



Menopausal Symptoms as markers of CVD disease susceptibility

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ARE POSTMENOPAUSAL WOMEN ALL THE SAME ?

Estrogen deprivation and hot flushes (HF)

- HF are not just a symptom
- HF underline the brain susceptibility to estrogen deprivation

Menopausal symptoms as markers of difference and disease vulnerability

Postmenopausal Hot Flush and CVD

A thermoregulatory event associated with

- Lower FMD
- Increased carotid intima–media thickness
- Aortic calcifications
- Adverse lipid profile/body weight & fat
- Reduced high frequency heart rate variability
- Adverse blood pressure levels

A marker of difference and CVD susceptibility ?

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EDITORIAL

Are hot flashes linked to cardiovascular risk? It is too early to tell

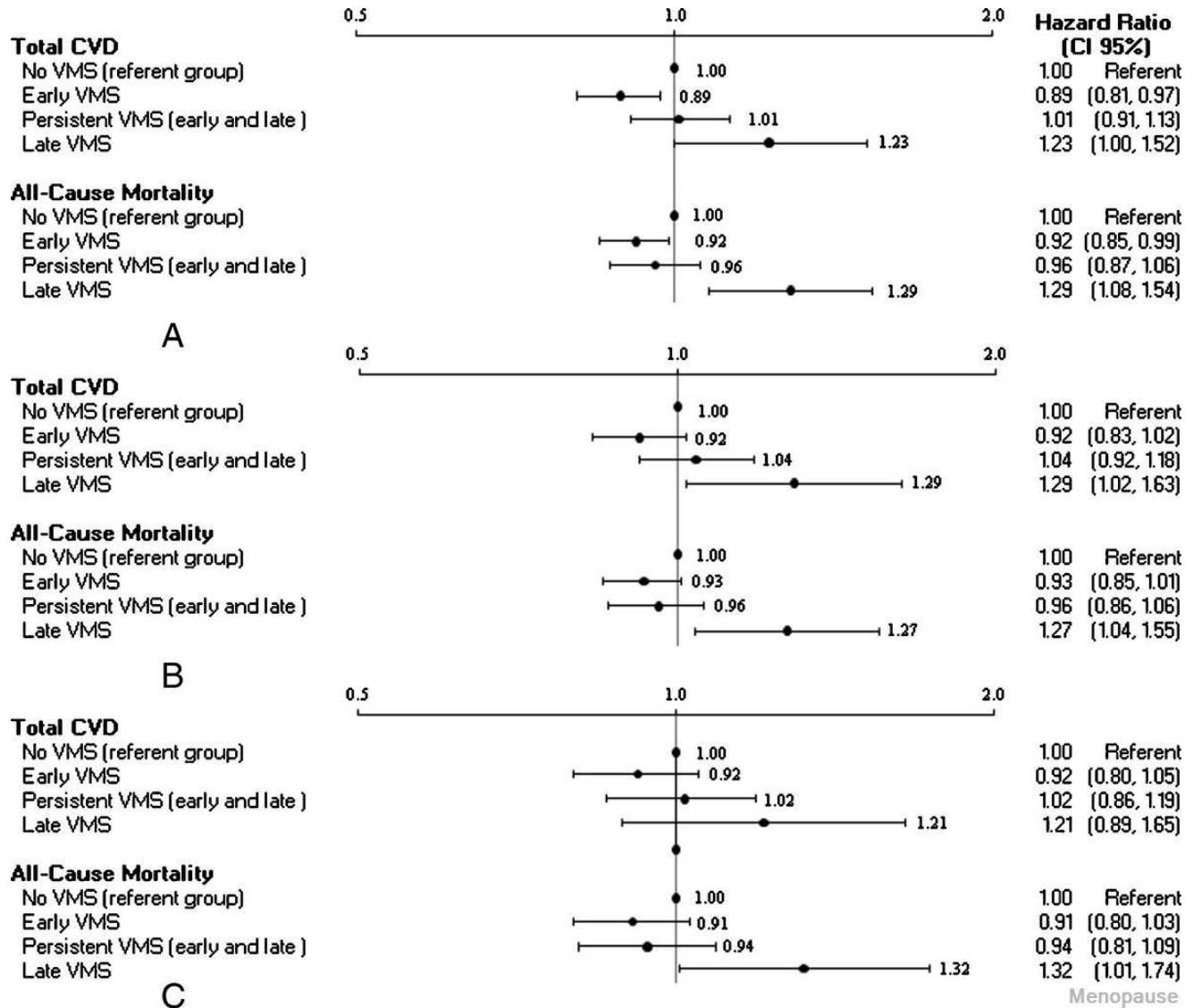
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Cleveland Clinic
Cleveland, OH

Vasomotor symptoms and mortality: the Rancho Bernardo Study

- n = 867, 11.5-year average follow-up compared with women who did not report HF, symptomatic women had
- all-cause mortality HR, 0.85 (0.68-1.07)
- CVD mortality HR 0.92 (0.66-1.27)
- CHD mortality HR, 0.90 (0.52-1.53)

However : limited power and possible recall bias

Vasomotor symptoms and cardiovascular events in PMW



Forest plot of the risks of total CVD and all-cause mortality by VMS status among the total cohort (A), women with natural (nonsurgical) menopause (B), and women who never used hormone therapy (C). Data shown are from the fully adjusted models. CVD, cardiovascular disease; VMS, vasomotor symptoms

VMS are associated with increased risk of CHD

Dutch and Swedish population-based sample of 10,787 women enrolled between 1995 and 2000, aged 46 to 64 years, and free of CVD at baseline.

	Hot flushes	Night sweats
No. of cases	150	134
Model 1	1.11 (0.89-1.40)	1.39 (1.11-1.74)
Model 2	1.06 (0.84-1.35)	1.33 (1.05-1.69)
Model 3	1.01 (0.79-1.28)	1.25 (0.99-1.58)

Models were stratified by study center.

Model 1, adjusted for age (continuous); model 2, adjusted for education level (low, medium, high), smoking (never, past, current), physical activity (inactive, active), ovariectomy (yes, no), hormone therapy use (never, past, current), oral contraceptive use (never, past, current), and menopause status (premenopausal, postmenopausal, perimenopausal); model 3, model 2 with body mass index (continuous), systolic and diastolic blood pressure (continuous), and total cholesterol (continuous).

Menopause

Postmenopausal Hot Flush and CVD

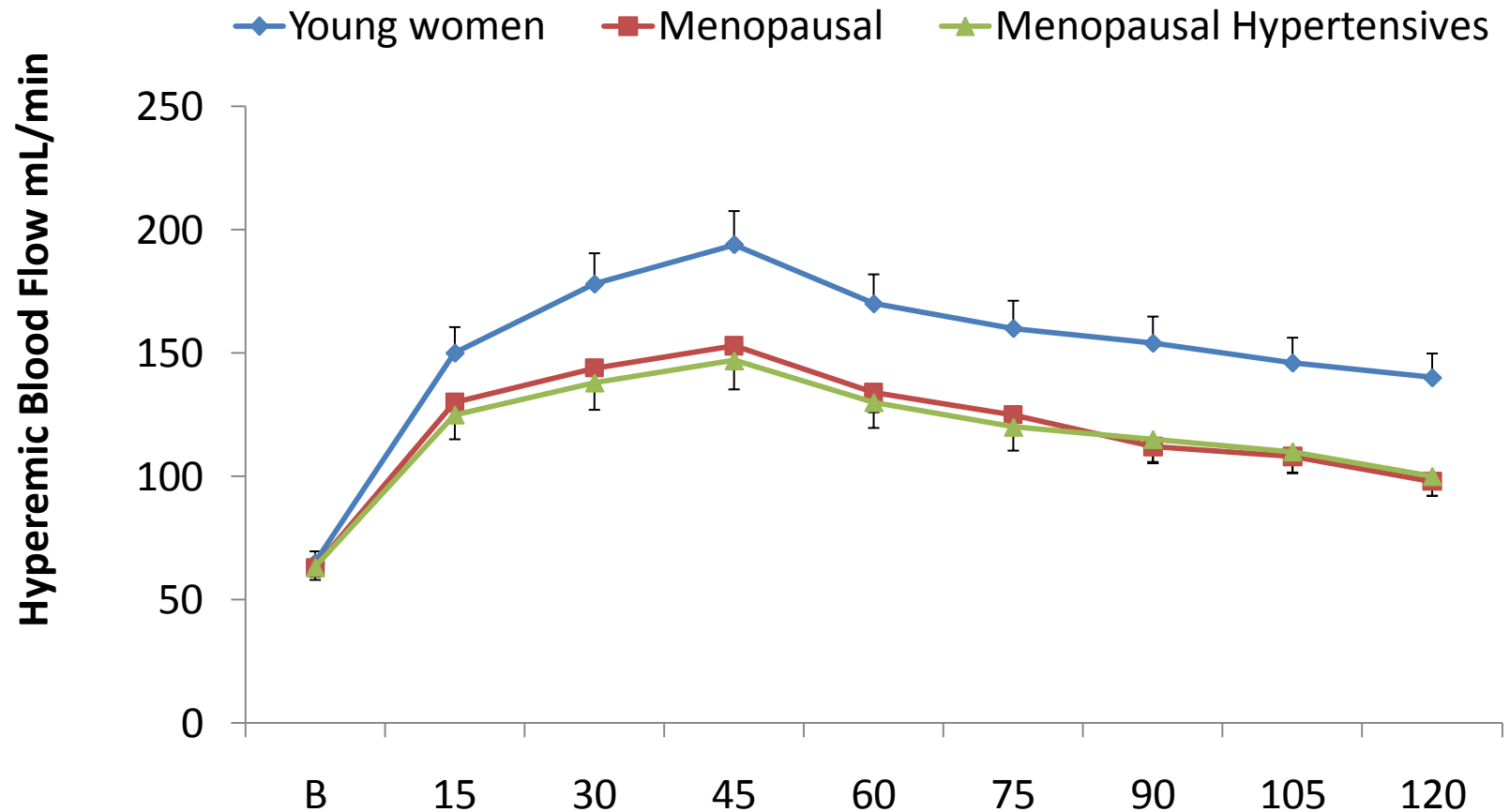
A thermoregulatory event associated with

– **Lower FMD**

- Increased carotid intima–media thickness
- Aortic calcifications
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A marker of difference and CVD susceptibility ?

Menopause Is Associated with Endothelial Dysfunction in Women



Hot Flashes and Subclinical Cardiovascular Disease

Findings From the Study of Women's Health Across the Nation Heart Study

Association Between Hot Flashes and FMD

Model	FMD	
	β (SE)*	P
1	-1.01 (0.41)	0.01
2	-1.02 (0.39)	0.01
3	-0.99 (0.41)	0.02
4	-0.97 (0.44)	0.03

Model 1: age, site, and race.
Model 2: model 1 covariates plus baseline lumen diameter, BMI, education, DBP, and HT use.
Model 3: model 2 covariates plus education, menopausal status, HDL, LDL, triglycerides, glucose, diabetes history, lipid medication use, smoking status, and physical activity.
Model 4: model 3 covariates plus $E2_{log}$ and blood draw timing.
*Regression coefficient for any versus no hot flashes.

Women with hot flashes had significantly lower FMD

Postmenopausal Hot Flush and CVD

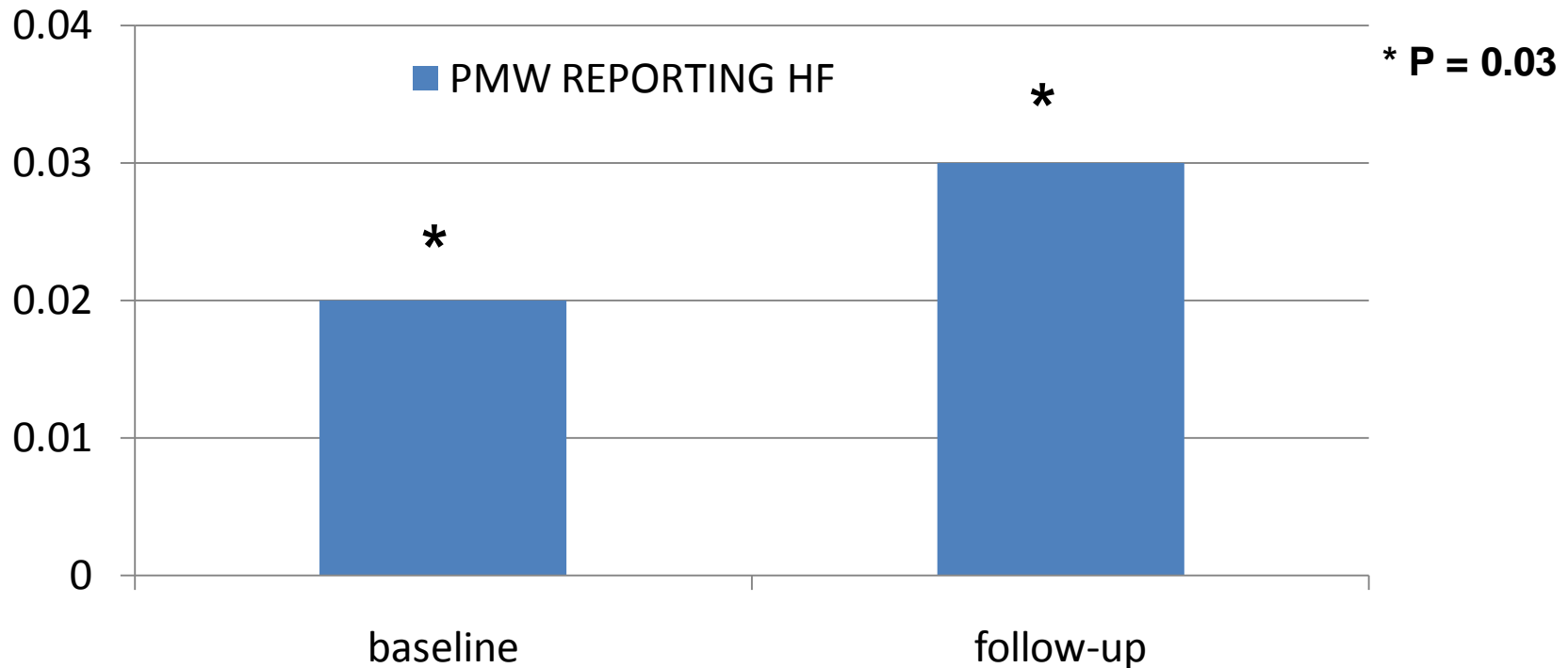
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Hot flashes and carotid intima media thickness among midlife women

Difference of IMT vs asymptomatic women



women reporting HF may have higher IMT than do women without HF

Association between HF frequency and IMT

SWAN, Study of Women's Health Across the Nation

	IMT at follow-up			
	Model 1		Model 2	
	Regression coefficient (SE) ^a	<i>P</i>	Regression coefficient (SE) ^a	<i>P</i>
Hot flashes at follow-up				
None	–		–	
1-5 d	0.02 (0.01)	0.09	0.02 (0.01)	0.14
≥6 d	0.02 (0.01)	0.04	0.03 (0.01)	0.02
Hot flashes across visits				
None	–		–	
Hot flashes at one visit	0.02 (0.01)	0.20	0.02 (0.01)	0.13
Hot flashes at both visits	0.03 (0.01)	0.03	0.03 (0.01)	0.03

•Model 1 covariates: age, site, race, education, menopause, BMI, smoking, SBP, DBP, HDL, LDL, triglycerides, glucose, physical activity, diabetes/medication use, CVD status/medication use, and HT use.

•Model 2 covariates: age, site, race, education, BMI, smoking status, SBP, DBP, HDL, LDL, triglycerides, glucose, physical activity, diabetes status/medication use, CVD status/medication use, HT use, cycle day of blood draw, and estradiol.

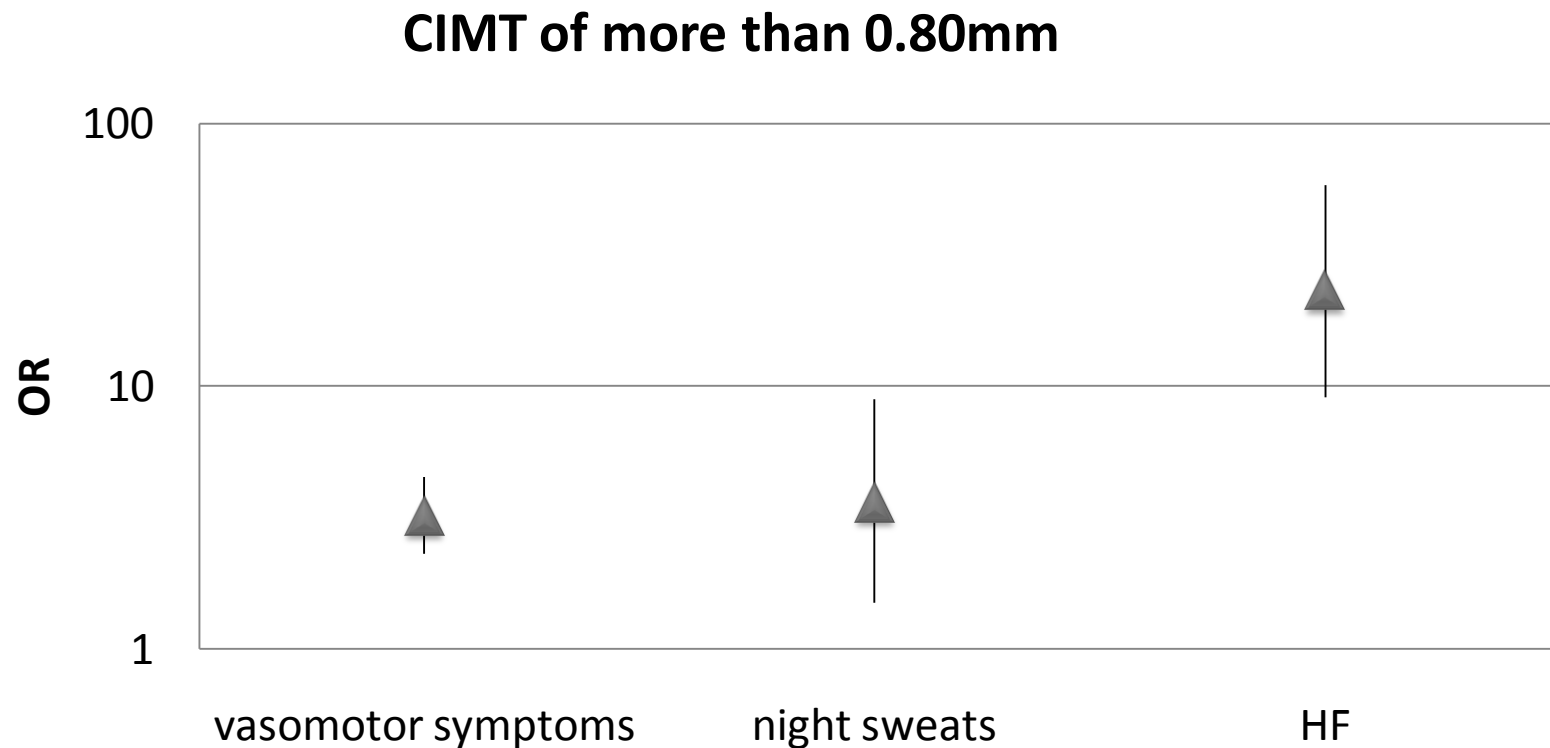
•Hot flashes at follow-up and hot flashes across visits modeled in separate Models.

•SWAN, Study of Women's Health Across the Nation; IMT, intima media thickness;

•^aRegression coefficient corresponds to mean IMT difference (mm) from referent of no hot flashes.

Impact of hot flashes and night sweats on carotid intima-media thickness among PMW

carotid intima-media thickness (CIMT) was determined and the relationship with vasomotor symptoms evaluated in PMW with (n=87) or without (n=117) vasomotor symptoms.



Postmenopausal Hot Flush and CVD

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Hot Flashes and Subclinical Cardiovascular Disease

*OR for any vs no hot flashes.

Model	aortic calcification		coronary artery calcification	
	OR (CI)*	P	OR (CI)*	P
1	1.55 (1.10–2.19)	0.01	1.48 (1.04–2.12)	0.03
2	1.53 (1.02–2.29)	0.04	1.34 (0.88–2.05)	0.17
3	1.53 (1.02–2.29)	0.04	1.33 (0.87–2.03)	0.19
4	1.63 (1.07–2.49)	0.02	1.31 (0.84–2.05)	0.24

Model 1: age, site, and race.

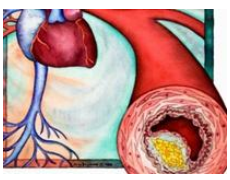
Model 2a: model 1 covariates plus BMI, smoking, education, SBP, LDL, HDL, triglycerides, glucose, physical activity, antidepressant use, depressive symptoms, HT use, lipid medication use, and menopausal status.

Model 2b: model 1 covariates plus BMI, education, SBP, LDL, HDL, triglycerides, glucose, diabetes history, antidepressant use, depressive symptoms, HT use, and menopausal status.

Model 3a: model 2a covariates plus diabetes history.

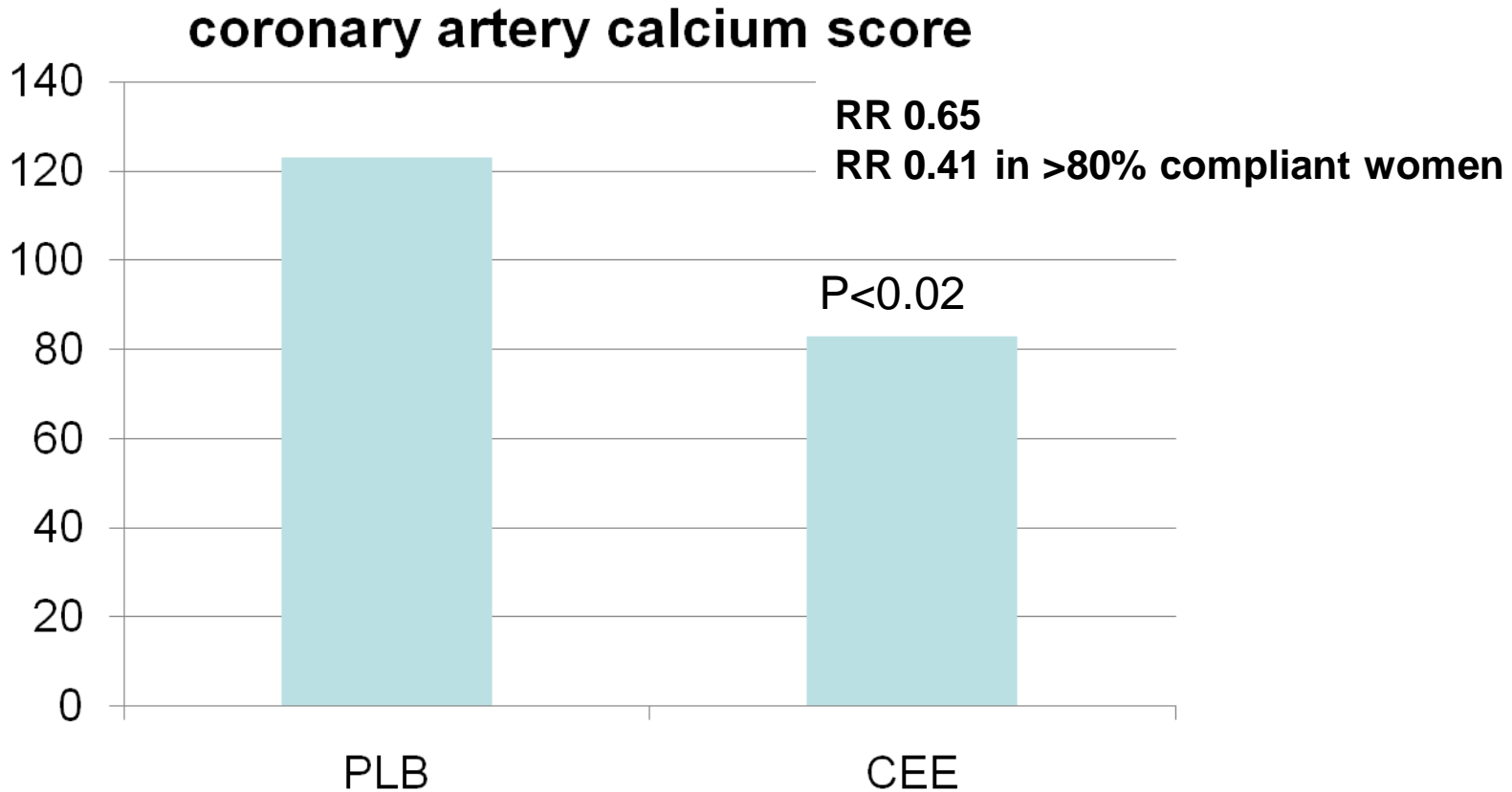
Model 3b: model 2b covariates plus diabetes history, smoking, physical activity, and lipid medication use.

Model 4: model 3 covariates plus E2_{log} and blood draw timing



Estrogen Therapy and Coronary-Artery Calcification

- ancillary substudy of the WHI; CEE(0.625 mg per day) vs PLB
- CT of the heart in 1064 women (50-59 yrs) at randomization and after f 7.4 yrs of treatment.

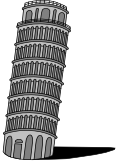


Postmenopausal Hot Flush and CVD

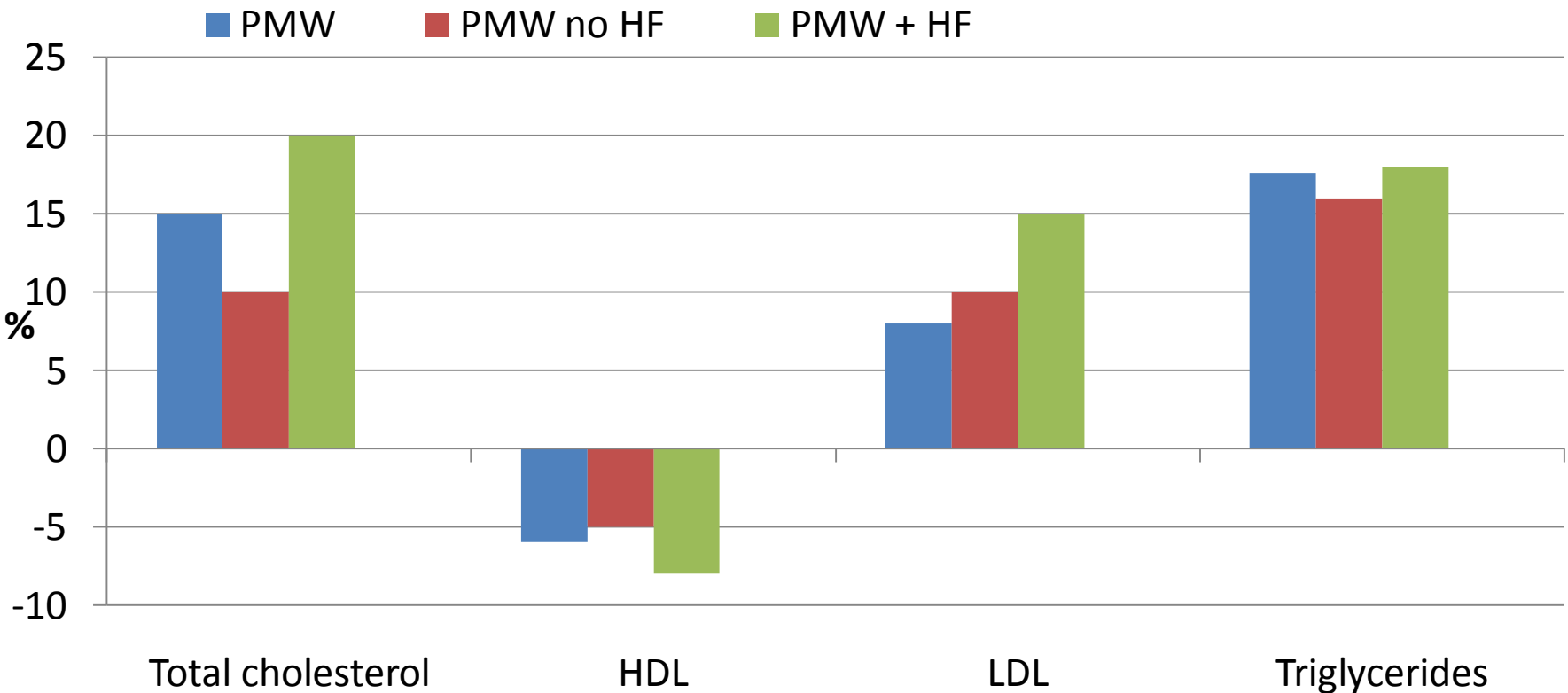
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Effect of Menopause & symptoms on Lipid Profile



% change compared to premenopause

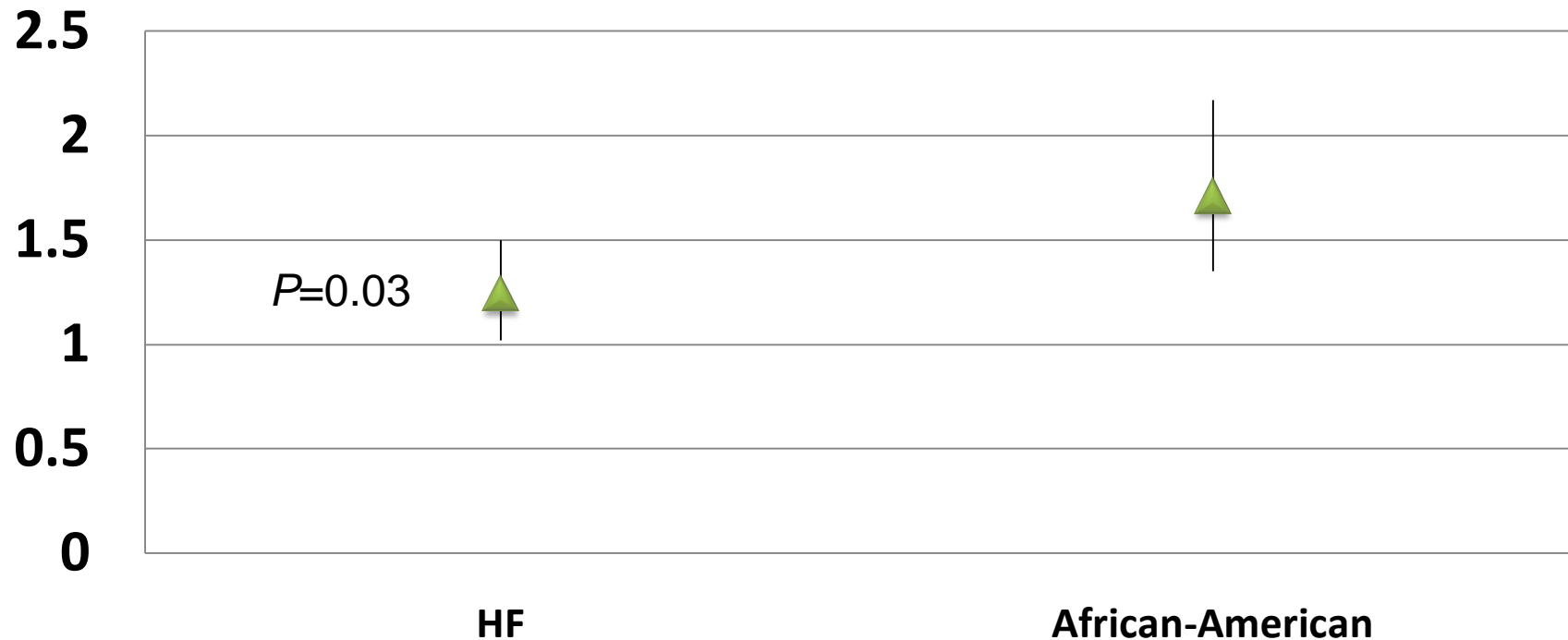
P<0.05 vs corresponding premenopausal levels

NS among groups

Gains in Body Fat and Vasomotor Symptom Reporting Over the Menopausal Transition

The Study of Women's Health Across the Nation

Body fat gain associated with greater odds of reporting hot flashes



adjusted for age, site, race/ethnicity, education, smoking, parity, anxiety, and menopausal status

Odds ratios of hot flashes associated with three measures of abdominal adiposity

The Study of Women's Health Across the Nation Heart Study

adiposity	Model 1	Model 2
Total abdominal	1.28 (1.06-1.55) ^b	1.24 (1.01-1.52) ^b
Visceral	1.15 (0.95-1.39)	1.15 (0.93-1.41)
Subcutaneous	1.30 (1.07-1.58) ^c	1.26 (1.02-1.55) ^b

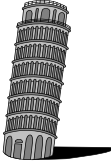
Model 1: Adjusted for age and site.

Model 2: Adjusted for age, site, race/ethnicity, education, smoking, menopausal status, hormone use, antidepressant use, anxious symptoms.

^aOdds ratios correspond to every 1-SD increase in adiposity.

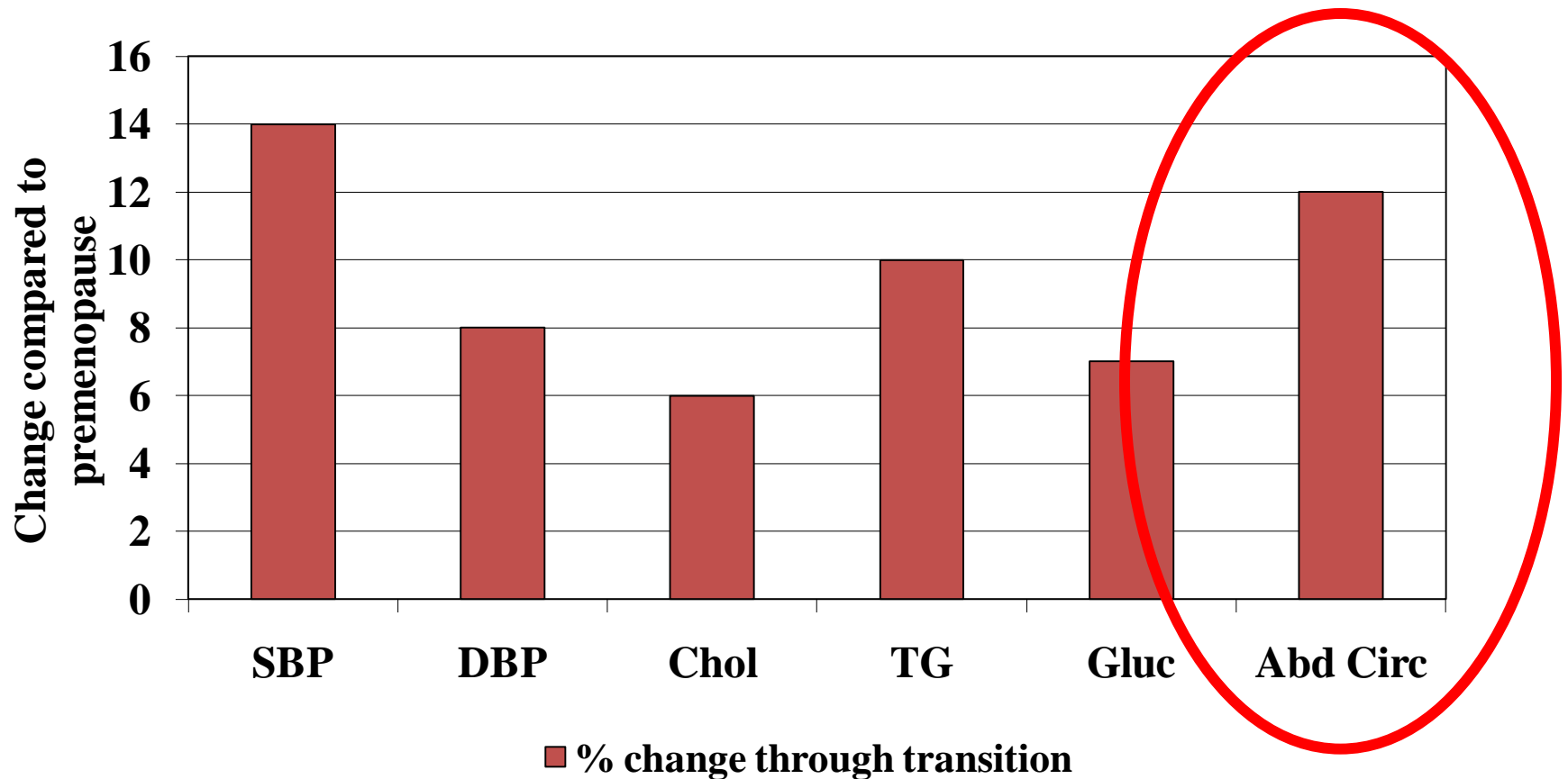
^b $P < 0.05$.

^c $P < 0.01$.

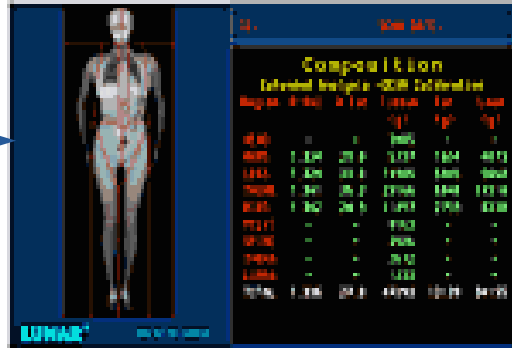
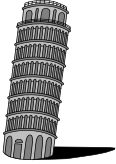


MENOPAUSAL TRANSITION : EFFECTS ON CARDIOVASCULAR RISK FACTORS

Longitudinal evaluation of 496 normal women



DEXA MEASUREMENT OF BODY FAT DISTRIBUTION



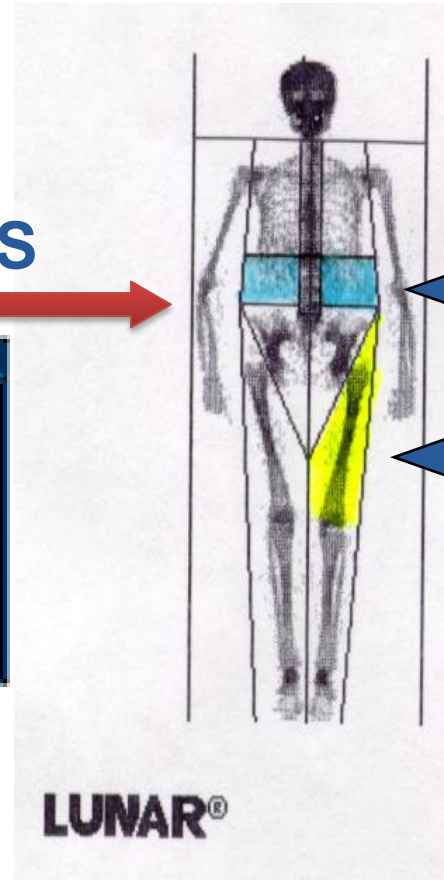
ARMS



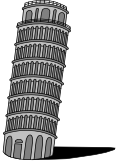
TRUNK



LEGS

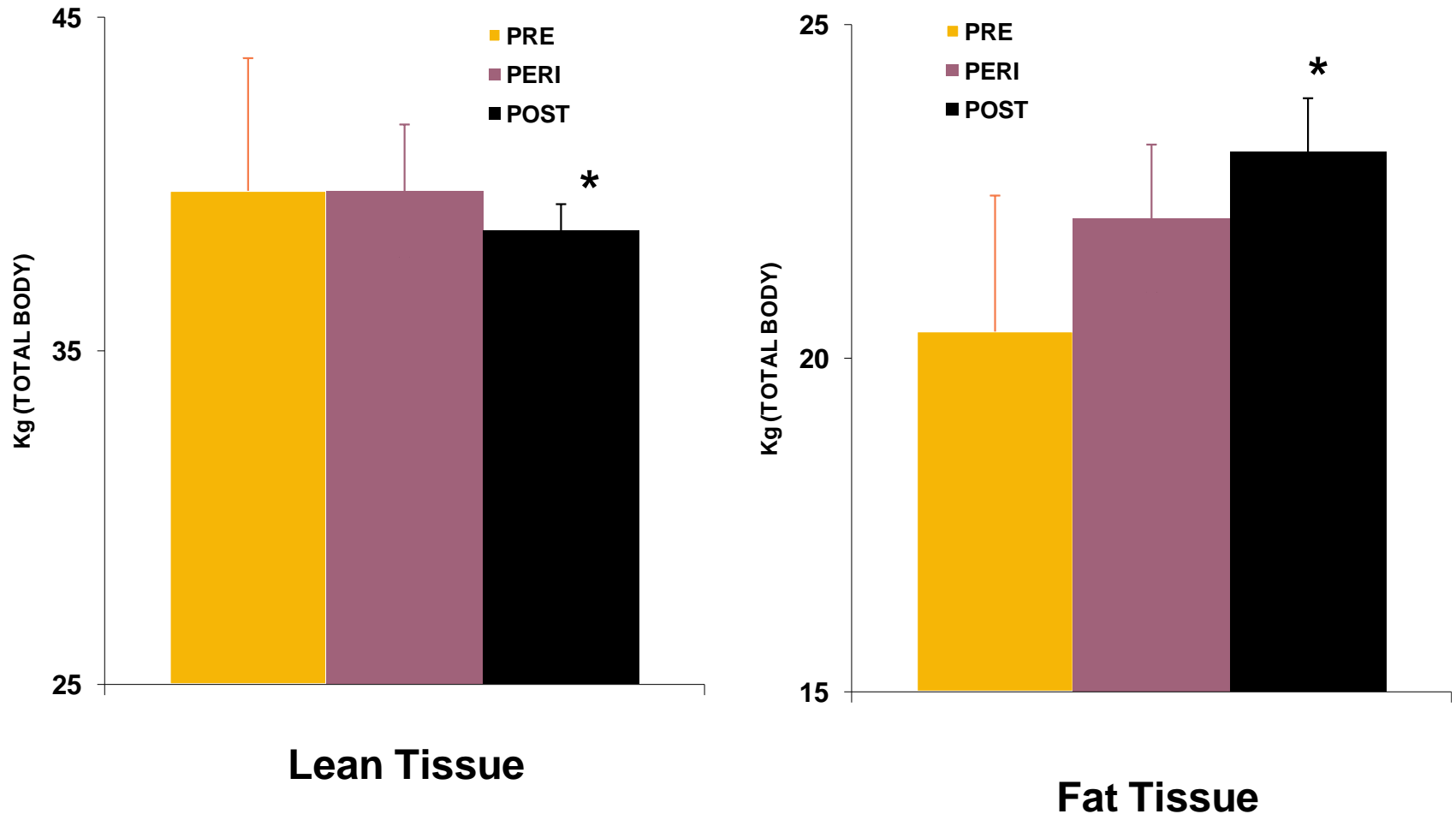


BODY COMPOSITION & BODY FAT DISTRIBUTION IN DIFFERENT REGIONS

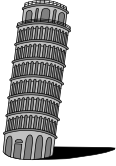


BODY WEIGHT and BODY COMPOSITION

in pre (n=380), peri (n=263) and postmenopausal (n=432) women

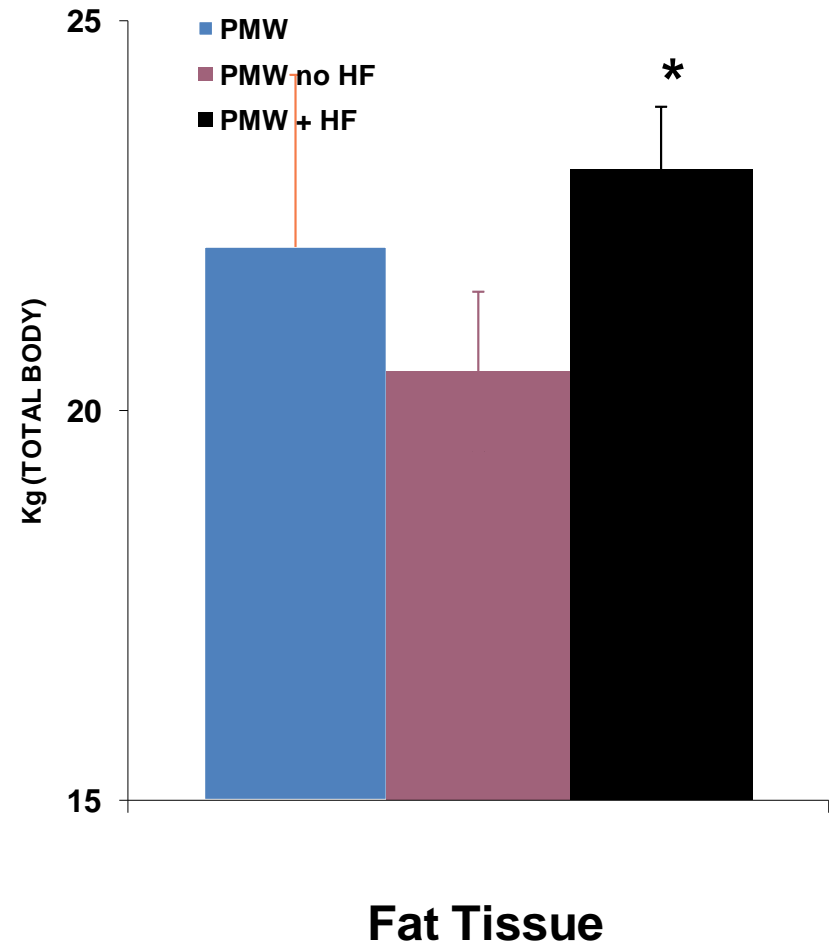
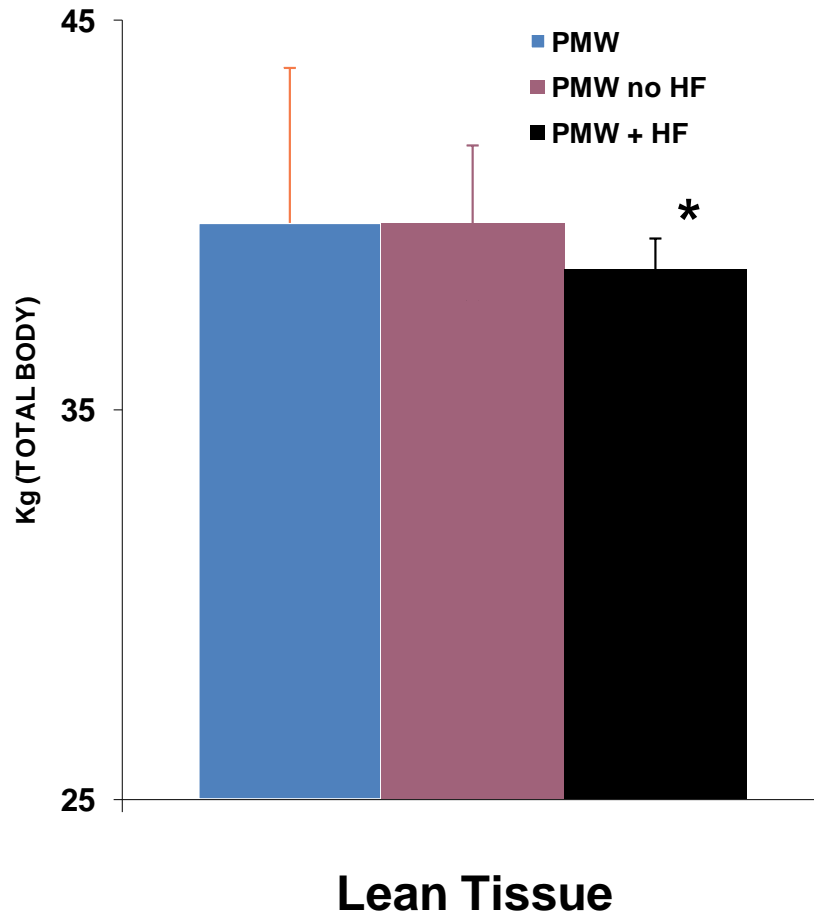


* p<0.05 (vs premenopausal values)



BODY WEIGHT and BODY COMPOSITION

in postmenopausal (n=132) women



* p<0.05 (vs PMW no HF values)

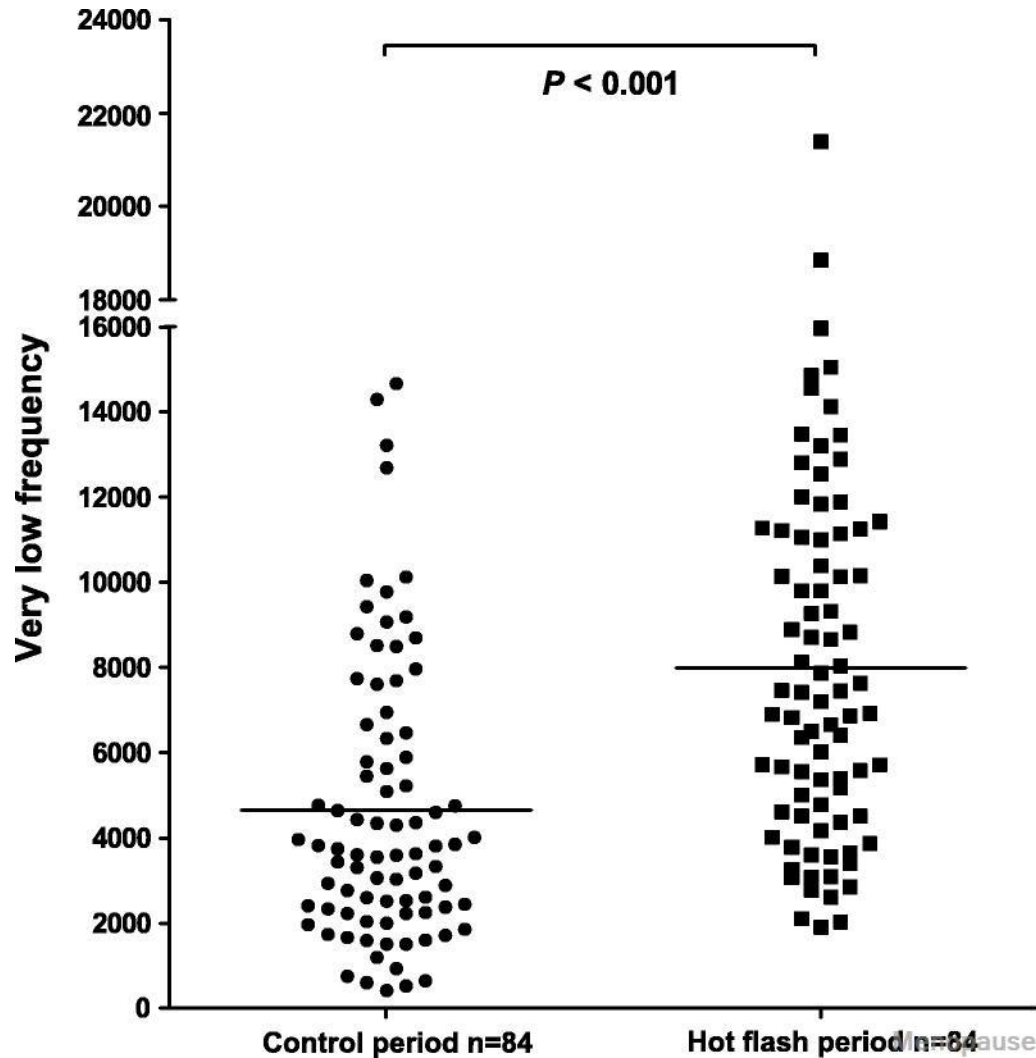
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A marker of difference and CVD susceptibility ?

Association between hot flashes and heart rate variability in recently postmenopausal women

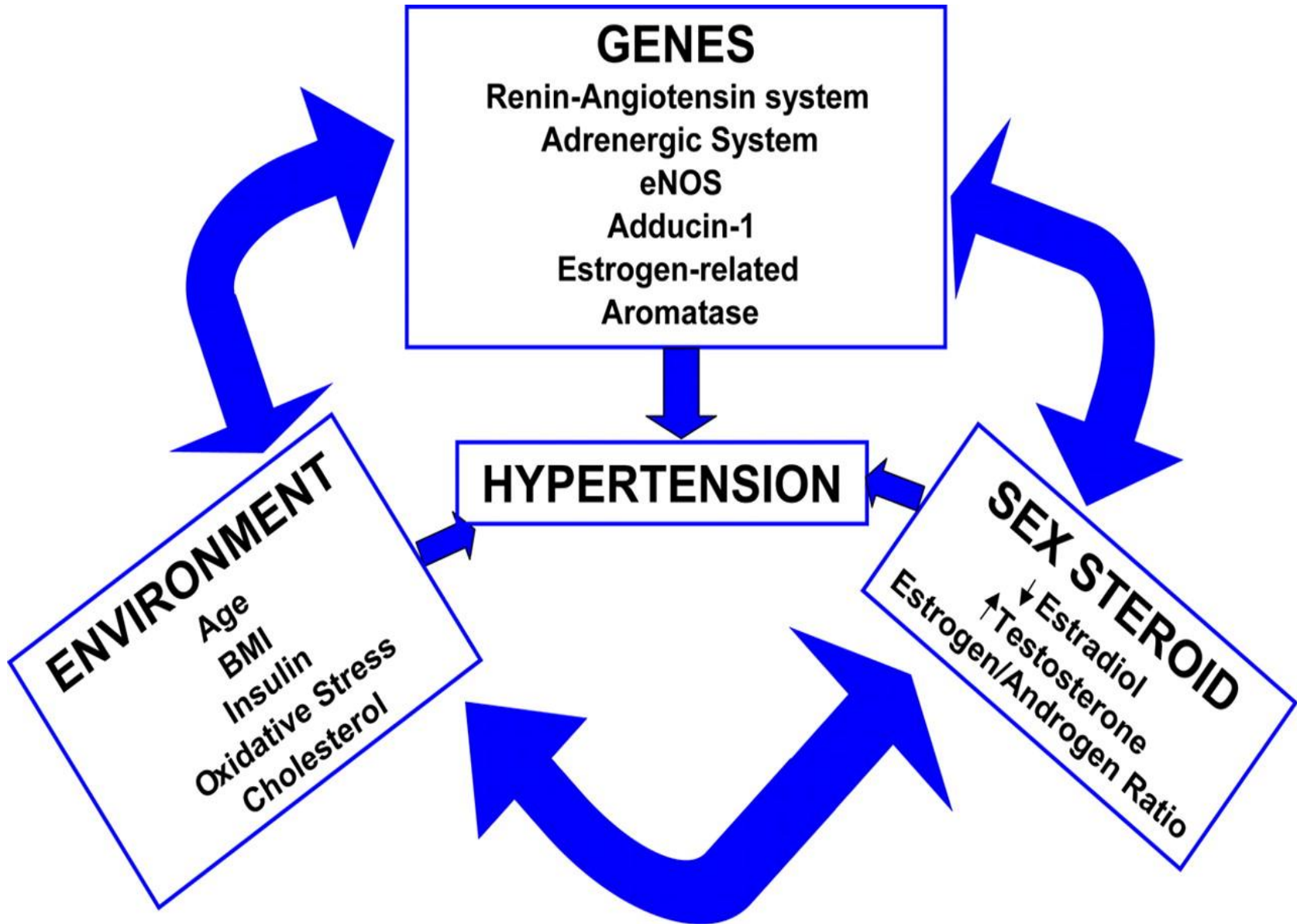


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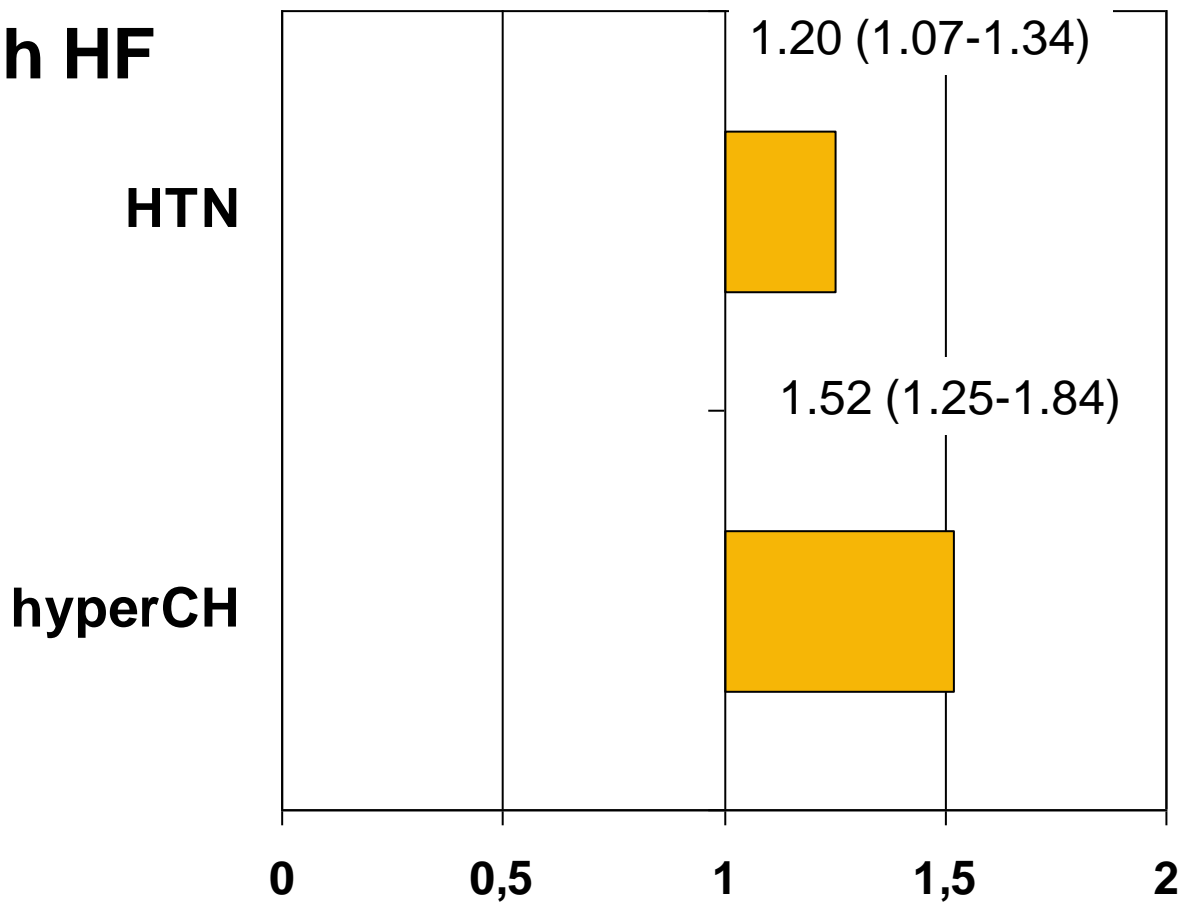
A marker of difference and CVD susceptibility ?



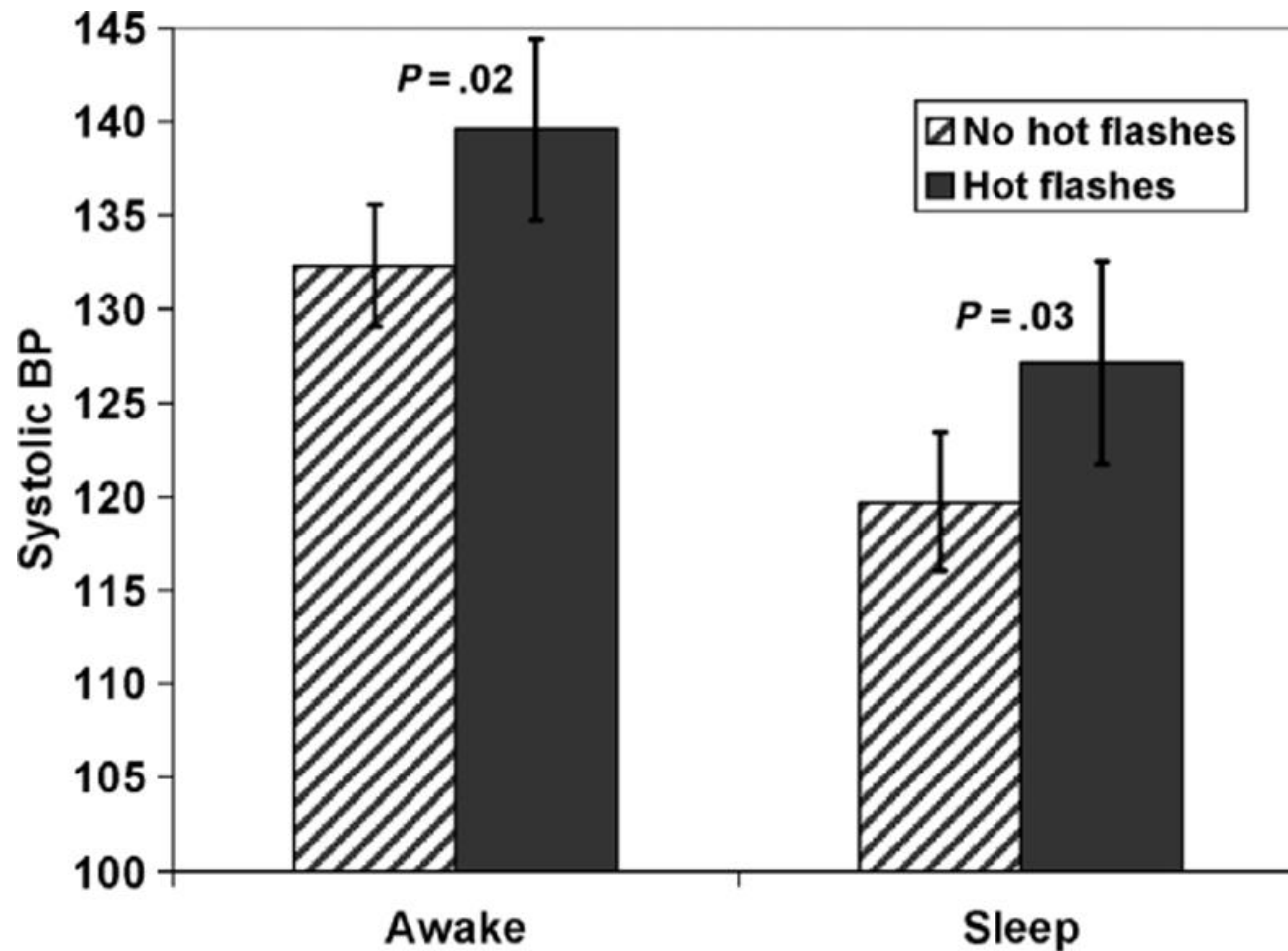
HF worsen cardiovascular risk

5523 women aged 46-57 years, of whom 38 percent reported night sweats and 39 percent hot flashes

OR in PMW with HF

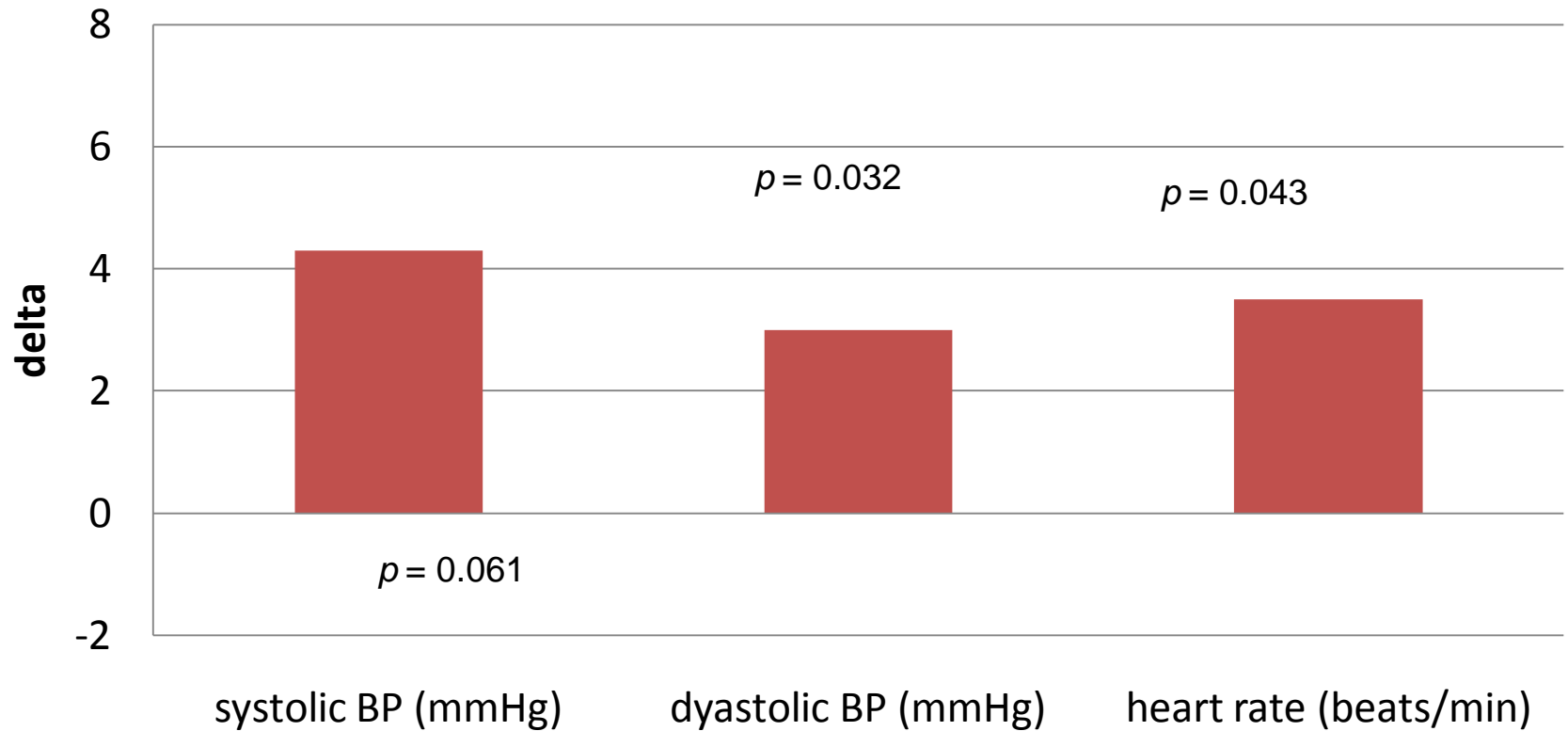


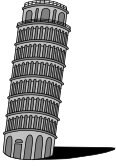
Hot flash correlates with high blood pressure



Vasomotor hot flushes and 24-hour ambulatory blood pressure in recently post-menopausal women

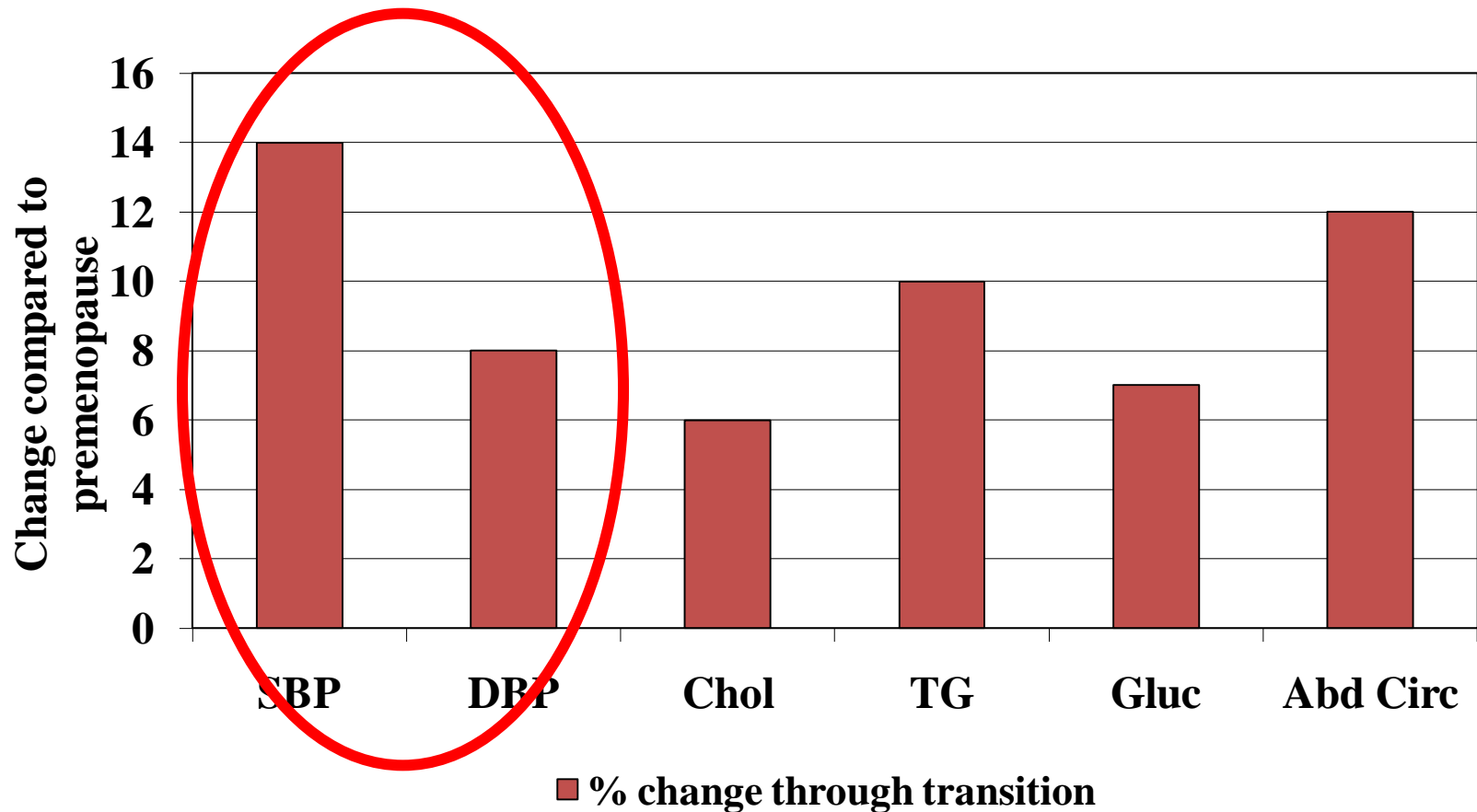
Changes associated with severe night-time HF





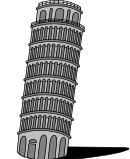
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Longitudinal evaluation of 496 normal women

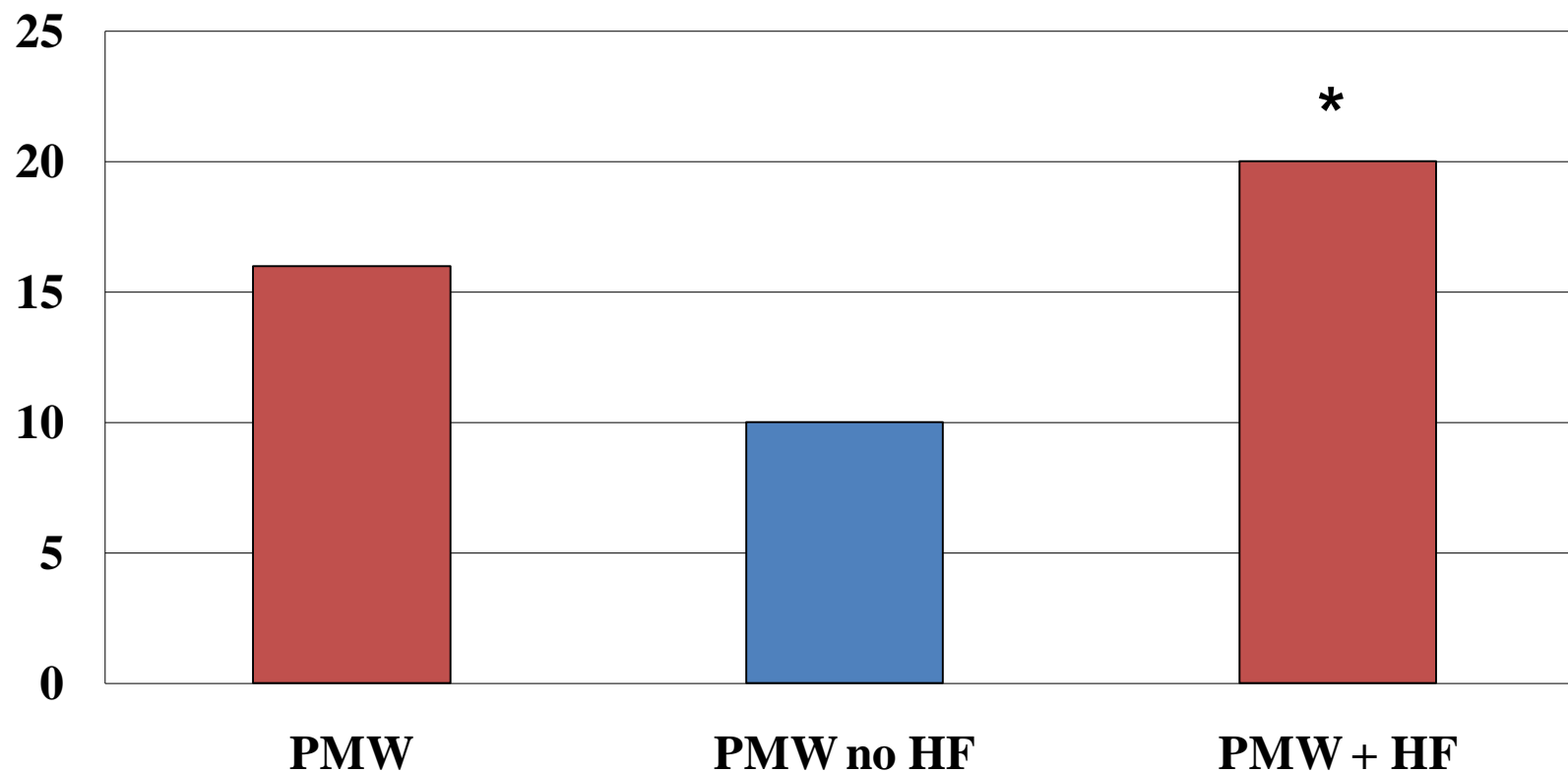


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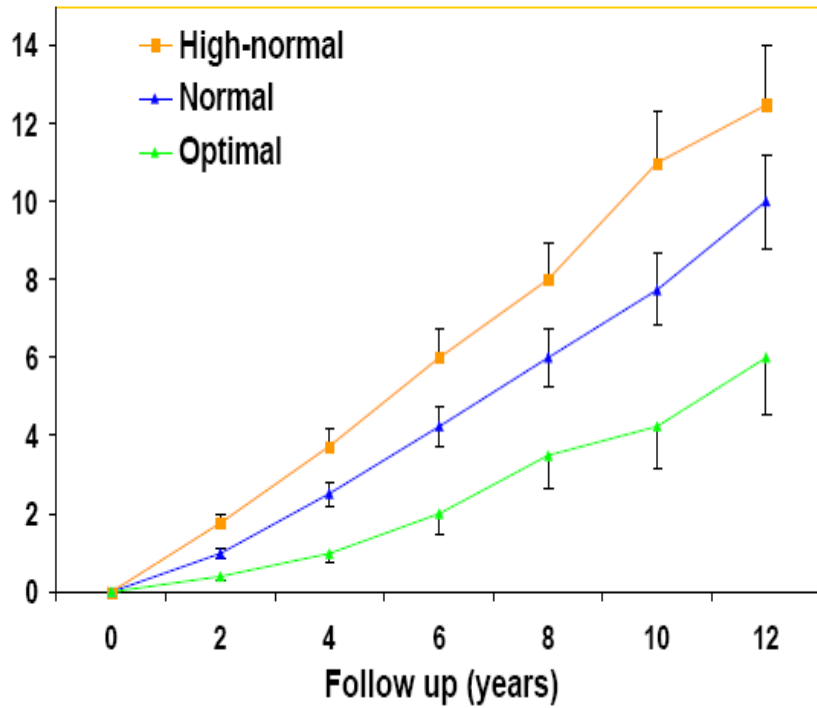
Systolic Blood Pressure % change through transition



* p<0.01 vs the other groups

Impact of High-Normal Blood Pressure on the Risk of CVD

Impact of High-normal BP on CV Events in Women (Cumulative Incidence %)



Adapted from: Vasan RS. *N Engl J Med* 2001;345:1291-1297

Definitions and Classification of Blood Pressure Levels
European Society of Hypertension – European Society of Cardiology (2003)

<i>Category</i>	<i>Systolic (mmHg)</i>	<i>Diastolic (mmHg)</i>
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	>180	>110
Isolated systolic hypertension	>140	90

Journal of Hypertension 2003, Vol 21 No 6

Vasomotor Symptoms and CVD

- women with persistent VMS had adverse changes in parameters of subclinical atherosclerosis/ surrogate end points for CVD
- further research examining the mechanisms underlying these associations is needed.
- the predictive value of VMS for clinical CVD events and the effects of targeting HRT need to be further evaluated in appropriate prospective trials