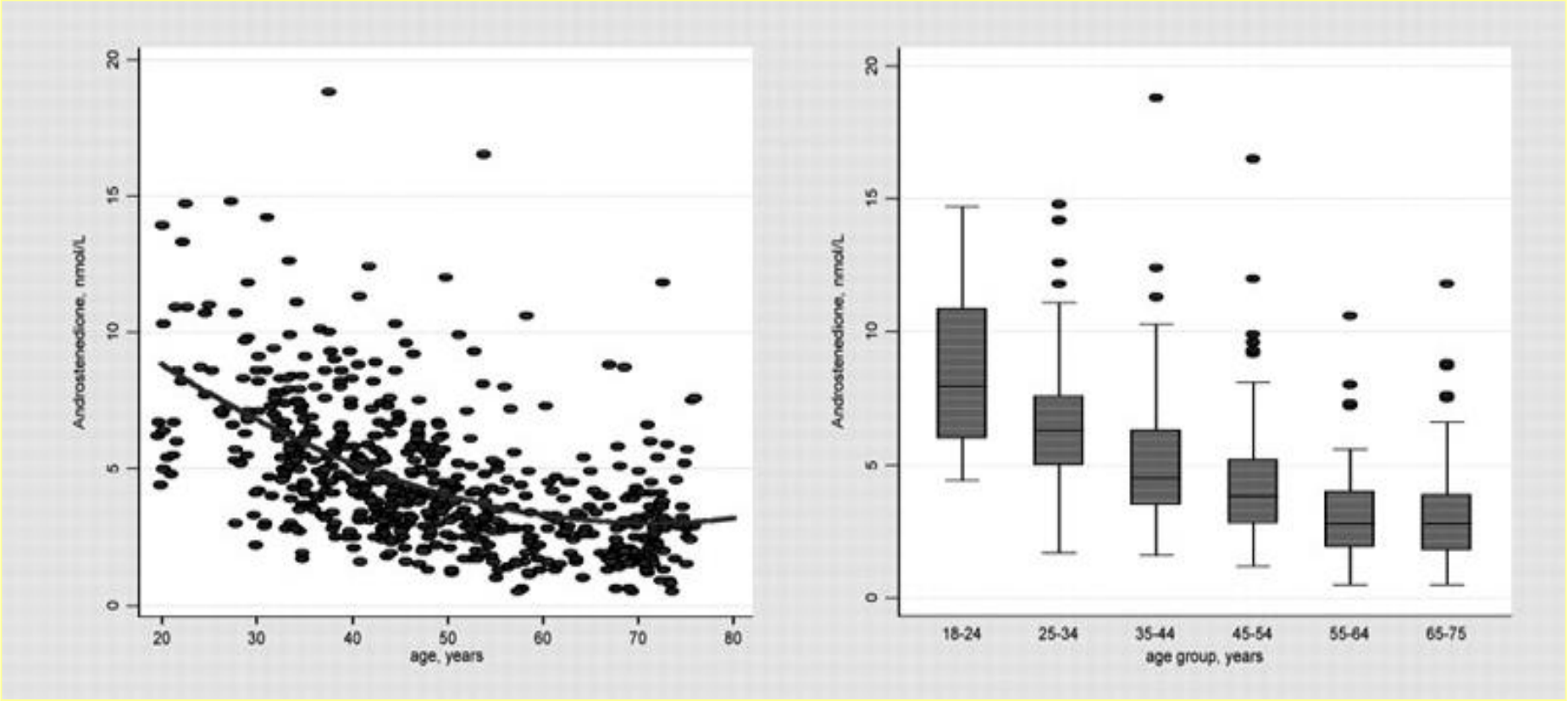
From Audet-Walsh et al J Clin Endocrinol Metab 2011; 96:E330-39

Decline of estrogen precursors with aging: DHEAS



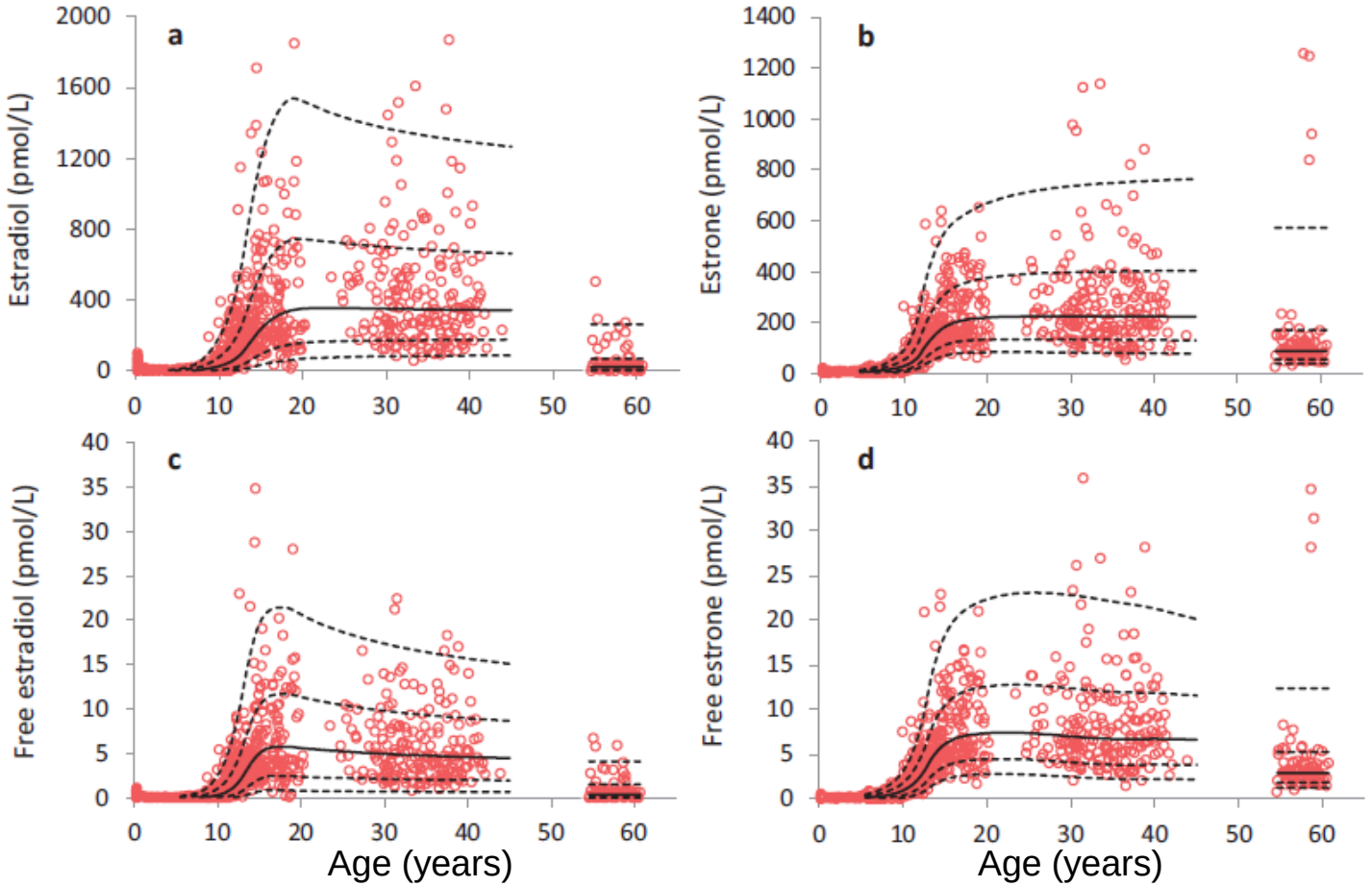
Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853

Decline of estrogen precursors with aging: androstenedione



Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853

Estrogen levels from infancy to late adulthood determined by LC-MS/MS



Frederiksen et al J Clin Endocrinol Metab 2020;105:1-15

1970

Extraction (1-2 ml serum)
Separation
RIA – tritiated tracer

1980

Direct RIA's ^{125}I-tracer
(50 – 100 µl serum)

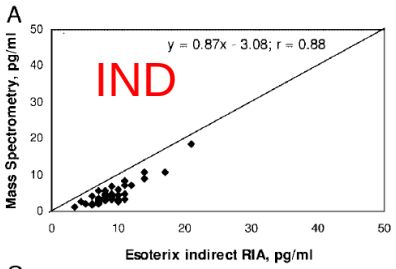
1990

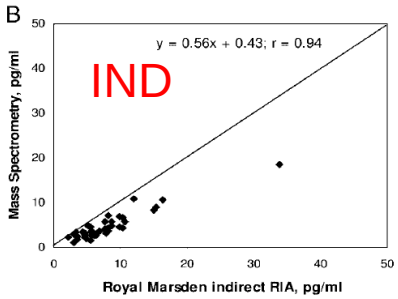
"Cold" RIA methods
Non-isotopic tracer-labels
Automated platforms
(20-50 µl serum)

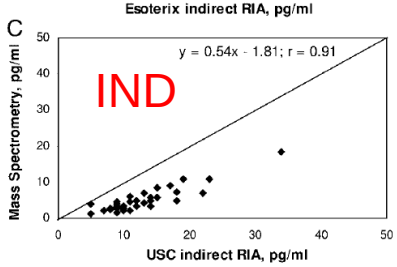
2000

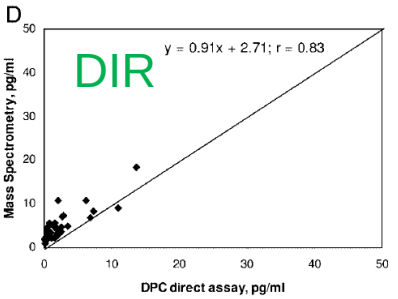
Liquid chromatography
Tandem mass spectrometry
LC-MS/MS (100-200µl serum)

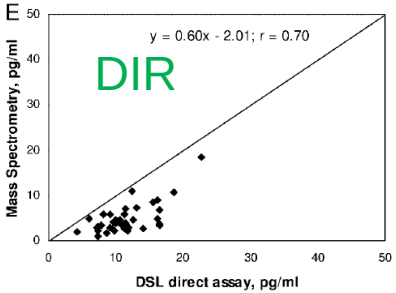
Comparison of methods to measure low serum levels estradiol in postmenopausal women: direct and indirect immunoassay *versus* GC-MSMS

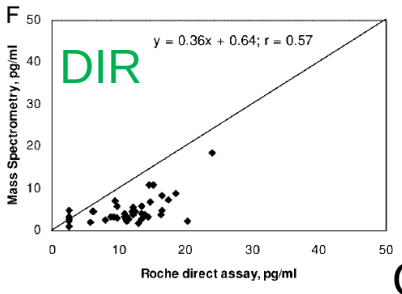


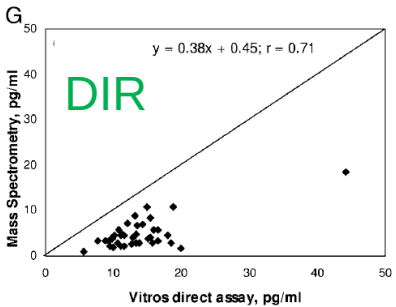




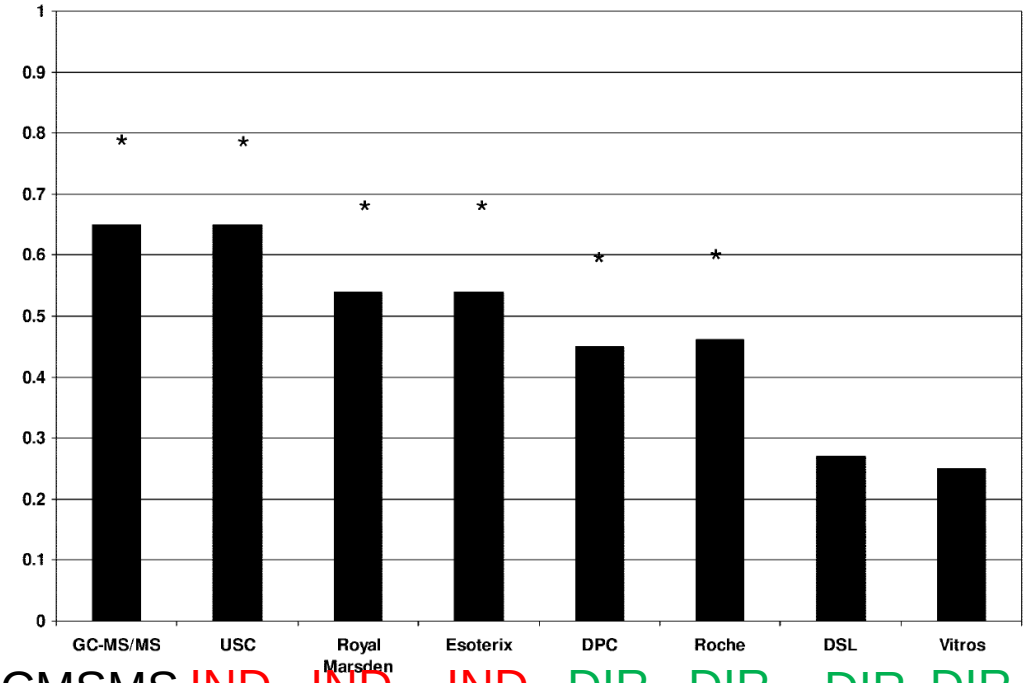








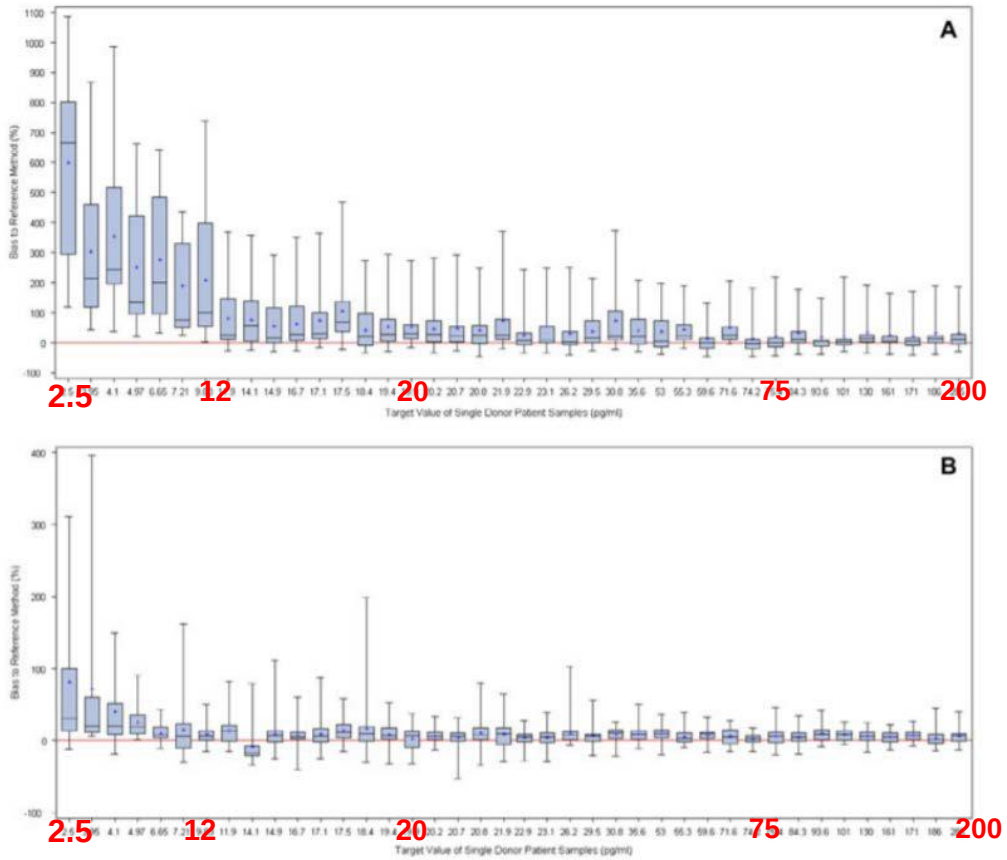
Pearson Corr. Coeff. E2 vs BMI according to E2 assay



GCMSMS IND IND IND DIR DIR DIR DIR

Lee et al J Clin Endocrinol Metab 2006;91:3791-3797

% bias relative to target



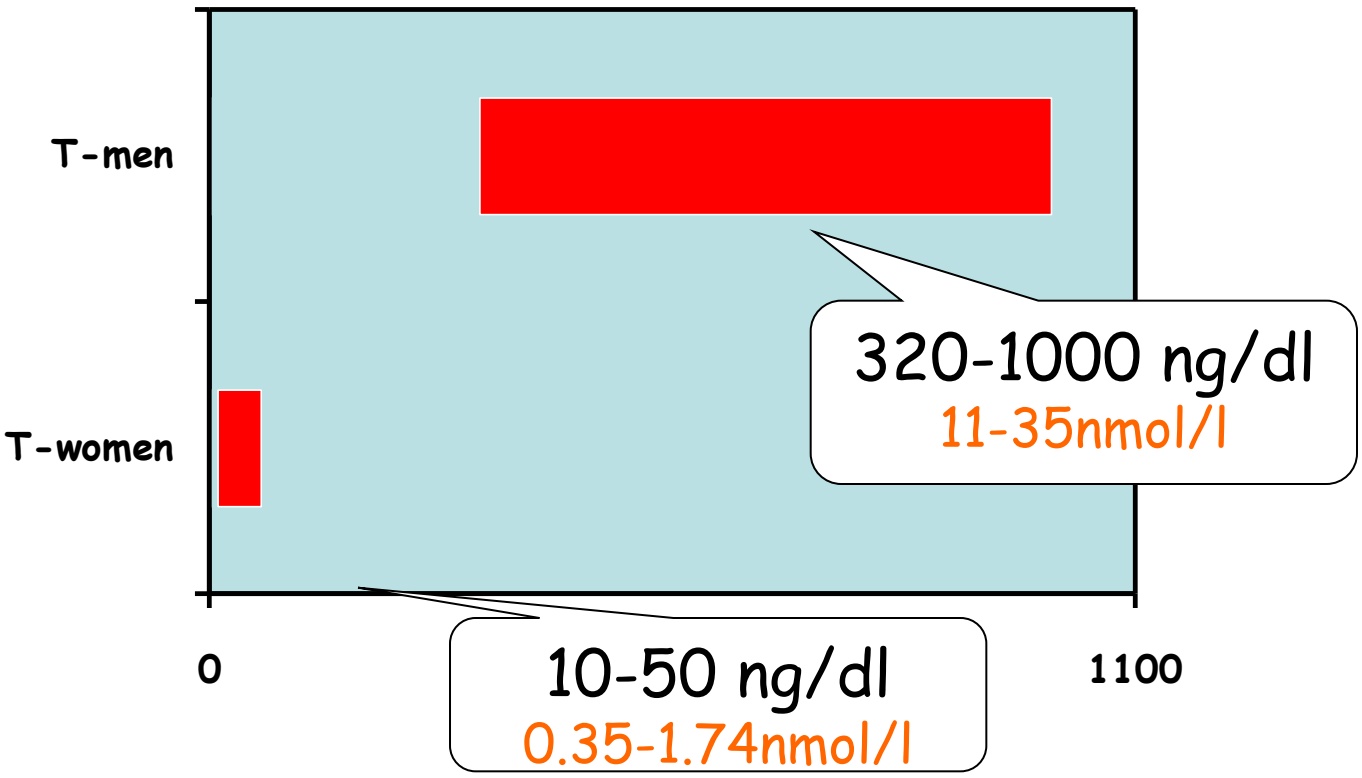
Immunoassays

Mass spectrometry

Target value (pg/ml)

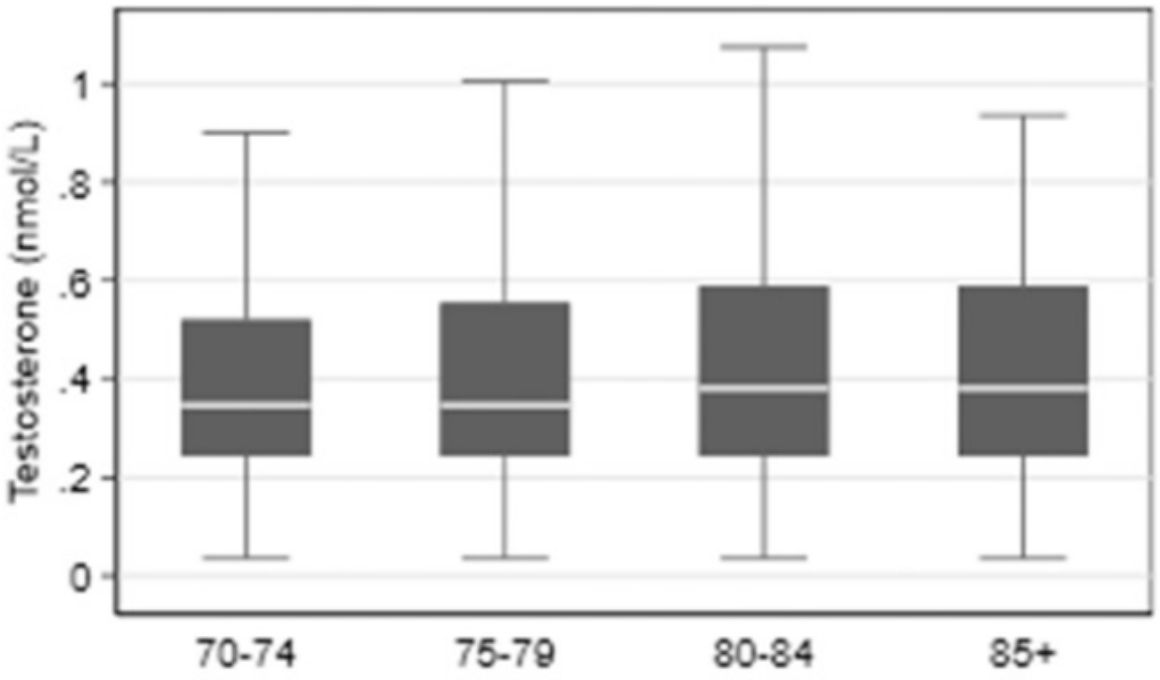
Bias distribution of individual E2 results by sample and assay technology (Panel A: Immunoassays, Panel B: Mass spectrometry assays). Vesper et al, Steroids, 2014

The low testosterone levels in women



Testosterone after age 70y (by LC-MS/MS)

1nmol/L = 29ng/dL



Davis et al J Clin Endocrinol Metab 2019;104:6291-6300

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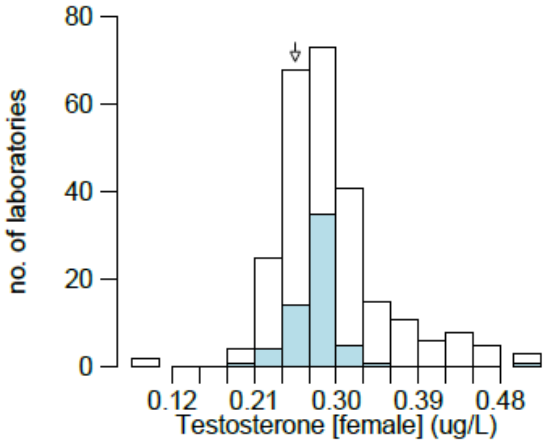
Specimen : 521B

	n	Mean	SD	CV(%)
All methods [ALTM]	259	0.292	0.050	17.2
Abbott Alinity [AB20]	48	0.317	0.021	6.6
Abbott Architect [AB13]	9	0.369	0.028	7.7
Beckman Access/Dxi [SF1]	20	0.426	0.036	8.5
Mass Spectrometry [MS2]	61	0.279	0.020	7.3
QuidelOrtho [AM12]	6	0.321	0.057	17.9
Roche Cobas Pro [RO20]	5	0.284	0.012	4.2
Roche Cobas [BO5]	75	0.265	0.024	8.9
Siemens ADVIA Centaur [CO10]	14	0.234	0.028	12.0
Siemens Atellica [SM20]	18	0.256	0.037	14.6
non-numeric results	5			



Your result	0.26275
Target (Mass Spectrometry [MS2])	0.279
Standard Uncertainty	0.003
Your specimen: %bias	-5.8
Accuracy Index	24
Your method mean Mass Spectrometry [MS2]	0.279

The Relationship of Longitudinal Change in Reproductive Hormones and Vasomotor Symptoms during the Menopausal Transition

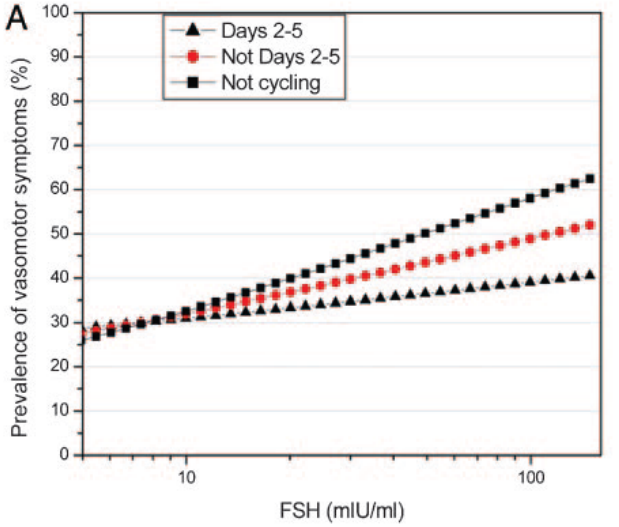


TABLE 4. Estimated odds ratios (OR) of reporting VMSs for selected variables when both FSH and E2 are included in the multivariate model[a]

Estimated parameter	OR (95% CI)
Day of phlebotomy	
D 2–5 of cycle	0.50 (0.42, 0.60)
Not d 2–5 of cycle	0.60 (0.49, 0.73)
Women with no menses for 3+ months	0.66 (0.49, 0.89)
Log (FSH) effect	
D 2–5 of cycle	1.19 (1.09, 1.30)
Not d 2–5 of cycle	1.33 (1.21, 1.46)
Women with no menses for 3+ months	1.60 (1.33, 1.93)
Log (E2) effect	
D 2–5 of cycle	1.03 (0.96, 1.11)
Not d 2–5 of cycle	0.96 (0.87, 1.05)
Women with no menses for 3+ months	1.02 (0.88, 1.18)
Age	1.07 (1.05, 1.09)
BMI	1.02 (1.02, 1.03)
Ethnicity (Caucasian as reference)	
African-Americans	1.47 (1.26, 1.73)
Chinese	0.83 (0.61, 1.13)
Hispanics	1.21 (0.84, 1.74)
Japanese	0.70 (0.52, 0.94)
Smoking (never as reference)	
Current	1.53 (1.30, 1.81)
Past	1.33 (1.16, 1.54)
Difficulty paying for basics (not hard at all as a reference)	
Somewhat hard	1.18 (1.03, 1.35)
Very hard	1.48 (1.18, 1.85)

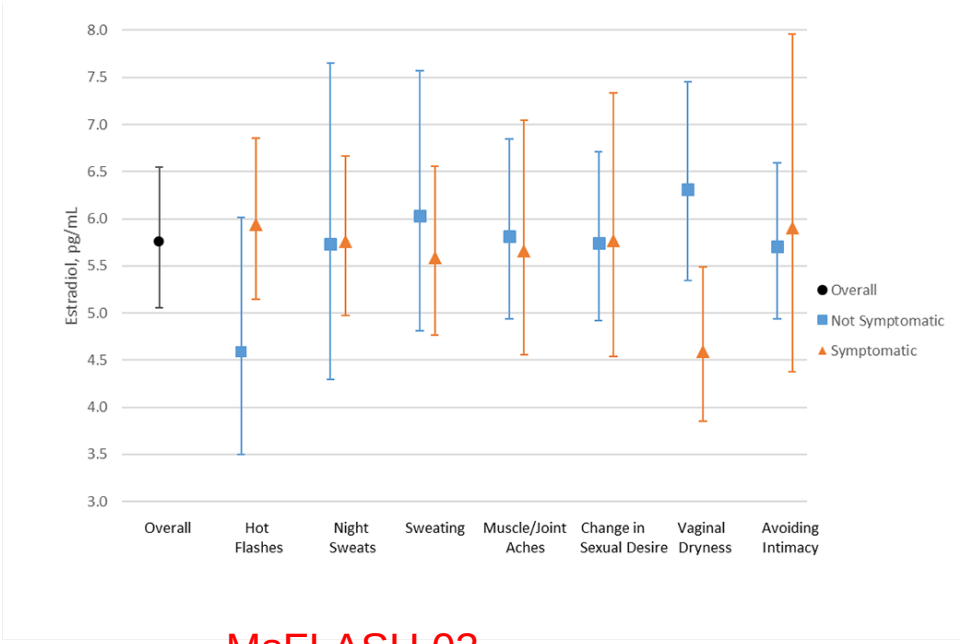
[a] Odds ratios for site not shown.

Randolph et alJ Clin Endocrinol Metab 2005;90:6106-12

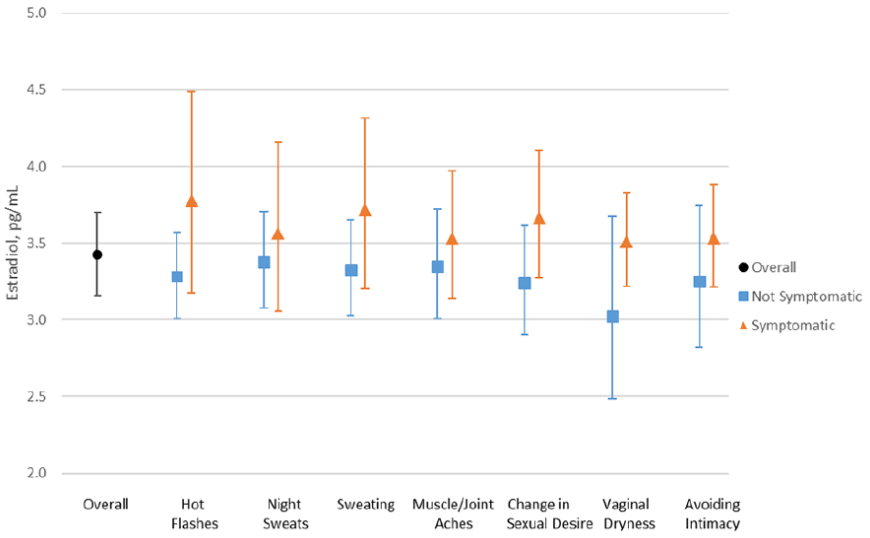
Are serum estrogen concentrations associated with menopausal symptom bothers? Baseline results from two MsFLASH clinical trials:

trial 03 n=178 peri-/postmenopausal; mean 54y; VM sy (≥v14 HF or NS/week)
trial 05 n=181; postmenopausal mean 61y: moderate-to-severe vulvovaginal sy

Estradiol (pg/ml)



MsFLASH 03



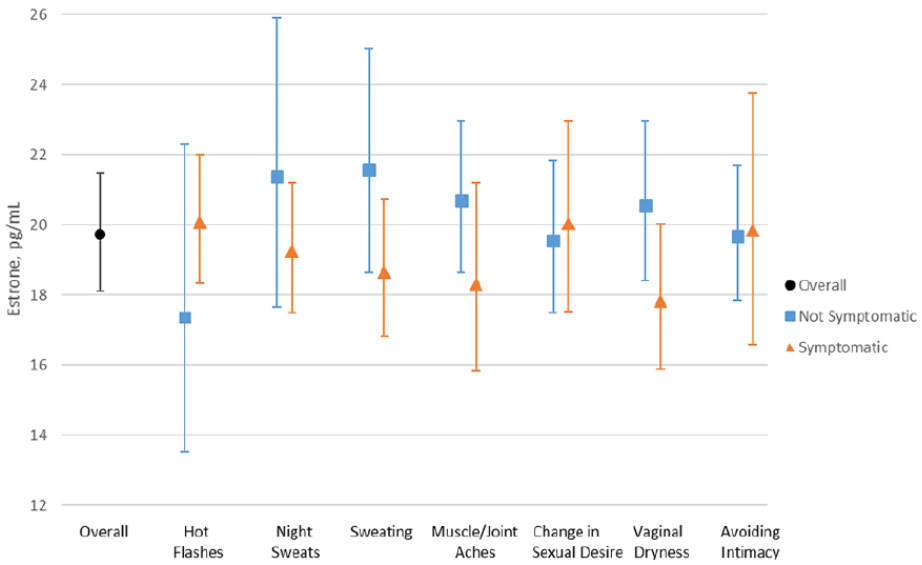
MsFLASH 05

Crandall et al Maturitas 2022;162:23-30

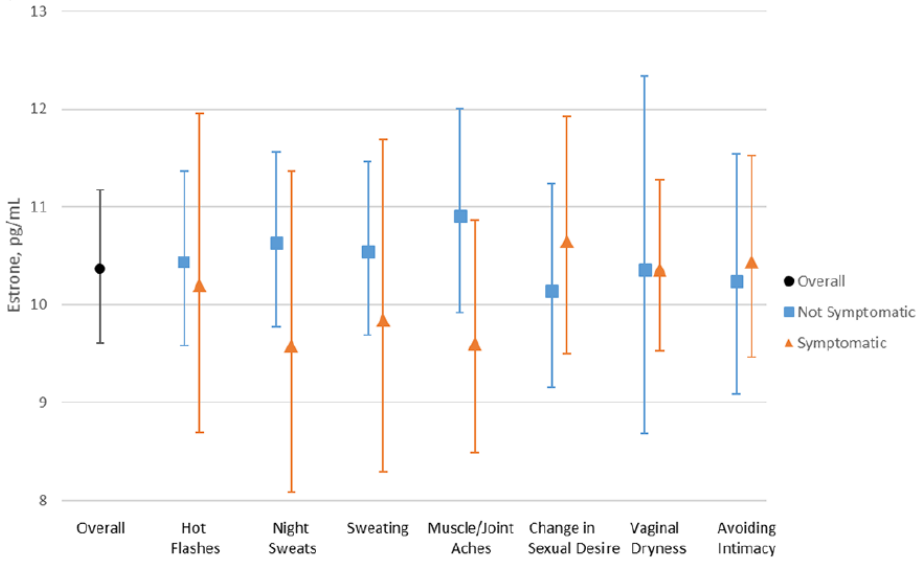
Are serum estrogen concentrations associated with menopausal symptom bothers? Baseline results from two MsFLASH clinical trials:

trial 03 n=178 peri-/postmenopausal; mean 54y; VM sy (≥v14 HF or NS/week)
trial 05 n=181; postmenopausal mean 61y: moderate-to-severe vulvovaginal sy

Estrone (pg/ml)



MsFLASH 03



MsFLASH 05

Crandall et al Maturitas 2022;162:23-30

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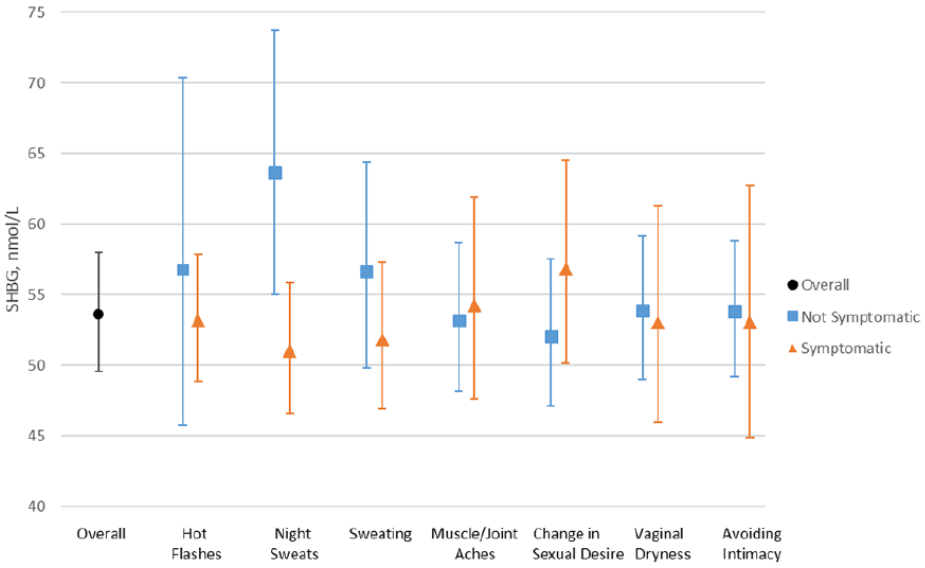
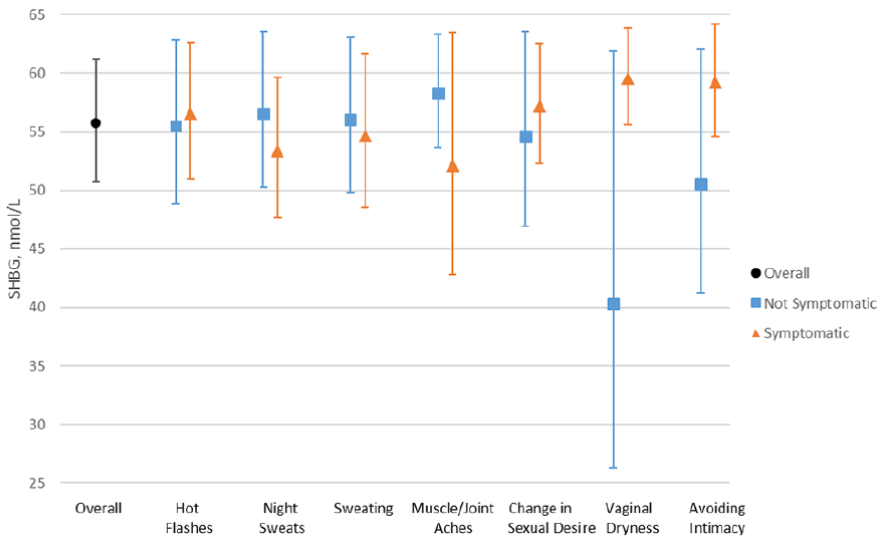
trial 03 n=178 peri-/postmenopausal; mean 54y; VM sy (≥v14 HF or NS/week)
trial 05 n=181; postmenopausal mean 61y: moderate-to-severe vulvovaginal sy

SHBG (nmol/L)



MsFLASH 03



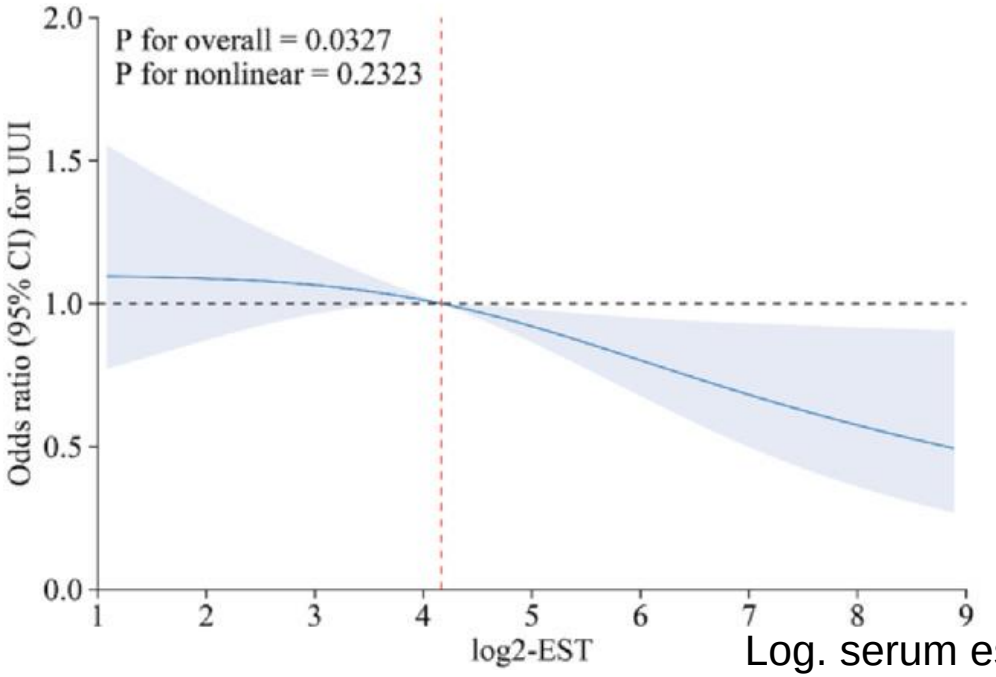
MsFLASH 05

Crandall et al Maturitas 2022;162:23-30

Associations Between Serum Estrogen Levels and Urinary Incontinence in Women: A Cross-sectional Analysis of NHANES 2013 to 2016

Variables	Overall (n = 4114)	Q1 (n = 1027)	Q2 (n = 1030)	Q3 (n = 1028)	Q4 (n = 1029)	*P*-Value
log2-EST (median [IQR])	4.166 [2.436, 6.231]	1.082 [1.080, 2.029]	3.111 [2.756, 3.533]	5.263 [4.755, 5.750]	7.098 [6.672, 7.607]	< .0001
EST (median [IQR]), pg/mL	17.950 [5.410, 75.100]	2.117 [2.114, 4.080]	8.640 [6.752, 11.575]	38.400 [27.000, 53.800]	137.000 [102.000, 195.000]	< .0001
Age (%), years						
< 50	2120 (51.53)	133 (12.95)	184 (17.86)	844 (82.10)	959 (93.20)	< .0001
≥50	1994 (48.47)	894 (87.05)	846 (82.14)	184 (17.90)	70 (6.80)	

A Odds Ratio Urgency Urinary Incontinence



Log. serum estradiol

Li et al Urology 2024;188:63-69

Reproductive hormones and subclinical cardiovascular disease in midlife women (40 to 60 y; mean 54y)

Table 2. Relations Between Sex Hormones, SHBG, and FMD

	FMD β(SE)		
	Model 1	Model 2	Model 3
E1	0.60 (0.36)	0.69 (0.35)[a]	0.77 (0.37)[a]
E2	0.06 (0.15)	0.11 (0.15)	0.14 (0.16)
T	0.15 (0.69)	−0.08 (0.65)	−0.05 (0.67)
SHBG	1.27 (0.36)[b]	1.12 (0.36)[c]	1.31 (0.40)[c]
FT[d]	−1.41 (0.47)[c]	−1.42 (0.47)[c]	−1.58 (0.52)[c]

Table 3. Relations Between Hormones and Carotid IMT, Adventitial Diameter, and Plaque

	Mean IMT β(SE)		IAD β(SE)		Plaque Presence OR (95% CI)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
E1	0.008 (0.009)	0.01 (0.009)	0.02 (0.05)	−0.003 (0.05)	1.14 (0.82–1.59)	1.31 (0.88–1.95)
E2	−0.0003 (0.004)	0.001 (0.004)	−0.04 (0.02)[a]	−0.06 (0.02)[b]	1.01 (0.88–1.16)	1.10 (0.93–1.32)
T	0.016 (0.018)	0.007 (0.016)	−0.006 (0.10)	−0.06 (0.10)	0.84 (0.43–1.64)	0.91 (0.44–1.89)
SHBG	−0.01 (0.009)	0.01 (0.01)	0.02 (0.05)	0.15 (0.06)[b]	1.27 (0.89–1.79)	1.84 (1.16–2.91)[c]
FT[d]	0.02 (0.01)	−0.013 (0.01)	−0.03 (0.07)	−0.19 (0.08)[b]	0.69 (0.43–1.09)	0.49 (0.28–0.88)[b]

Thurston et al J Clin Endocrinol Metab 2018;103:3070-3077

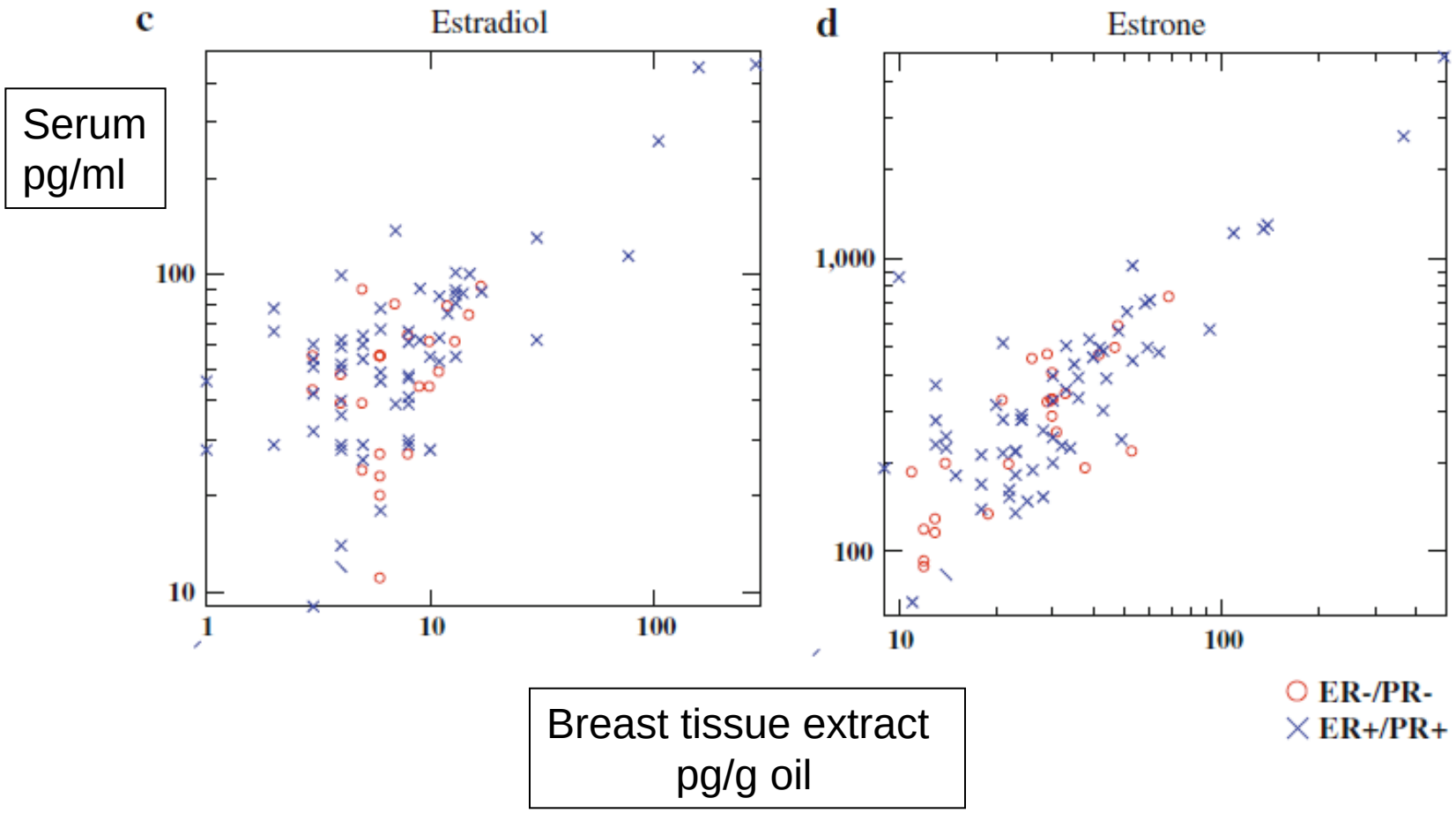
Prospective study of endogenous circulating estradiol and risk of stroke in older women

Table 3. OR Estimates for Stroke by Baseline Serum Quartiles of E_2, FEI, and SHBG in Age-Adjusted and MV-Adjusted Models in Postmenopausal Women in a Prospective Case-Control Study of Incident Stroke From the Study of Osteoporotic Fractures

	OR Estimate (95% CI)		
Endogenous Estradiol	**Age-Adjusted**	**MV Model[a]**	**MV Model[a] Plus Waist Circumference**
E_2 level[b]			
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	1.26 (0.62-2.57)	1.24 (0.58-2.64)	1.24 (0.58-2.63)
Quartile 3	1.55 (0.87-2.74)	1.37 (0.73-2.54)	1.35 (0.72-2.52)
Quartile 4 (highest)	1.71 (0.94-3.13)	1.13 (0.58-2.22)	1.09 (0.55-2.19)
P_{trend}	.07	.69	.76
FEI[c]			
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	1.46 (0.80-2.68)	1.10 (0.57-2.10)	1.09 (0.57-2.09)
Quartile 3	1.52 (0.83-2.78)	1.15 (0.59-2.24)	1.14 (0.58-2.24)
Quartile 4 (highest)	2.31 (1.28-4.17)	1.26 (0.63-2.52)	1.23 (0.59-2.57)
P_{trend}	.007	.51	.58
SHBG level[d]			
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	0.60 (0.34-1.05)	0.66 (0.35-1.25)	0.67 (0.36-1.25)
Quartile 3	0.33 (0.18-0.58)	0.42 (0.22-0.81)	0.42 (0.22-0.82)
Quartile 4 (highest)	0.58 (0.34-1.01)	0.84 (0.44-1.62)	0.85 (0.43-1.67)
P_{trend}	.01	.37	.40

Lee et al Arch Neurology 2010;67:195-201

Sex steroid hormone levels in breast adipose tissue and serum in postmenopausal women

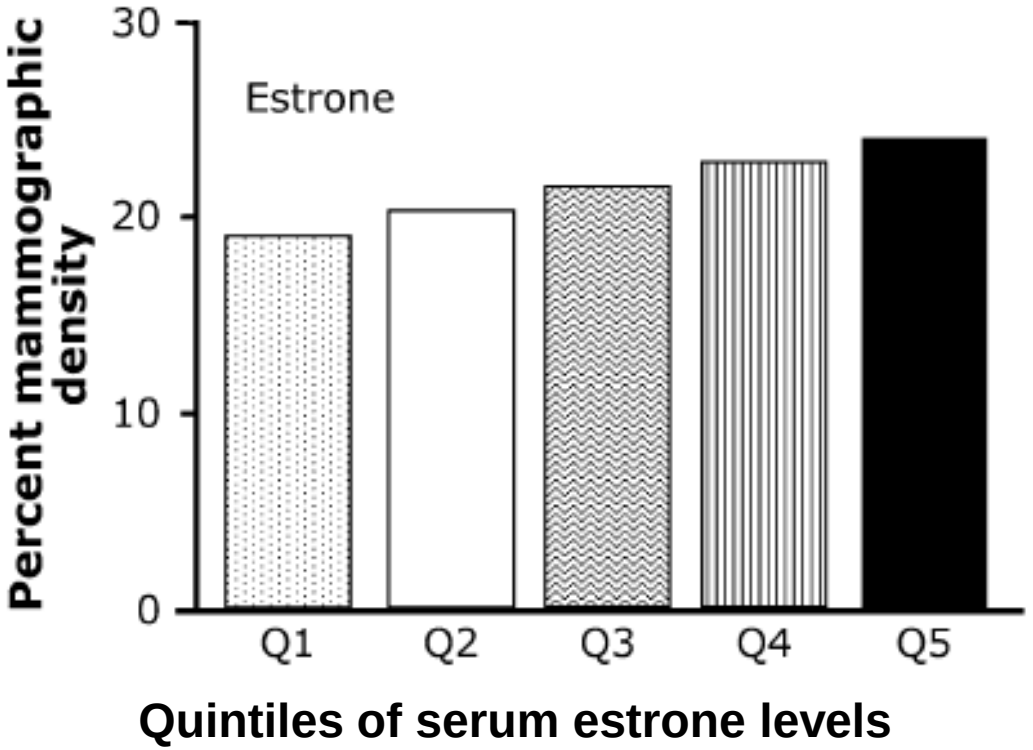


Falk et al Breast Cancer Res Treat 2012;131;287-294

Endogenous estrogen levels are associated with mammographic density in postmenopausal women

(mean age 56yr; mean 5.1yr after menopause) baseline data from the PEPI trial

Adjusted least squares mean estimates of percent mammographic density



In a multivariate model adjusted for confounders density is associated with Estrone- (p=0.014), estradiol- (P=0.009) and bioavailable estradiol levels (p= 0.018)

Greendale et al Am J Epidemiol 2005;162:826-35

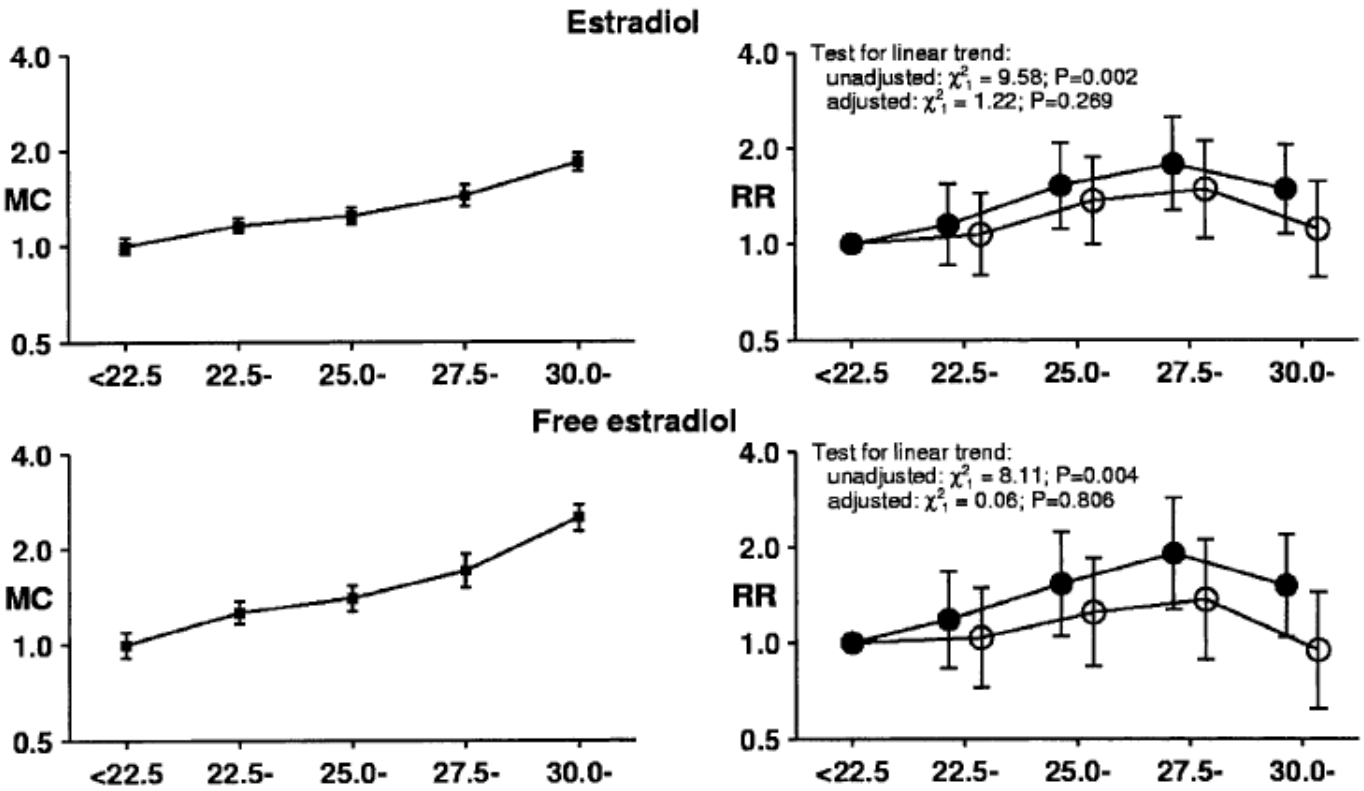
Body Mass Index, Serum Sex Hormones, and Breast Cancer Risk in Postmenopausal Women

Endogenous Hormones and Breast Cancer Collaborative Group

E2 Mean Concentration
rescaled: level lowest BMI=1

RR breast cancer
unadjusted and adjusted for E2 level

A



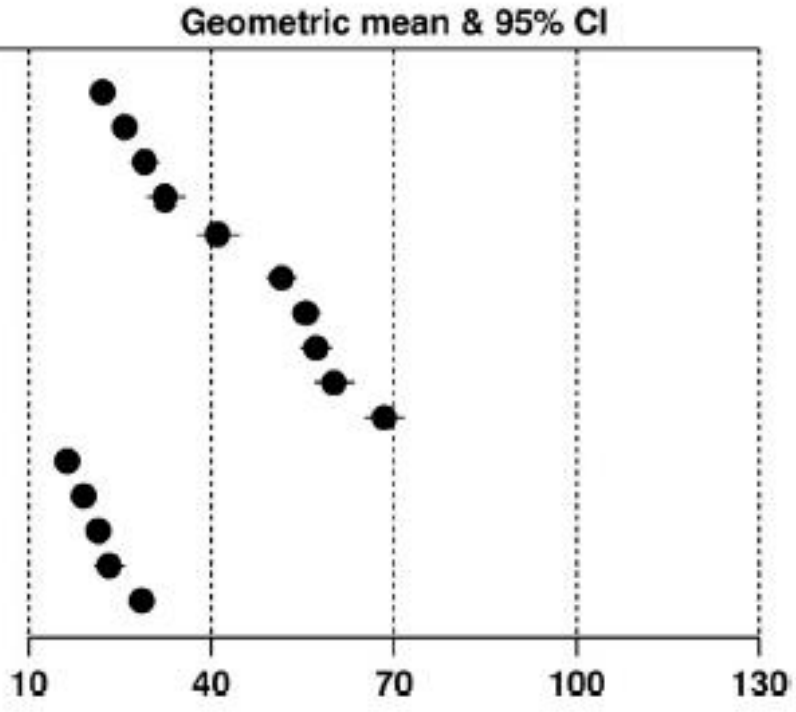
Body Mass Index (kg/m²)

J Nat Cancer Institute 2003:95:1218-1226

Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies

Endogenous Hormones and Breast Cancer Collaborative Group Steroids 2015; 99:49-55

Assay type	BMI (kg/m^2)	n	Mean (95% CI)
Extraction	<22.5	337	22 (20-24)
	22.5-24.9	423	26 (24-28)
	25.0-27.4	319	29 (27-31)
	27.5-29.9	225	32 (29-36)
	≥30.0	290	41 (38-45)
Direct	<22.5	964	52 (49-54)
	22.5-24.9	1225	56 (53-58)
	25.0-27.4	1106	57 (55-60)
	27.5-29.9	743	60 (57-63)
	≥30.0	962	68 (65-72)
Mass spectrometry	<22.5	266	16 (15-18)
	22.5-24.9	320	19 (18-21)
	25.0-27.4	274	21 (20-23)
	27.5-29.9	183	23 (21-26)
	≥30.0	342	29 (26-31)



Geometric mean of estradiol (pmol/L)

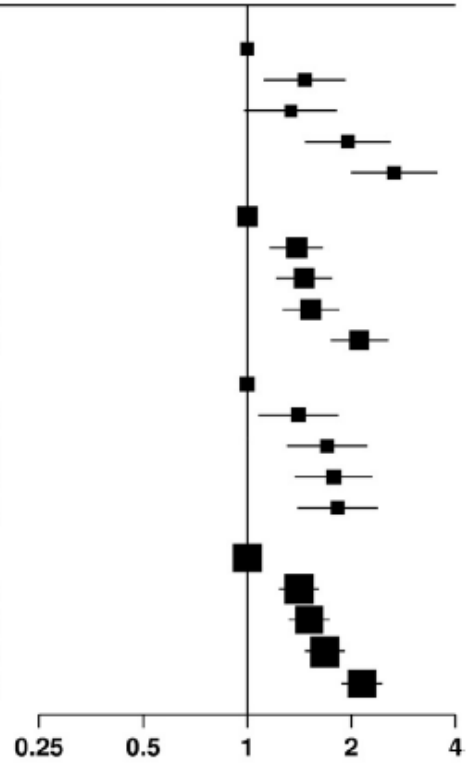
Findings similar for estrone

Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies

Endogenous Hormones and Breast Cancer Collaborative Group *,[1] Steroids 2015; 99:49-55

Assay type	Fifth	Cases/ Controls	OR (95% CI)
Extraction	1	133/392	1.00
	2	174/386	1.47 (1.12-1.93)
	3	107/265	1.33 (0.98-1.82)
	4	177/313	1.95 (1.47-2.59)
	5	217/291	2.66 (1.99-3.54)
Direct	1	389/898	1.00
	2	462/881	1.39 (1.16-1.66)
	3	452/909	1.46 (1.21-1.76)
	4	435/878	1.53 (1.26-1.84)
	5	563/865	2.11 (1.74-2.56)
Mass spectrometry	1	160/275	1.00
	2	217/270	1.40 (1.08-1.83)
	3	259/264	1.70 (1.30-2.22)
	4	280/271	1.78 (1.37-2.30)
	5	277/267	1.82 (1.40-2.38)
Total	1	682/1565	1.00
	2	853/1537	1.41 (1.24-1.61)
	3	818/1438	1.51 (1.32-1.73)
	4	892/1462	1.68 (1.47-1.92)
	5	1057/1423	2.15 (1.87-2.46)

Test of linear trend (all studies): $\chi^2_1 = 117.87$; $P < 0.001$
Test of linear trend (extraction assay studies): $\chi^2_1 = 48.71$; $P < 0.001$
Test of linear trend (direct assay studies): $\chi^2_1 = 51.66$; $P < 0.001$
Test of linear trend (mass spectrometry assay studies): $\chi^2_1 = 21.74$; P
Test of heterogeneity between linear trends: $\chi^2_2 = 4.24$; $P = 0.120$

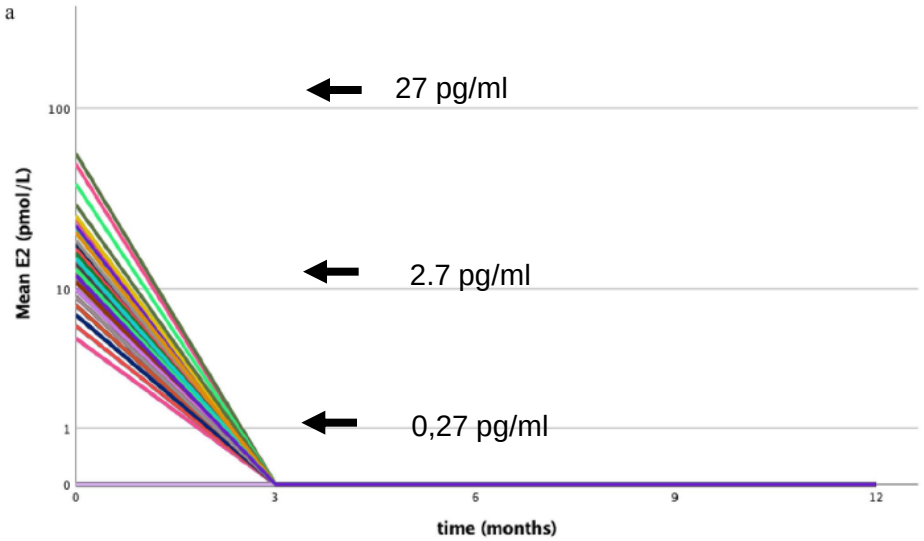


Odds ratio for breast cancer by fifth of estradiol

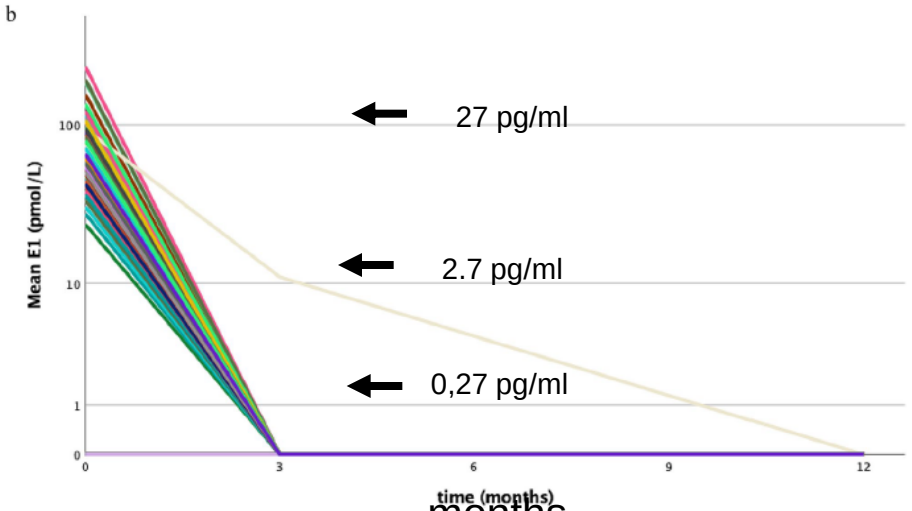
Findings similar for estrone

Effect of letrozole on serum E2 and E1 in postmenopausal women with breast cancer

E2 pmol/L



E1 pmol/L

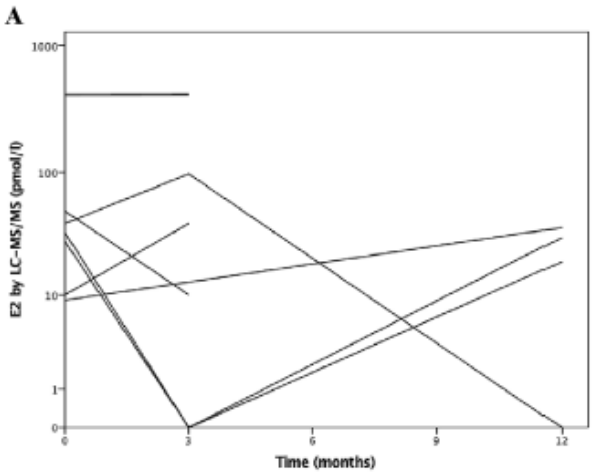


months

Faltinova et al Breast Cancer Research and Treatment 2023;201:425-435

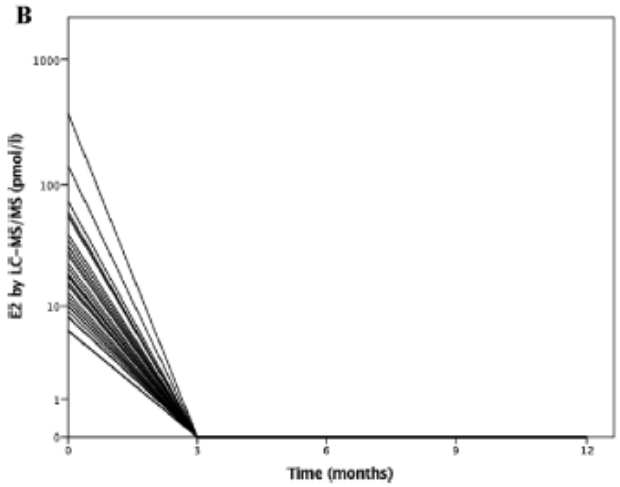
Monitoring serum estradiol levels in breast cancer patients during extended adjuvant letrozole treatment after five years of tamoxifen: a prospective trial

E2 pmol/L



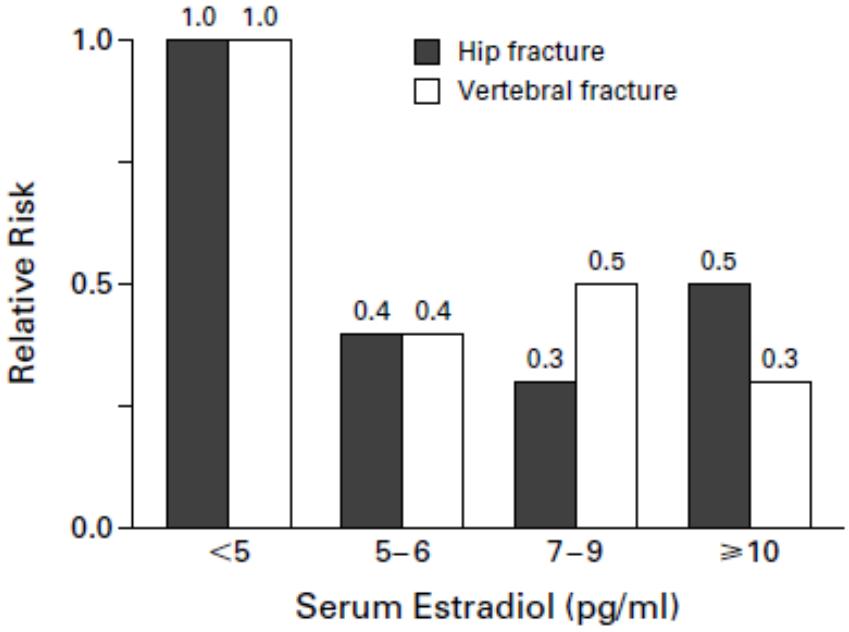
AI failures

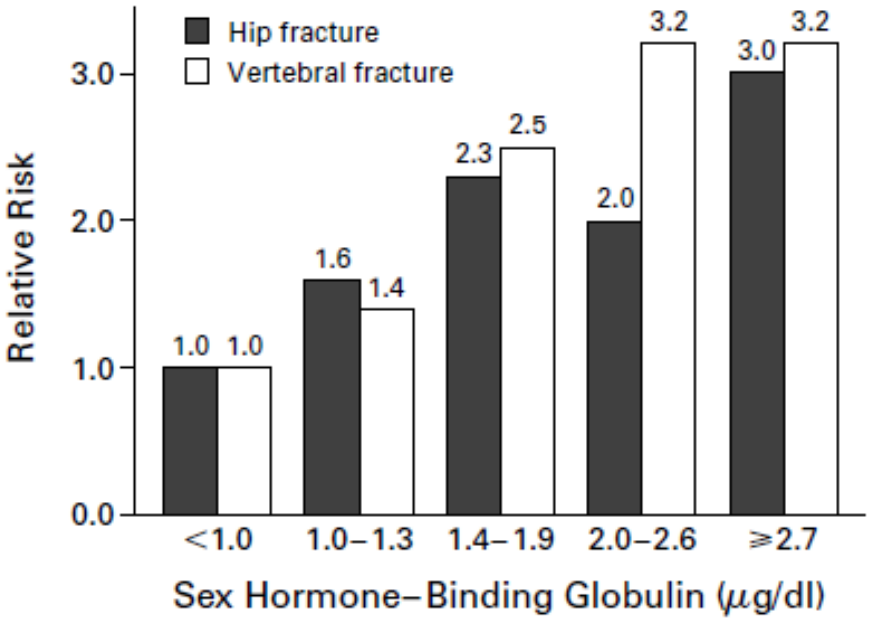
E2 pmol/L



Faltova et al Breast Cancer Res Treat 2021;187:769-775

Critical role of estrogens for skeletal health: RR of vertebral fracture as a function of endogenous serum E2 and SHBG in postmenopausal women (>65yr)

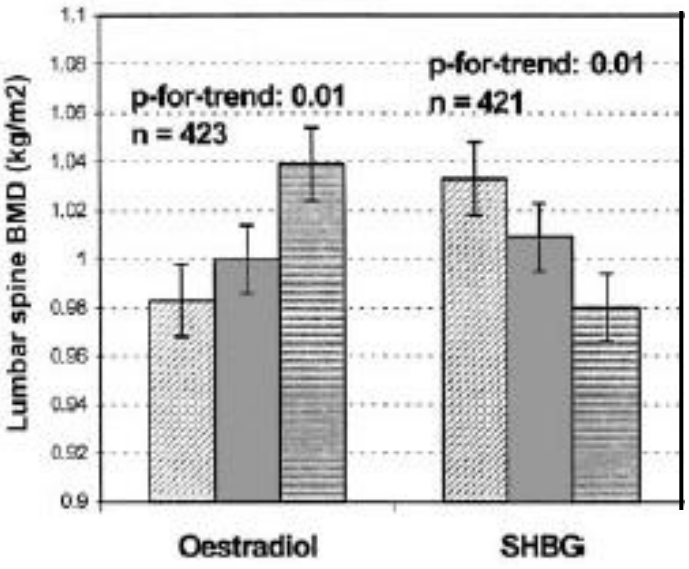




Cummings et al., NEJM 1998;339:733-738

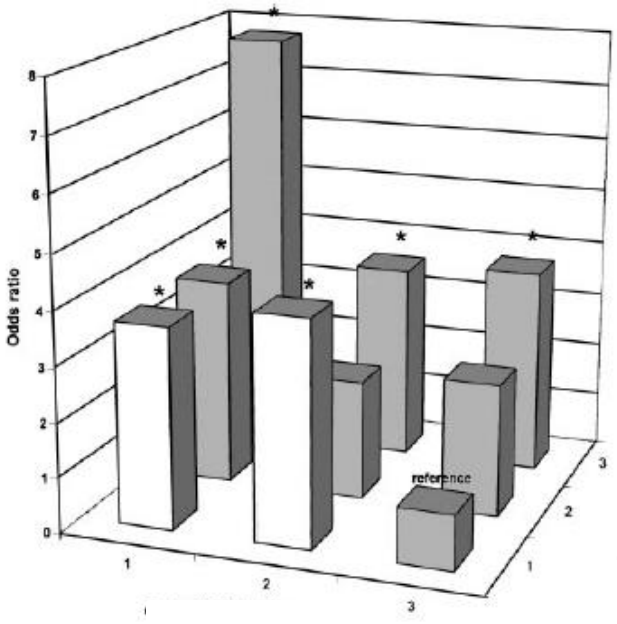
Endogenous hormone levels and risk of incident vertebral fractures in late postmenopausal women (mean age 68yr)

Lumbar spine bone mineral density



Tertiles of serum levels

Odds ratio for incident vertevral fracture



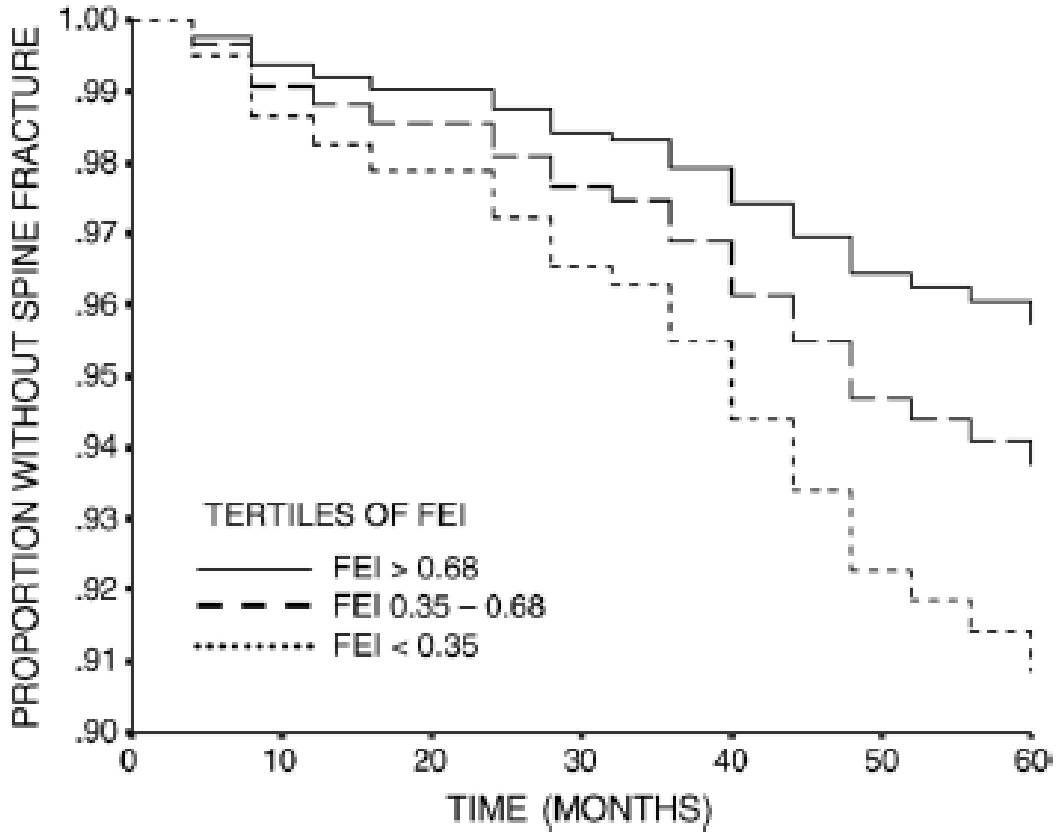
Tertiles of SHBG

Tertiles of estradiol

Goderie-Plomp et al J Clin Endocrinol Metab 2004;89:3261-69

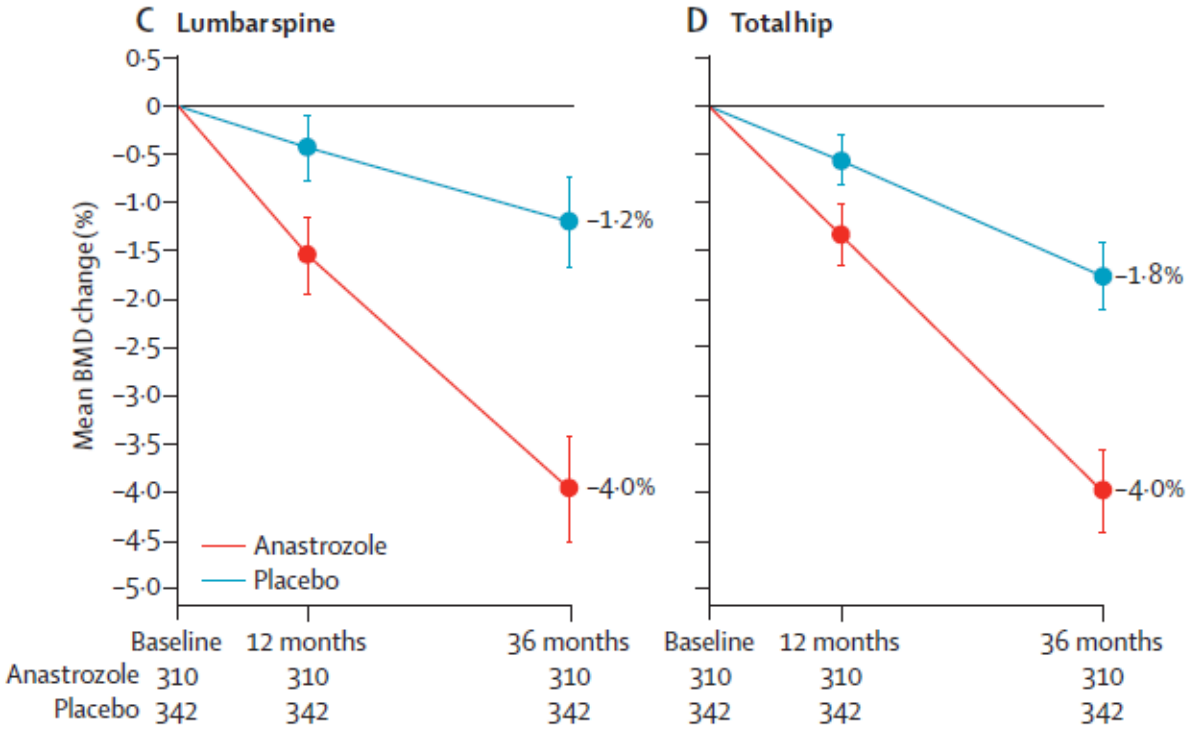
Endogenous estrogen and incident vertebral fracture in older women (mean age 75yrs)

Proportion of women without fracture according to tertile of free estradiol index (FEI)



Prince et al Bone 2007;41:33-38

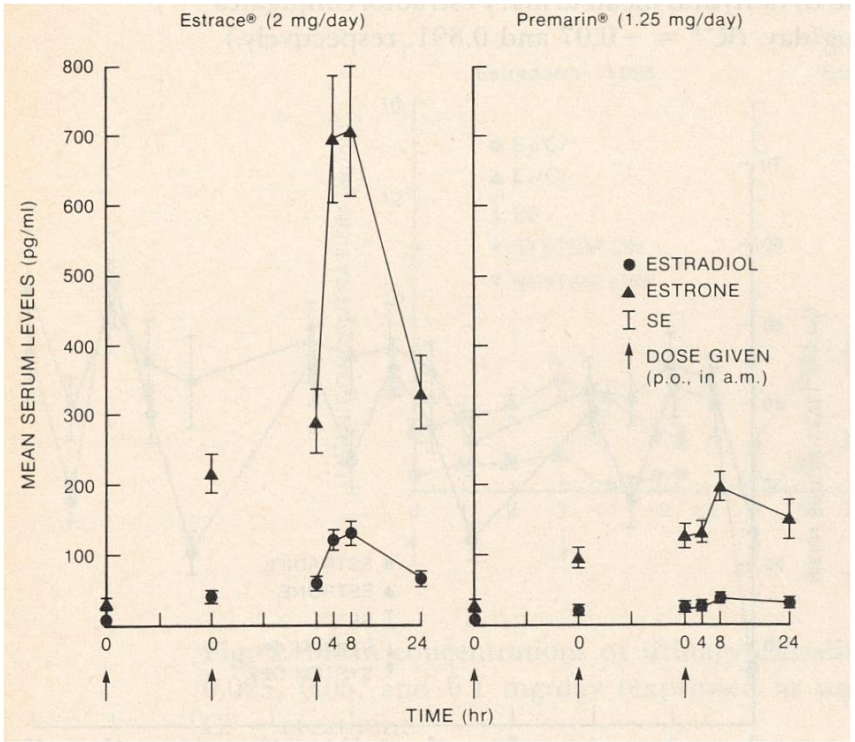
Effects on bone mineral density of aromatase inhibition with anastrozole in PM women



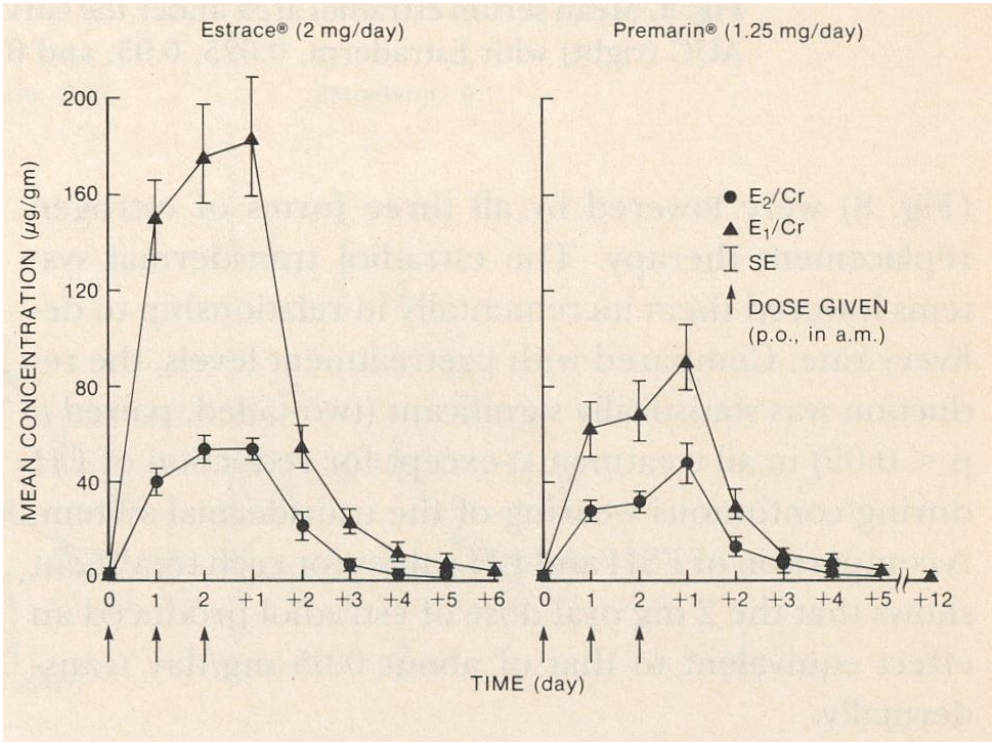
Sestak et al the Lancet Oncology 2014;15:1460-68

Pharmacokinetics of estradiol patch (0.025, 0.050 and 0,1 mg/d) compared to oral 2 mg micronized estradiol and 1.25 mg conjugate equine estrogen

Serum E2 and E1



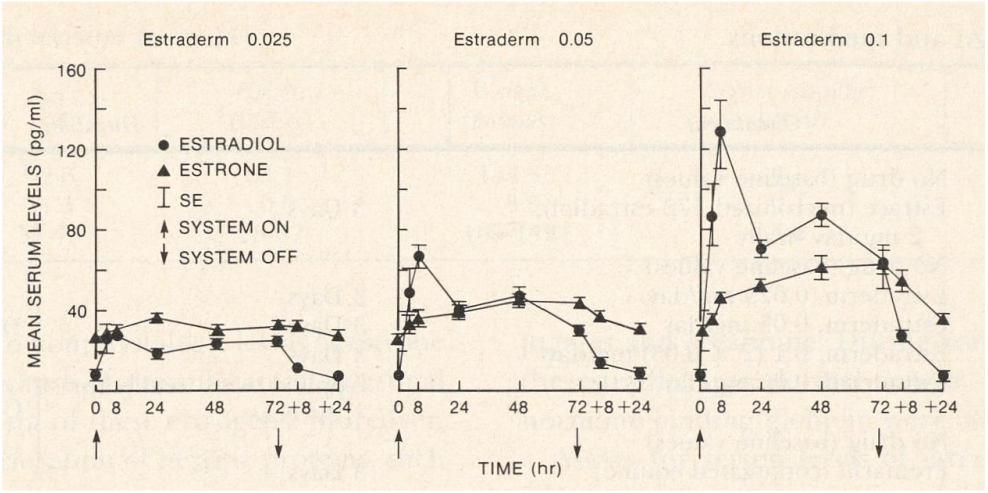
Urine E2- and E1 conjugates



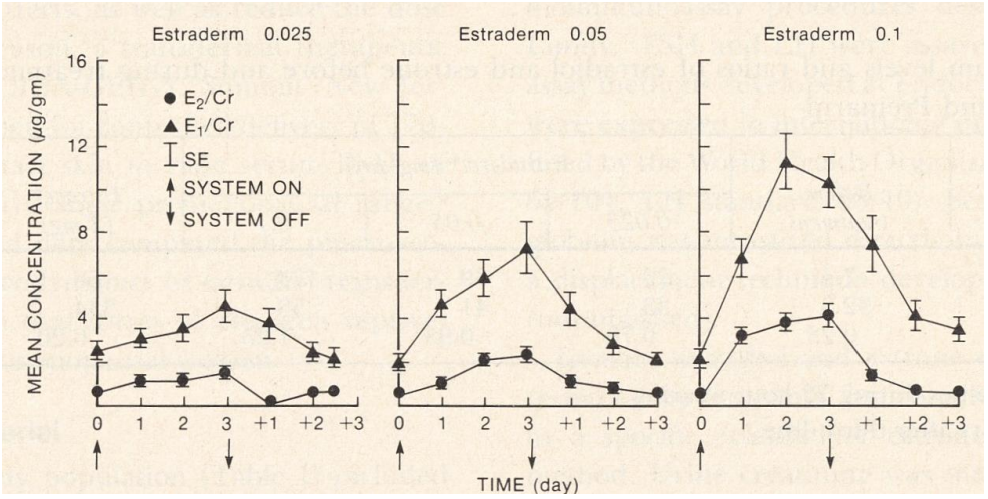
Powers et al Am J Obstet Gyneco 1985;145:1099-1106

Pharmacokinetics of estradiol patch (0.025, 0.050 and 0,1 mg/d) compared to oral 2 mg micronized estradiol and 1.25 mg conjugate equine estrogen

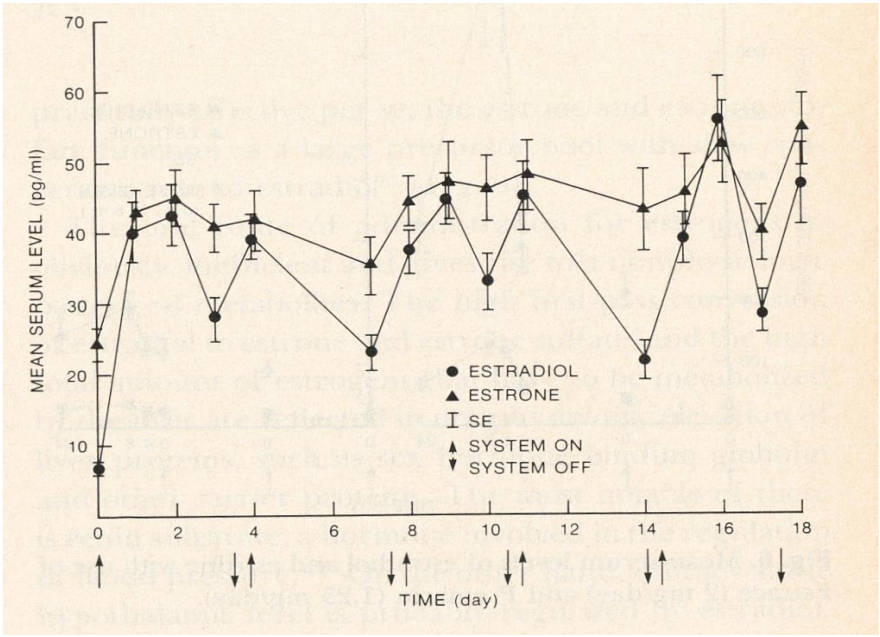
Serum E2 and E1



Urine E2- and E1 conjugates



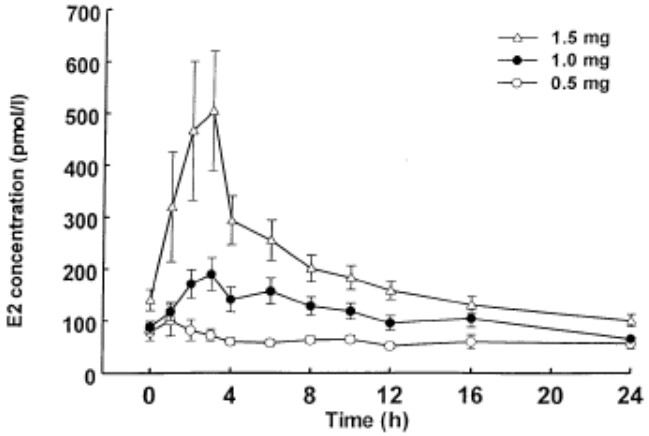
Serum E2 and E1 (long-term)



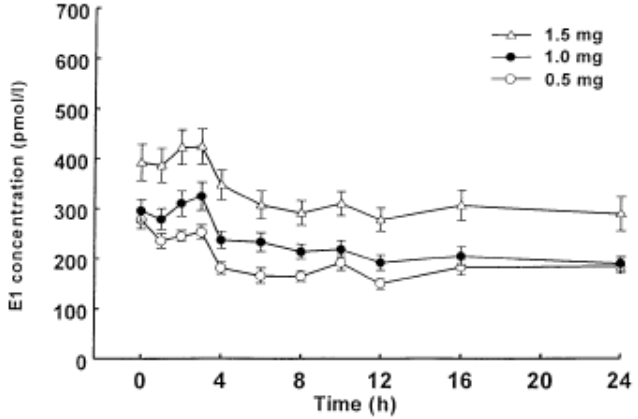
Powers et al Am J Obstet Gyneco 1985;145:1099-1106

Effect of dose on the absorption of estradiol from a transdermal gel

E2 (pmol/L)



E1 (pmol/L)



Järvinen et al Maturitas 2000;35:51-56

Factors associated with serum estradiol levels among postmenopausal women using hormone therapy

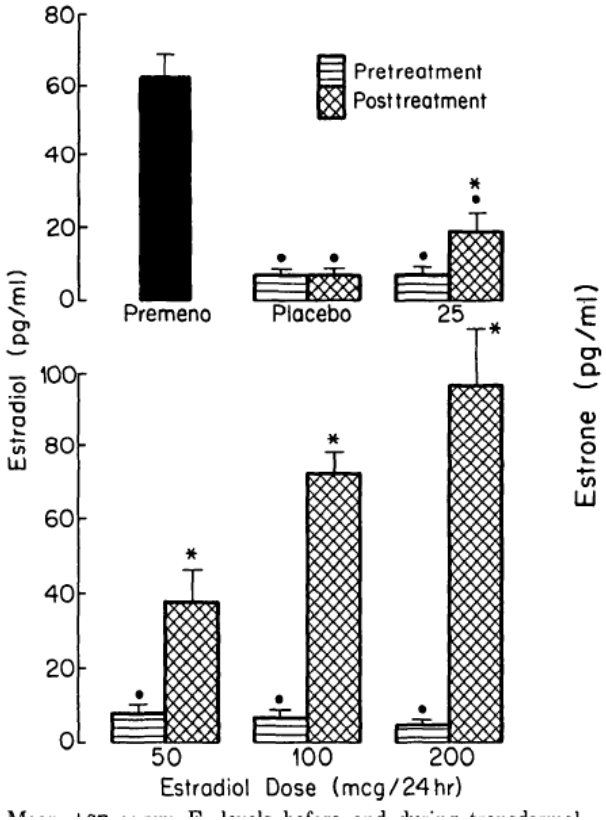
R/ Daily 1 mg oral micronized 17β-estradiol

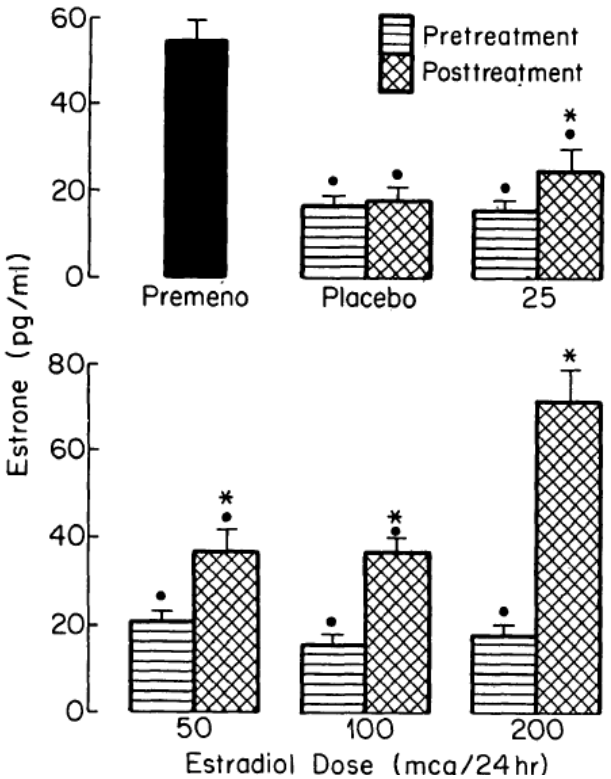
Table 3. Multivariable Association of Estradiol Levels While Taking Hormone Therapy With Demographic and Clinical Characteristics Among the Total Analysis Sample and by Postmenopausal Strata

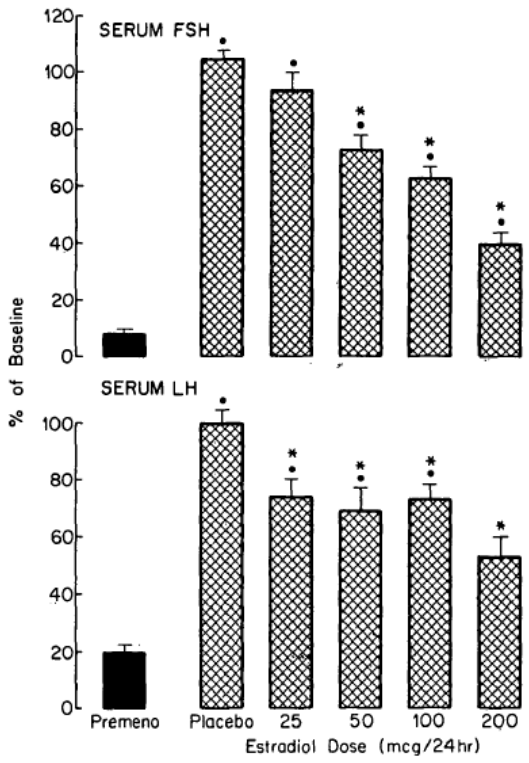
	Total Analysis Sample				
Variable	No. of Women	No. of Visits	Beta	95% CI	*P*
n	275	2,160			
BMI* (kg/m^2)	275	2,160	1.015	1.0067–1.0235	<.001
Smoking status*					<.001
Never	170	1,338		Ref	
Past smoker	101	741	0.8516	0.7651–0.9481	.003
Current smoker	14	81	0.6709	0.5545–0.8119	<.001
Alcohol use* (drinks/d)					<.001
None	167	1,059	Ref		
Less than 1	165	828	1.0414	0.9722–1.1157	.25
1–2	56	231	1.0999	0.9862–1.2268	.09
More than 2	11	42	1.6979	1.3572–2.1243	<.001

Sriprasert et al Obstet Gynecol 2020;136:675-684

Treatment of Hot Flashes with Transdermal Estradiol Administration*

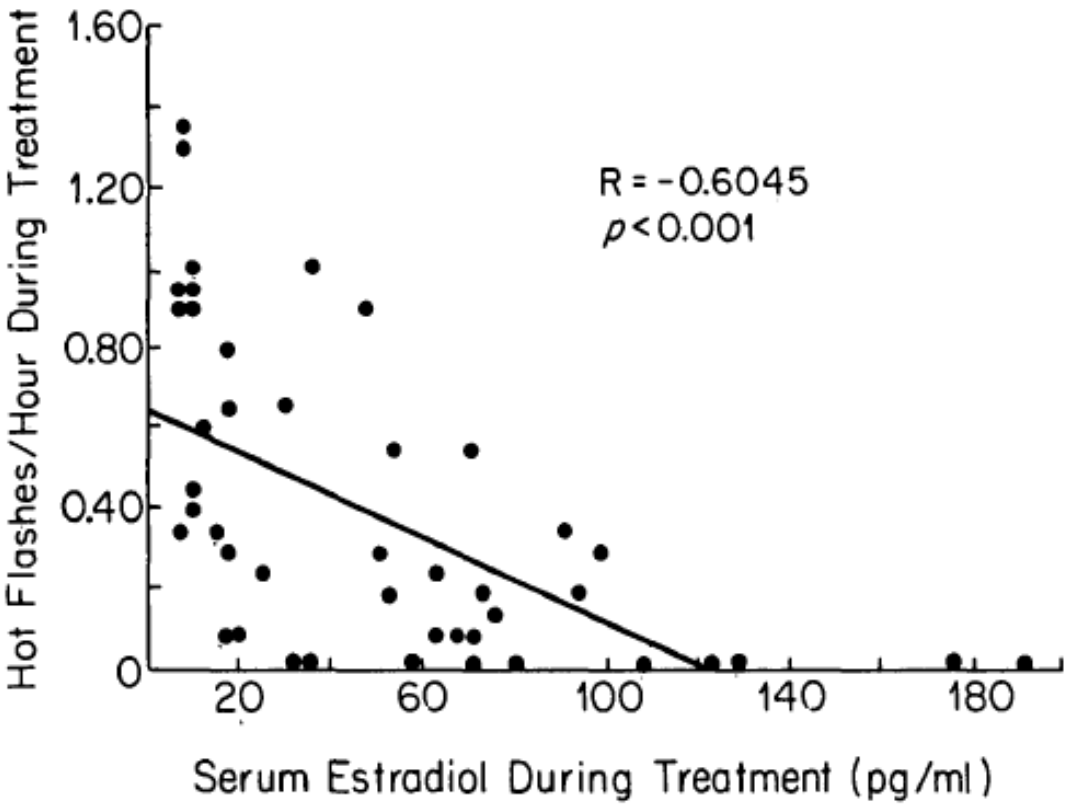






Steingold et al J Clin Endocrinol Metab 1985;61

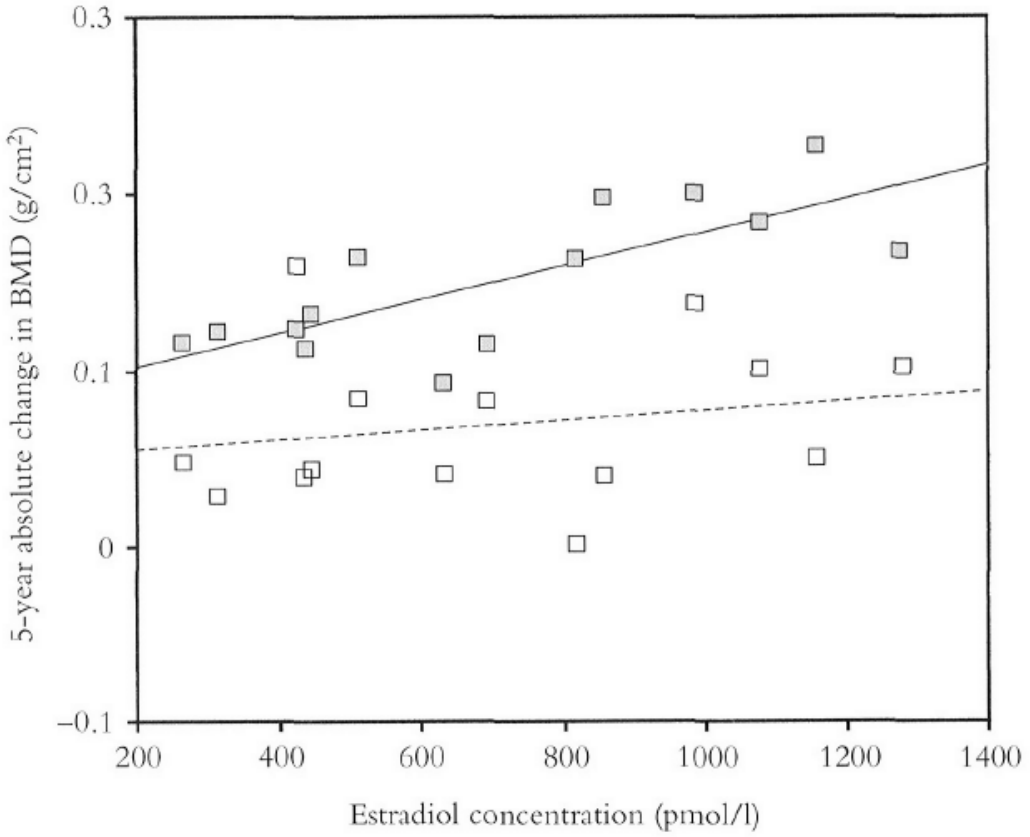
Treatment of Hot Flashes with Transdermal Estradiol Administration*



Steingold et al J Clin Endocrinol Metab 1985;61

Five-year changes in bone density and serum estradiol in postmenopausal women (mean 61y at baseline) using long-term estradiol implants

50mg implant every 6 months



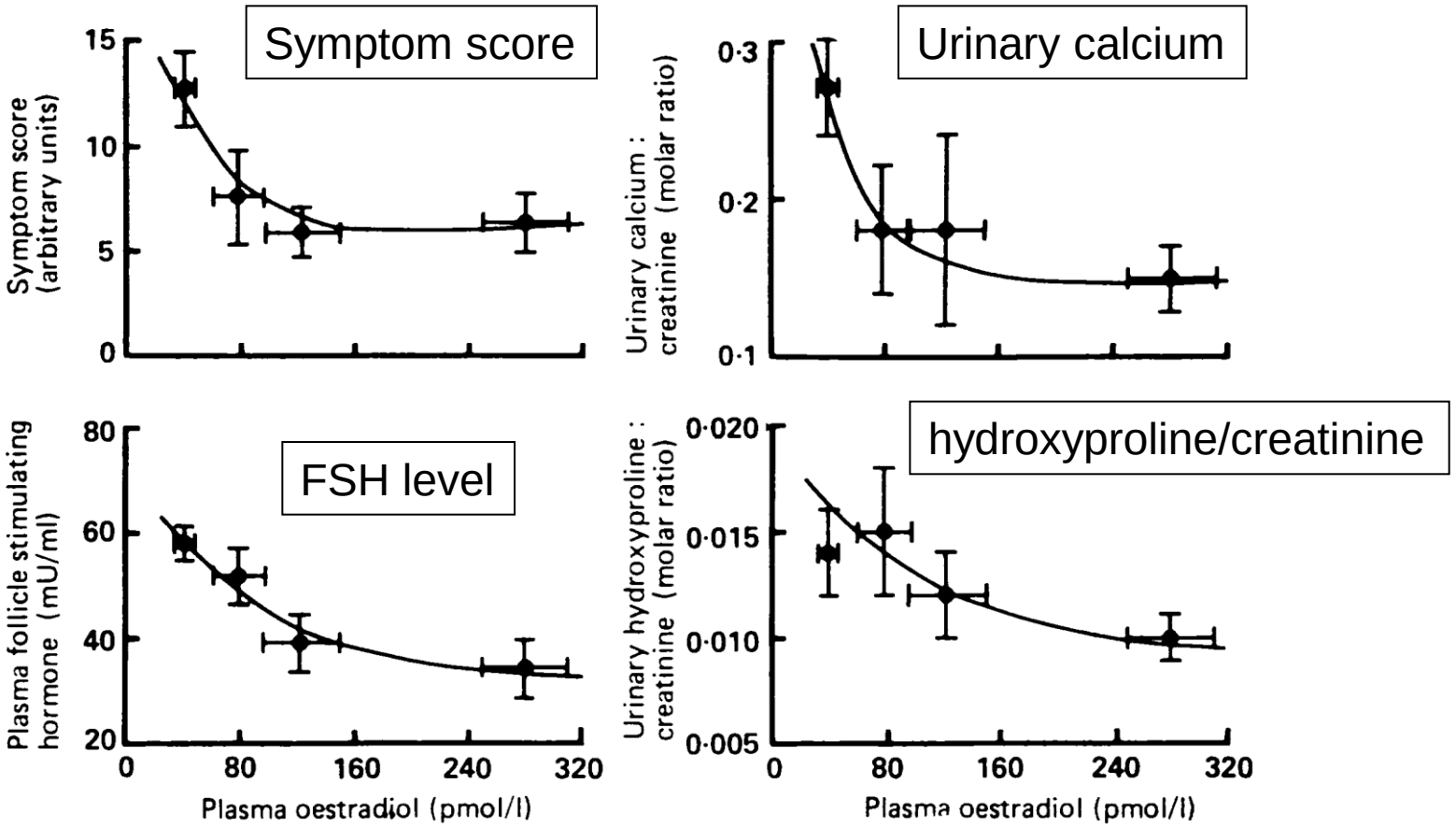
Lumbar spine

Femoral neck

Vashisht and Studd Gynecol Endocrinol 2003;17:463-470

Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women

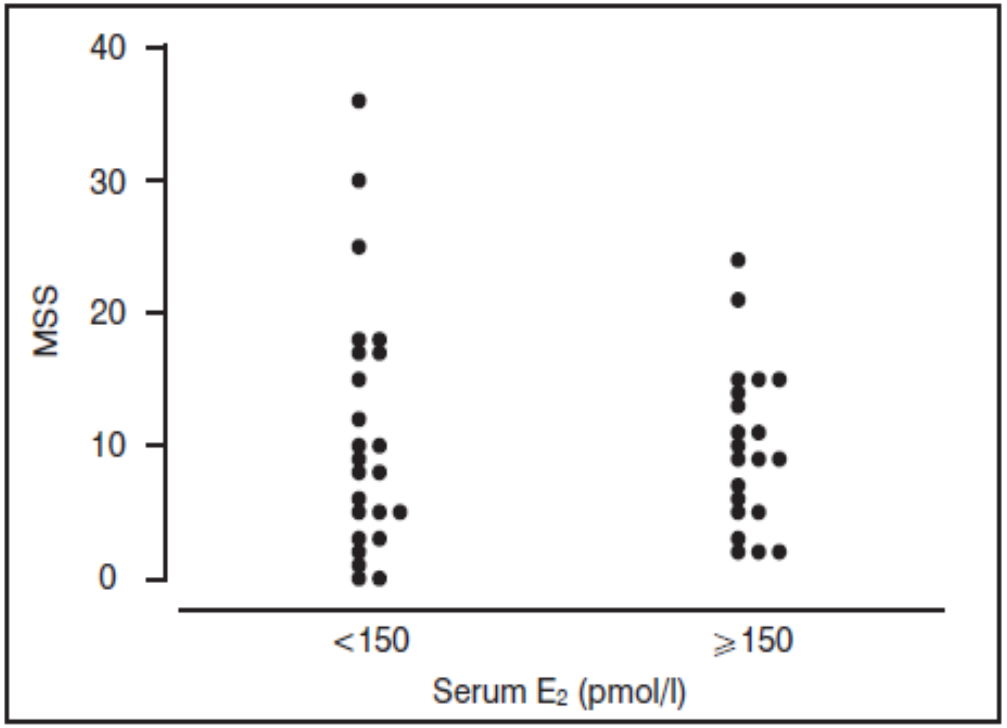
P L SELBY, M PEACOCK



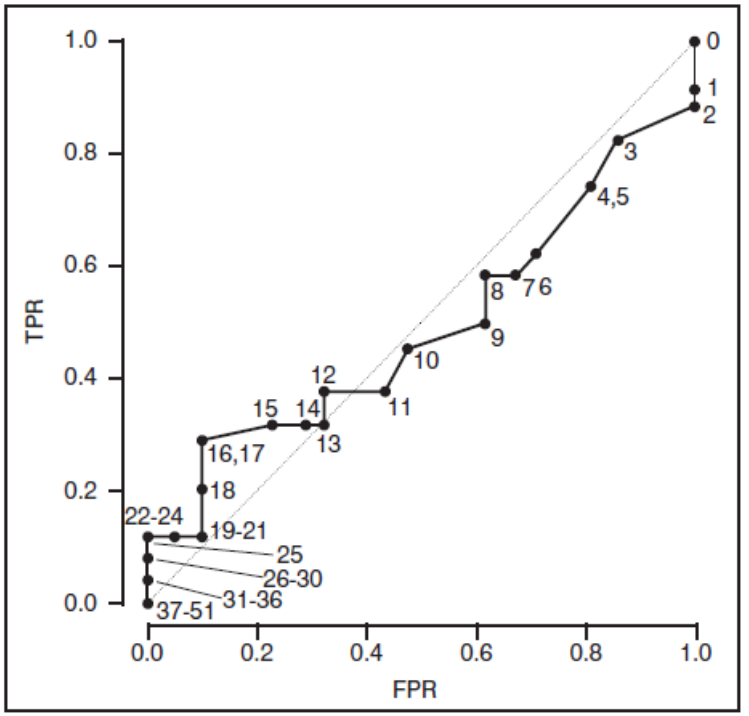
BMJ 1986;293:1337-1339

Adequacy of hormone replacement therapy for osteoporosis prevention assessed by serum oestradiol measurement, and the degree of association with menopausal symptoms

Menopausal Symptom Score for
E2 < 150 or ≥ 150 pmol/L (41 pg/ml)



ROC Curve showing lack of predictive value for MSS



Rodgers and Miller British J General Pract 1997; 47:161-165

Masturbation Frequency and Sexual Function Domains Are Associated With Serum Reproductive Hormone Levels Across the Menopausal Transition

Table 4. Change in Sexual Function Associated With a 1 SD Increase in Concurrent Individual Hormone Levels Adjusted for Demographic and Lifestyle Characteristics, Menopausal Status, and BMI in the Study of Women's Health Across the Nation

	Overall		No Partner		With a Partner		
Hormone	Desire ≥1/wk	Masturbation Ever	Desire ≥1/wk	Masturbation Ever	Desire ≥1/wk	Masturbation Ever	Arousal Almost Always/Always
T, ng/dL	1.052 (1.015, 1.091)[b]	1.073 (1.039, 1.108)[d]	1.043 (0.947, 1.149)	1.112 (1.019, 1.213)[a]	1.036 (0.992, 1.081)	1.074 (1.037, 1.111)[d]	1.039 (0.995, 1.085)
FSH, mIU/mL	0.982 (0.938, 1.029)	0.946 (0.911, 0.983)[c]	0.916 (0.811, 1.036)	0.920 (0.828, 1.022)	0.991 (0.937, 1.049)	0.957 (0.916, 1.001)	0.925 (0.873, 0.981)[b]
E2, pg/mL	0.994 (0.966, 1.022)	1.022 (0.999, 1.046)	0.973 (0.913, 1.036)	1.044 (0.971, 1.122)	0.996 (0.960, 1.033)	1.021 (0.996, 1.047)	1.014 (0.975, 1.054)
DHEAS, μg/dL	1.058 (1.013, 1.105)[a]	1.046 (1.006, 1.087)[a]	1.158 (1.046, 1.282)[b]	1.076 (0.980, 1.182)	1.039 (0.987, 1.094)	1.025 (0.980, 1.072)	1.051 (0.998, 1.107)
SHBG, nM	0.990 (0.952, 1.029)	1.028 (0.990, 1.068)	0.965 (0.874, 1.064)	1.059 (0.973, 1.153)	1.001 (0.955, 1.048)	1.025 (0.982, 1.070)	0.982 (0.935, 1.031)

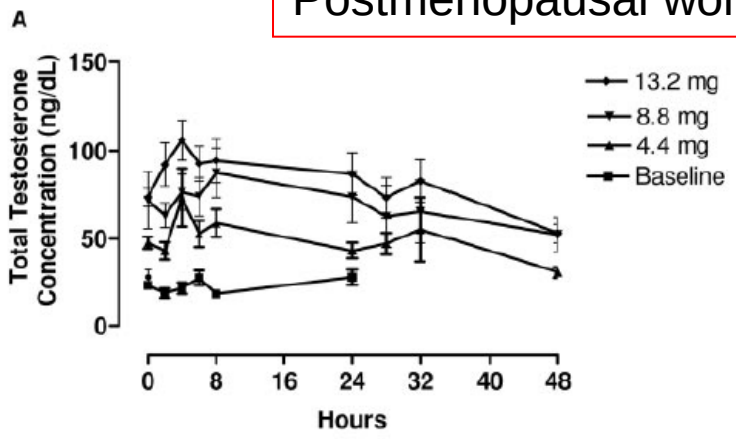
Data are expressed as adjusted odds ratio (95% confidence limit). Odds ratios correspond to 1-SD increments in individual hormone models. In addition to concurrent, baseline and change from baseline for all hormones, tertiles/quartiles of T were also evaluated; data are not reported in this table. Means (SD) in the overall models: T, 40.39 ng/dL (22.33); FSH, 52.25 mIU/mL (50.07); E2, 60.92 pg/mL (79.17); DHEAS, 131.21 μg/dL (81.00); and SHBG, 45.49 nM (26.46).

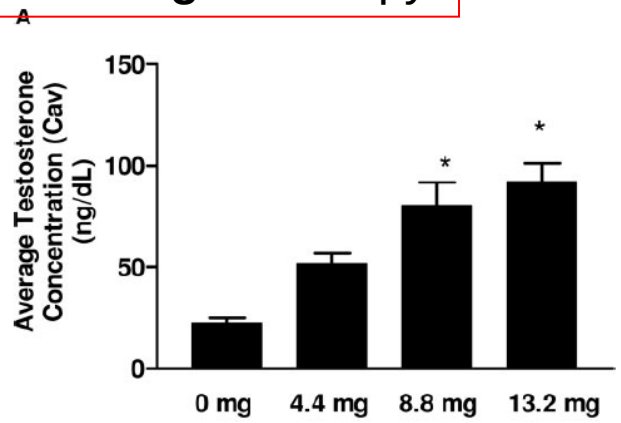
[a] $P < .05$; [b] $P < .01$; [c] $P < .001$; [d] $P < .0001$.

Randolph et al J Clin Endocrinol Metab 2015;100:258-266

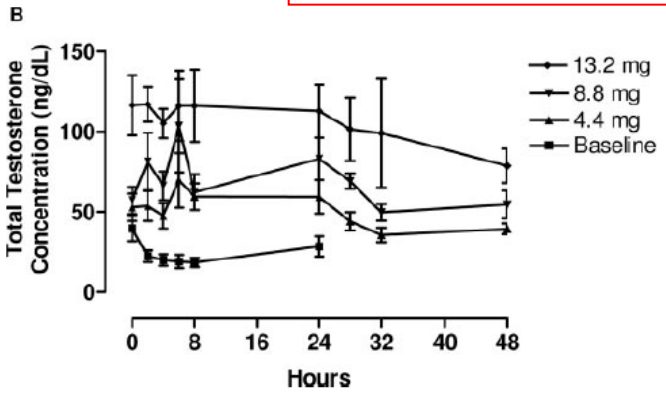
Pharmacokinetics of a testosterone gel in healthy postmenopausal women

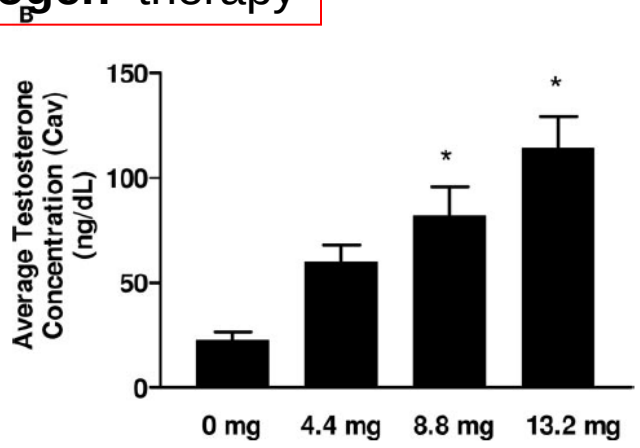
Postmenopausal women **not on estrogen** therapy





Postmenopausal women **on estrogen** therapy





Singh et al J Clin Endocrinol Metab 2006;91:136-144

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

Parish et al J Sex Med 2021;17:18:849-867

Monitoring

Total testosterone levels should be measured before initiating therapy to exclude women with midrange to high baseline testosterone concentrations. SHBG should also be measured as

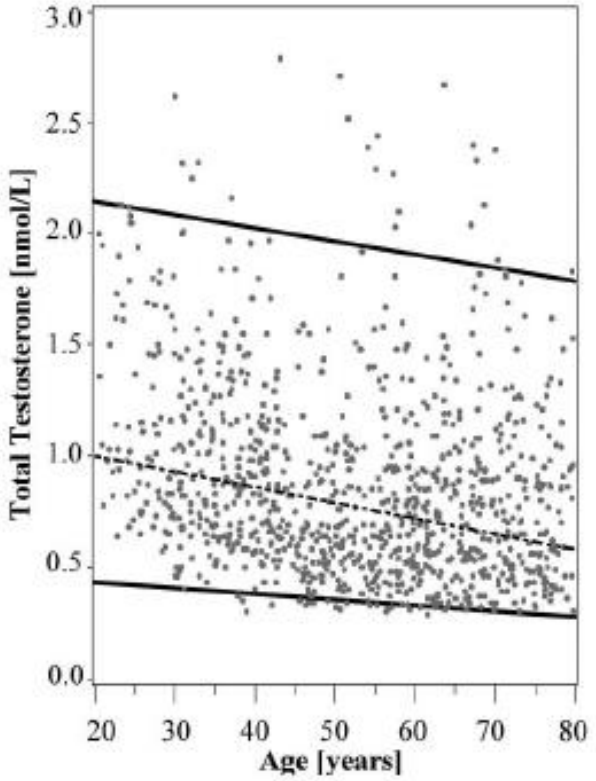
Total testosterone levels should be assessed 3–6 weeks after initiating therapy to enable titration and ensure the patient is not applying an excessive dose. If the dose is increased, based on

repeated within 6 weeks. Different preparations will have different absorption rates and hence different pharmacokinetics that determine when the peak blood level is achieved. As this is unknown for most products in women, the goal of testing blood levels is to prevent excessive dosing but not to treat to a target blood level of testosterone. Clinicians should ensure that the total testosterone does not significantly exceed the upper limit of the reference range for normal premenopausal women indicated by

Age-specific reference ranges for serum testosterone concentrations in women measured by LC-MS/MS

TABLE 3. Age-specific sex hormone reference ranges based on quantile regression models

	Reference range (2.5–97.5%)		
Age (yr)	TT (nmol/liter)	AD (nmol/liter)	Free T (nmol/liter)
20–29	0.42–2.12	1.61–7.46	0.0020–0.0294
30–39	0.39–2.06	1.20–6.00	0.0022–0.0280
40–49	0.37–2.00	0.89–4.77	0.0024–0.0262
50–59	0.34–1.94	0.66–3.79	0.0026–0.0246
60–69	0.31–1.88	0.52–3.04	0.0028–0.0230
70–80	0.29–1.82	0.48–2.52	0.0030–0.0213



Safety goal total Testosterone ≤ 2nmol/L (= 57ng/dL)

Haring et al J Clin Endocrinol Metab 2012;97:408-415

Summary and comments (I)

- Estrogen levels after menopause are low and reliable measurement requires robust and sensitive methodology:
  LC-MS/MS (or GC-MS/MS) present state-of-the-art.
- Although (very) low compared to the exposure before menopause, the persistent low estrogen exposure in postmenopausal women is physiologically and clinically important
- Although circulating estrogen levels are low, changes in these low levels, either by altered production or through altered bioavailability resulting from changes in SHBG binding, appear to have important clinical consequences
- Although differences in estrogen levels are clinically important and can have practical implications, endogenous estrogen levels in individual patients have very poor (if any) clinical predictive value and measurement is not clinically useful, with possible exception of monitoring of aromatase inhibition in cancer patients.

Summary and comments (II)

- For the different modes of administration of estradiol therapy, achieved blood levels are generally proportional to dosage.
- Interpretation of single point measurements of blood levels is complicated by factors such as pharmacokinetic profile, variation in timing of application, changes in SHBG.
- There are presently no validated target or safety estradiol levels for any specific clinical goal. Dosage can only be based on information from controlled trials and mainly on clinical monitoring
- Testosterone levels after menopause (as well as in premenopausal women) are very low compared to levels in men and reliable measurement requires robust and sensitive methodology: LC-MS/MS (or GC-MS/MS) present state-of-the-art.
- Clinical use is limited to women with clinical hyperandrogenism and safety monitoring of testosterone treatment (safety target: total T within range for premenopausal women, i.e. ≤ ~2nmol/L or 57ng/dL). Remark: improved specificity by use of free T (indicative <0,5ng/dL)

Thank you!

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