Alterations of Lipid and Metabolic Profiles after Menopause

Korea University Medical School

Nan Hee Kim, MD. PhD.

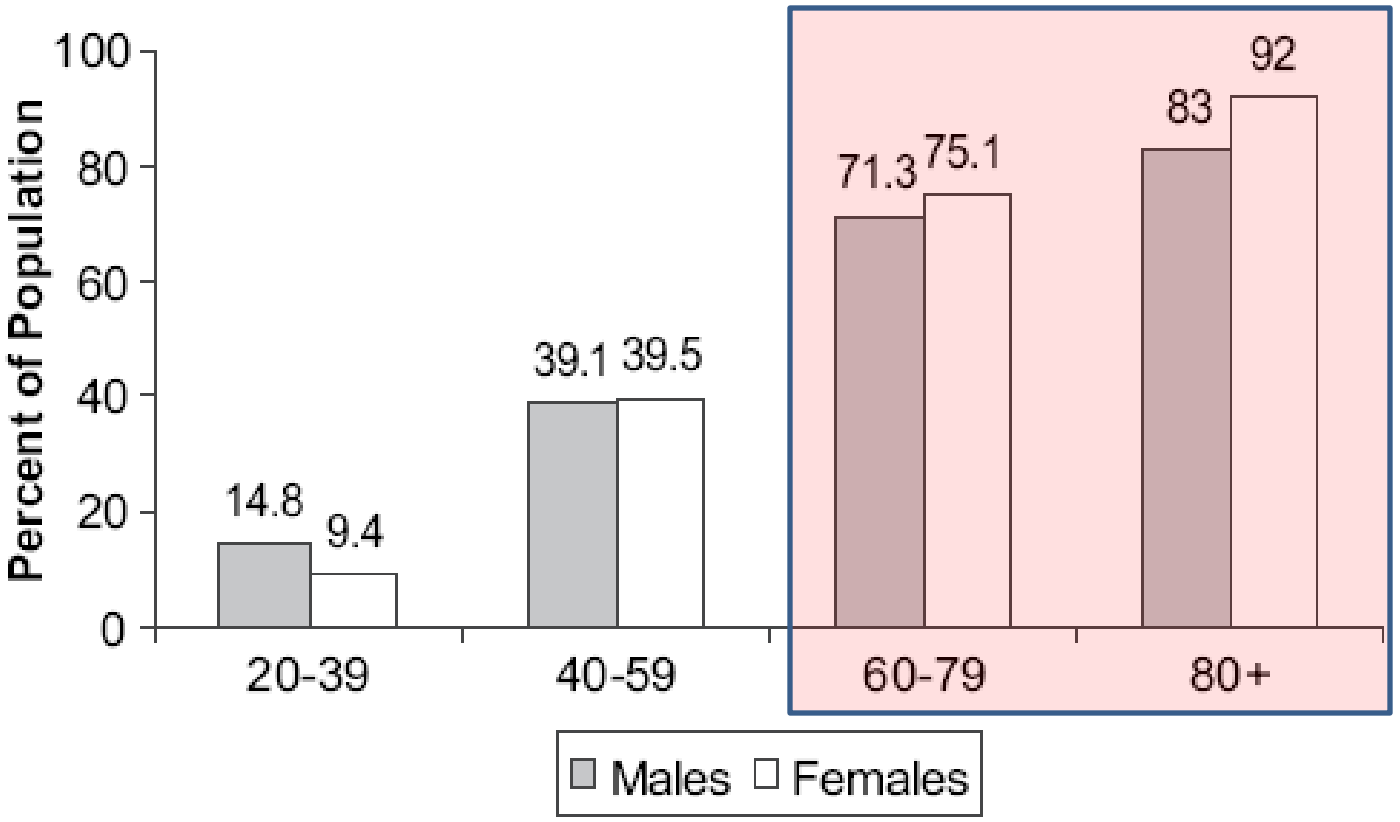
Abbreviations

- Premenopausal women: pre-M
- Perimenopausal women: peri-M
- Postmenopausal women: post-M
- Cardiovascular disease: CVD
- Metabolic syndrome: MetS
- Hypertension: HTN
- waist circumference: WC
- Final menstrual period: FMP

CVD increases after menopause

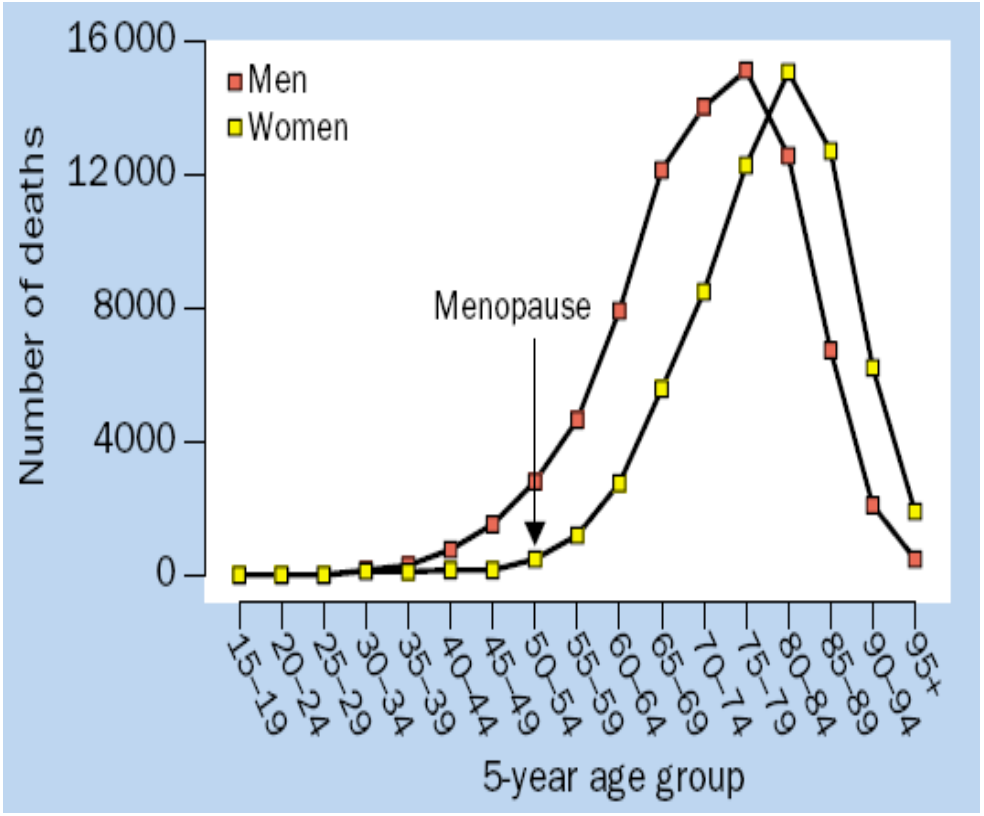
Heart Disease and Stroke Statistics—2007 Update

A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee

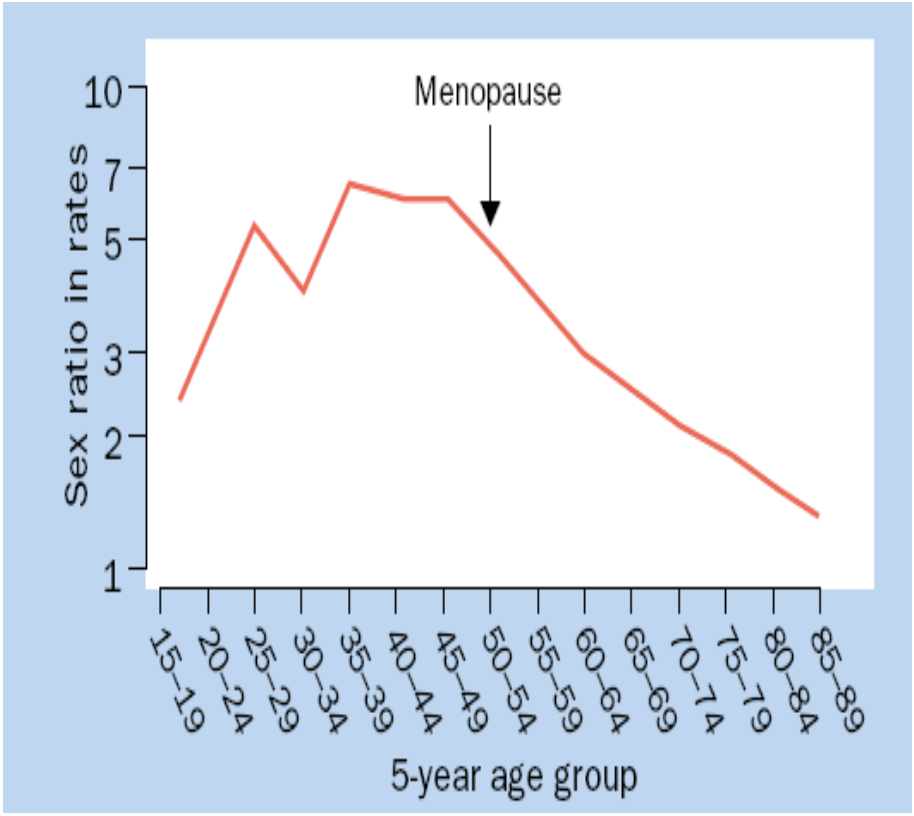


Circulation February 6. 2007

Increasing death rates in post-M in UK (1989-93)



Number of coronary death in both sexes



Ratio of M/F mortality rates by age

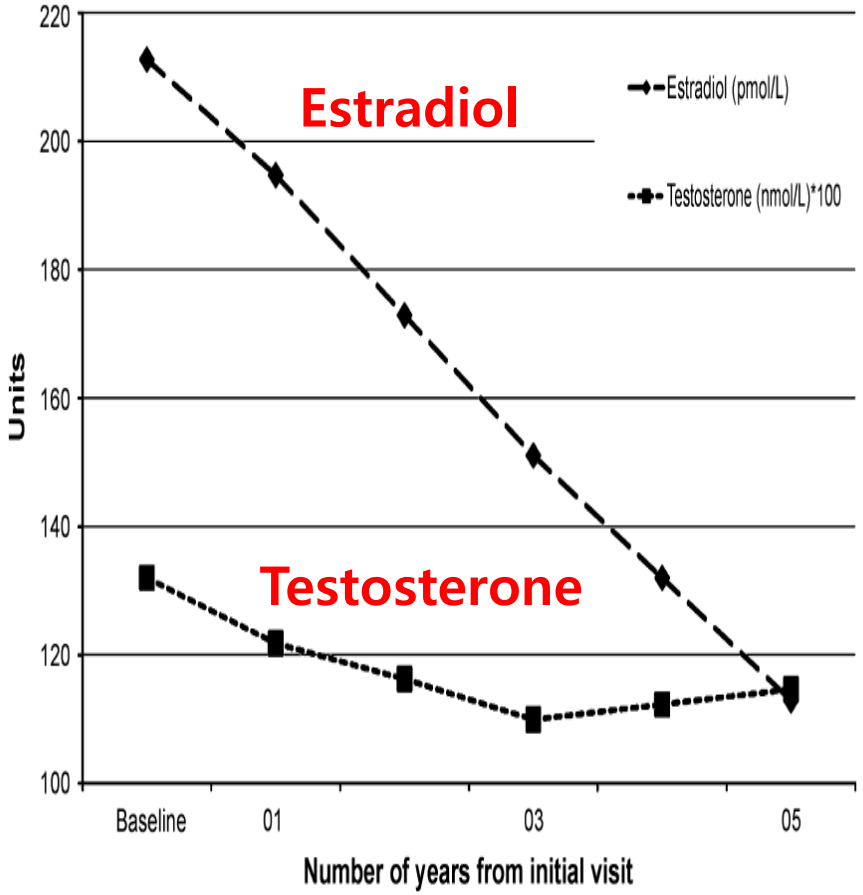
Lancet 1998; **351:** 1425–27

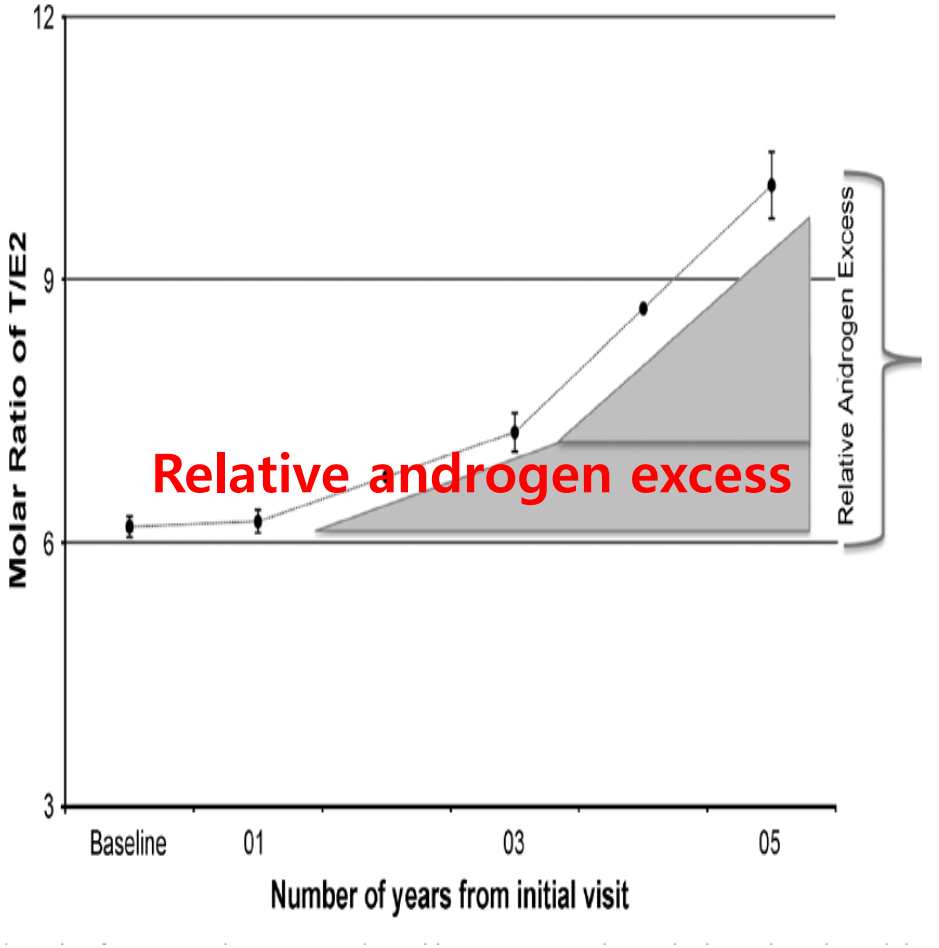
Mechanism of increased CVD risk in menopause

- Is this higher CV risk a function of aging or a consequence of menopause?

- It is very difficult to design studies that can separate the effects of the normal aging from menopause

Hormonal changes during menopausal transition





Menopause, 16(2), 2009

Changes of body weight and body composition

Change of weight and WC in midlife women

- The study of Women's Health Across the Nation (SWAN):

- Multicenter, multiethnic, longitudinal study designed to characterize the biological and psychosocial changes occurring during the menopausal transition

- The present study: 3064 subjects in SWAN, followed for over 3 yrs to evaluate weight and WC changes

Change of weight and WC in midlife women

- Mean weight increases by 2.1kg or 3%
- Mean WC increases by 2.2cm, 2.8%
- No association with menoapusal status and changes of weight or WC

	Weight gain		Waist gain	
	OR‡	95% CI‡	OR	95% CI
Baseline age (years)	0.98	0.94, 1.03	1.03	0.96, 1.05
Baseline menopausal status				
Premenopausal§				
Early perimenopausal	1.26	0.96, 1.64	1.39	1.04, 1.86
Change in menopausal status				
No change§				
From premenopausal to early perimenopausal	0.93	0.90, 1.71	0.97	0.68, 1.38
From pre-/early perimenopausal to hormone use	1.07	0.74, 1.54	0.93	0.78, 1.71
From pre-/early perimenopausal to late peri-/postmenopausal	1.24	0.93, 1.67	1.04	0.75, 1.44

Am J Epidemiol 2004;160:912–922

Patterns of body fat distribution

Post-M

Pre-M

Effect of menopausal status on body composition and abdominal fat distribution

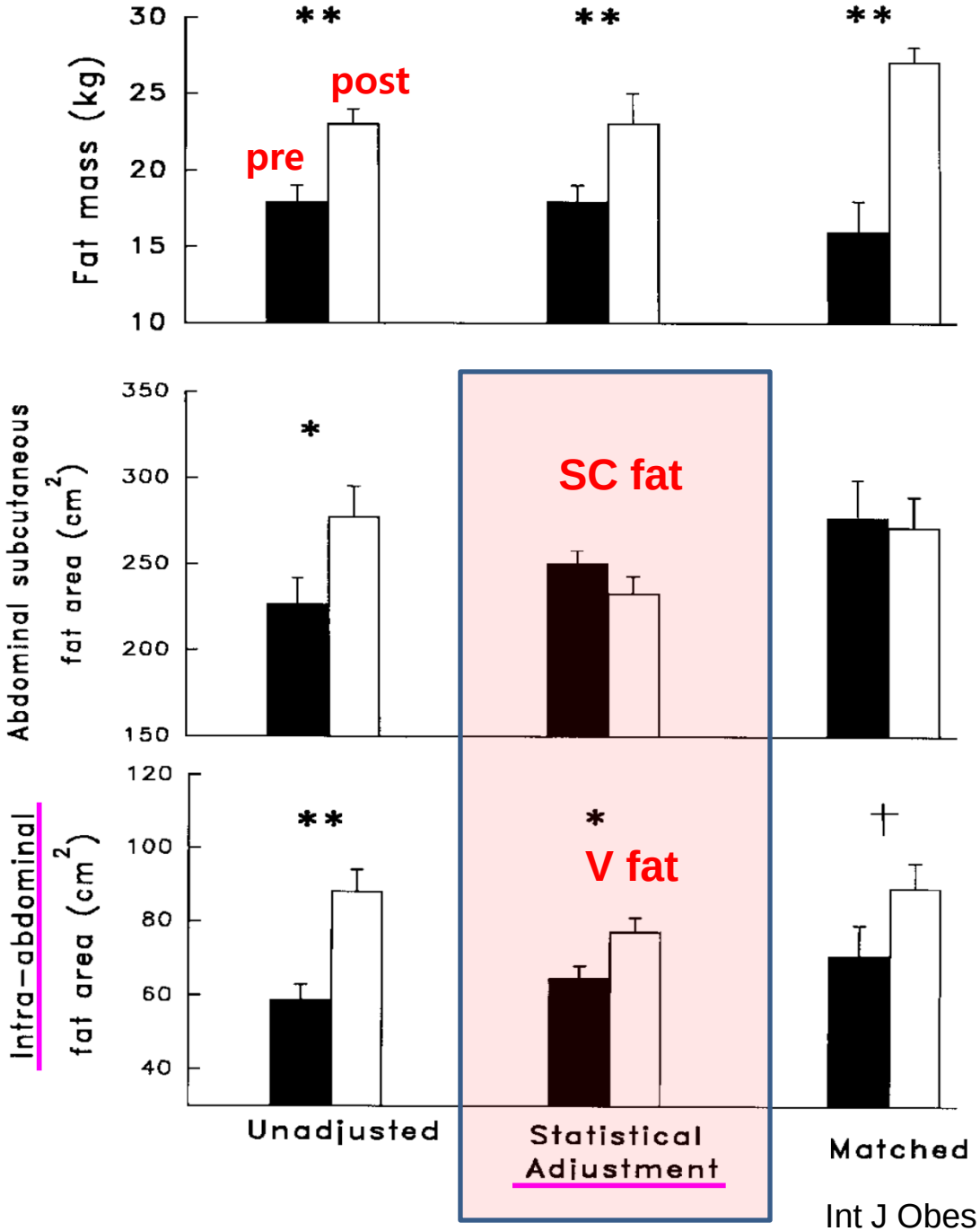
Variable	*Premenopausal*	*Postmenopausal*
n	53	28
Age (y)	47 ± 3	51 ± 4**
Height (cm)	165 ± 5	163 ± 6
Weight (kg)	62 ± 8	66 ± 10*
Body mass index (kg/m²)	23 ± 3	25 ± 4**
Time since menopause (months)		22 ± 15

Variable	*Premenopausal*	*Postmenopausal*
Fat mass (kg)	18 ± 7	23 ± 7**
Fat-free mass (kg)	40 ± 4	39 ± 3
Percentage fat (%)	30 ± 9	35 ± 6**
Arm fat-free mass (kg)	4.3 ± 0.5	4.2 ± 0.5
Leg fat-free mass (kg)	13.6 ± 1.5	13.2 ± 1.6
Appendicular skeletal muscle mass (kg)	18 ± 2	17 ± 2
Subcutaneous fat (cm^2)	227 ± 108	277 ± 93*
Intra-abdominal fat (cm^2)	59 ± 32	88 ± 32**

*p<0.05

**p<0.01

Int J Obes Relat Metab Disord. 2000 Feb;24(2);226-31



Even after adjustment of age & fat mass, intraabdominal fat : pre<postmenopausal women

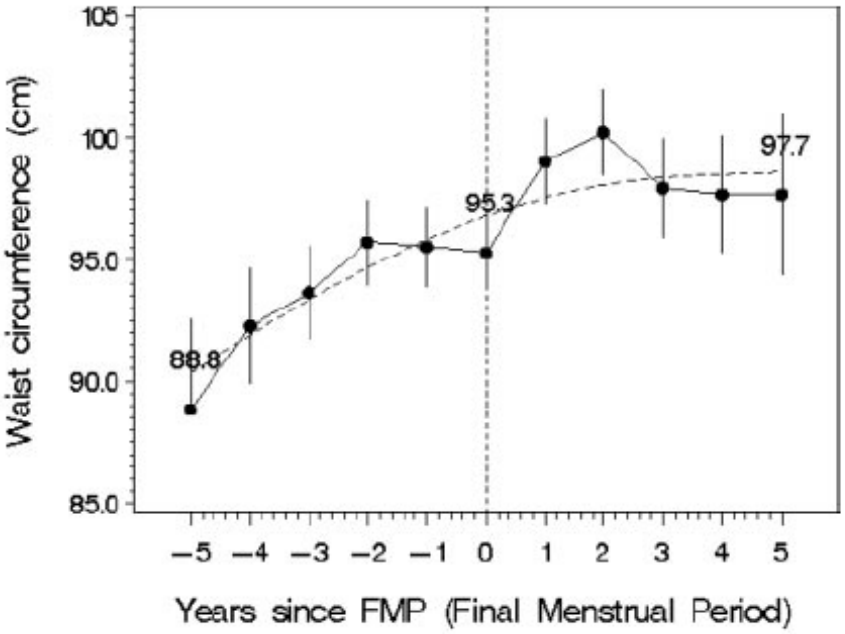
*p<0.05, **p<0.01, † p=0.01

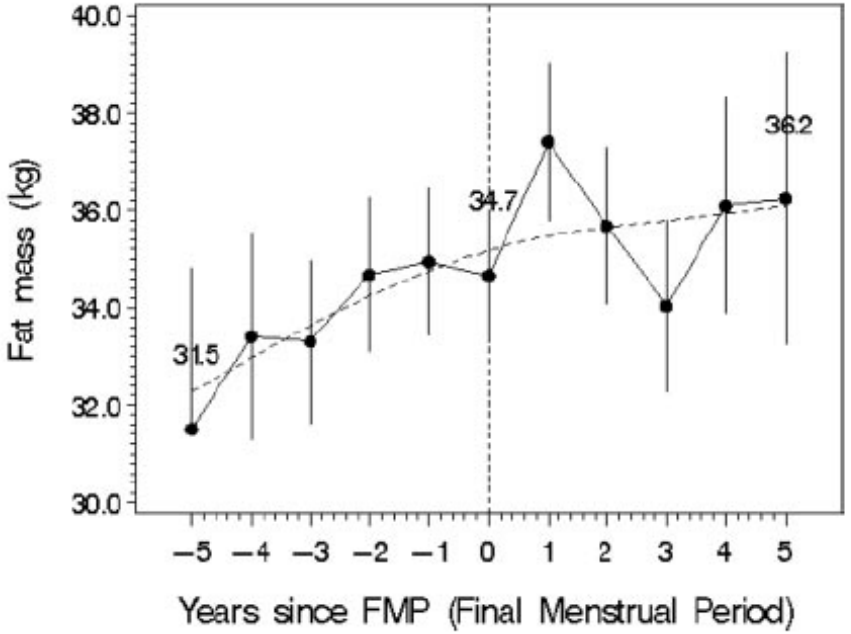
Int J Obes Relat Metab Disord. 2000, 24(2);226-31

Changes of body composition in women over 6 years at midlife

• **SWAN:**

-Participants; 543 premenopausal or early perimenopausal women aged 42-52yr



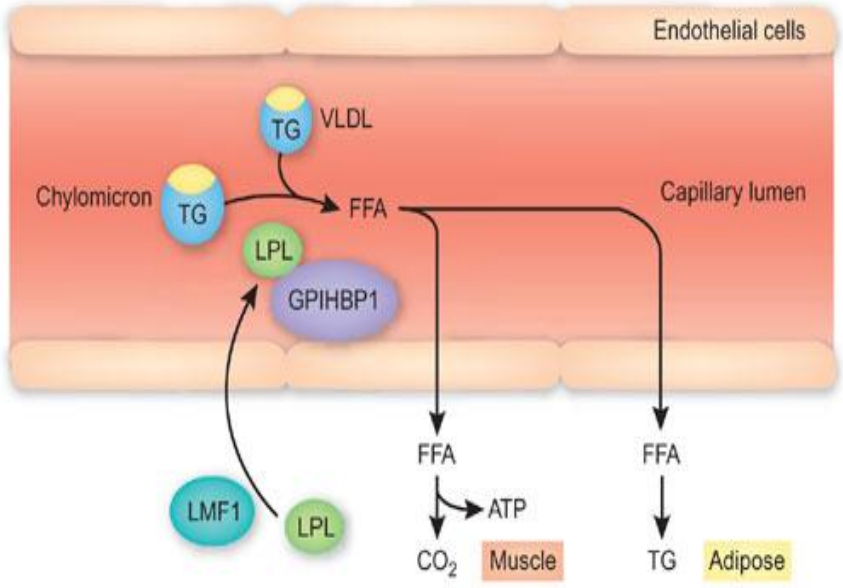


Both time and ovarian aging contributed to substantial changes in body composition

J Clin Endocrinol Metab 92: 895-901, 2007

Possible mechanism of visceral fat Accumulation in menopause

- adipocyte lipopysis, fat storage
- adipocyte lipoprotein lipase (LPL) activity



• Hydrolyze circulating TG into FFA
• Mediate fatty acid uptake → fat storage in adipose tissue

Estrogen↓– Body Fat Distribution

in pre vs. post-menopausal women

Adipose tissue depot	Group	Adipocyte size (μm)	LPL activity (μmol/10^6 cells/min)	Basal lipolysis (μmol gly/$\mu m^2 \times 10^8$/2h)
Subcutaneous	Regularly cycling	102 ± 3	10.40 ± 1.82	458 ± 105
	Ovarian hormone deficient	102 ± 4 (NS)	10.43 ± 4.40 (NS)	838 ± 345 (NS)
Omental	Regularly cycling	76 ± 3	5.39 ± 0.60	213 ± 82
	Ovarian hormone deficient	90 ± 6[a]	7.28 ± 1.58[b]	683 ± 292[c]

[a] p=0.04, [b] p=0.16, [c] p=0.01

The increased omental/sc LPL activity ratio supports the notion of a predominant VF storage in postmenopausal women

J Clin Endocrinol Metab 2004;89:3425-3430

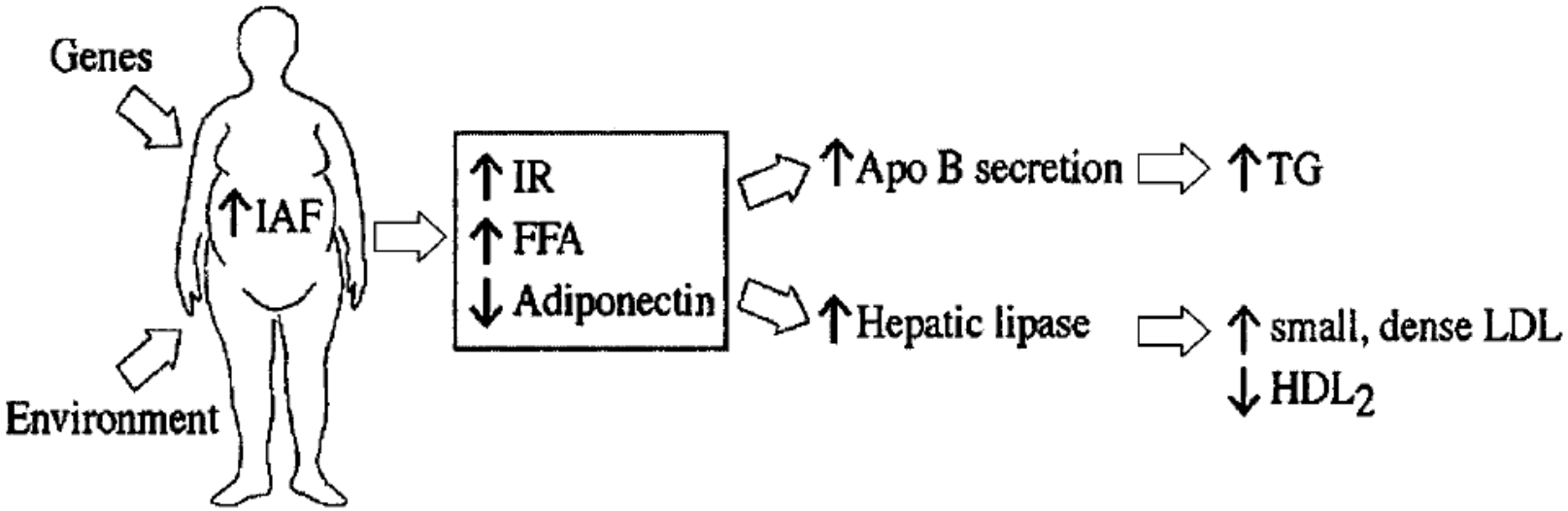
Changes in body composition

- Weight gain in peri-M is thought to be a result of aging, whereas changes of body composition are associated with menopausal status, independent of aging.

- Altered regional LPL activity in post-M supports the notion of a prominent VF storage

Changes of lipid profile

Changes in lipid profile after menopause



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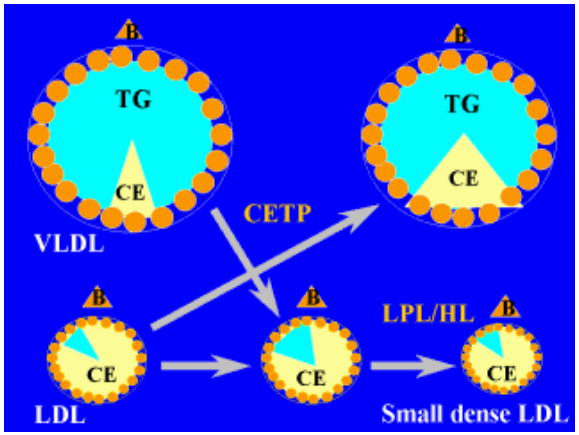
Estrogen 감소



J Clin Endocrinol Metab 88: 2404-2411, 2003

Lipoprotein change with menopause

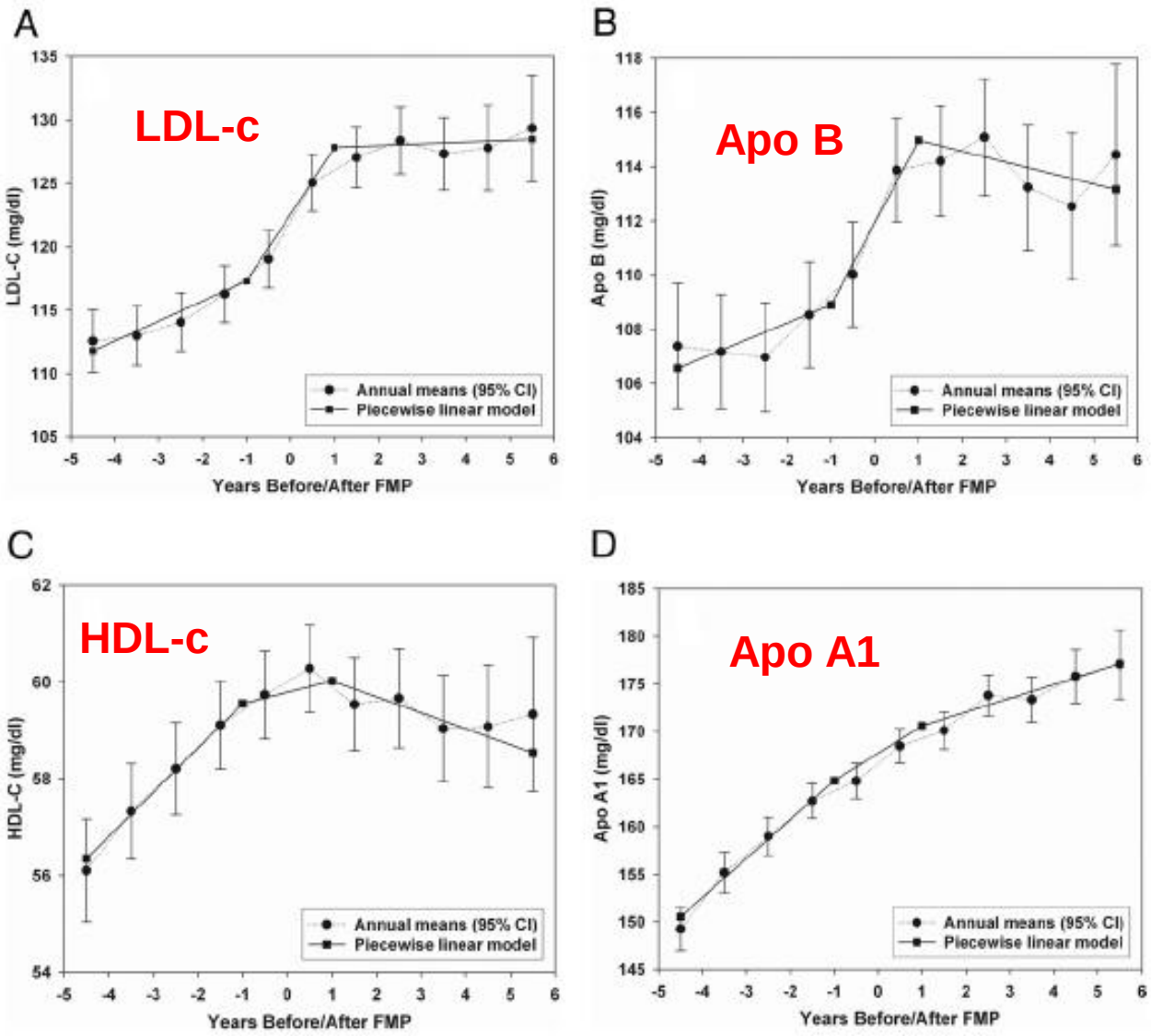
Cohort size	Total cholesterol	LDL	HDL	Triglycerides
150	–	–	↓	–
18	–	↑	↓	↑
10	↑	↑	↓	↑
69	↑	↑	↓	↑
343	↑	ND	ND	↑

	Premenopause		Postmenopause
51%	lbLDL	⇨	lbLDL
36%	lbLDL	⇨	sdLDL
13%	sdLDL	⇨	sdLDL

J Clin Endocrinol Metab 88: 2404-2411, 2003

Lipid change during menopausal transition

SWAN: initially pre or peri-M, f/u annually up to 10 yrs, N=3302



JACC 54(25), 2009

Changes in lipid profile

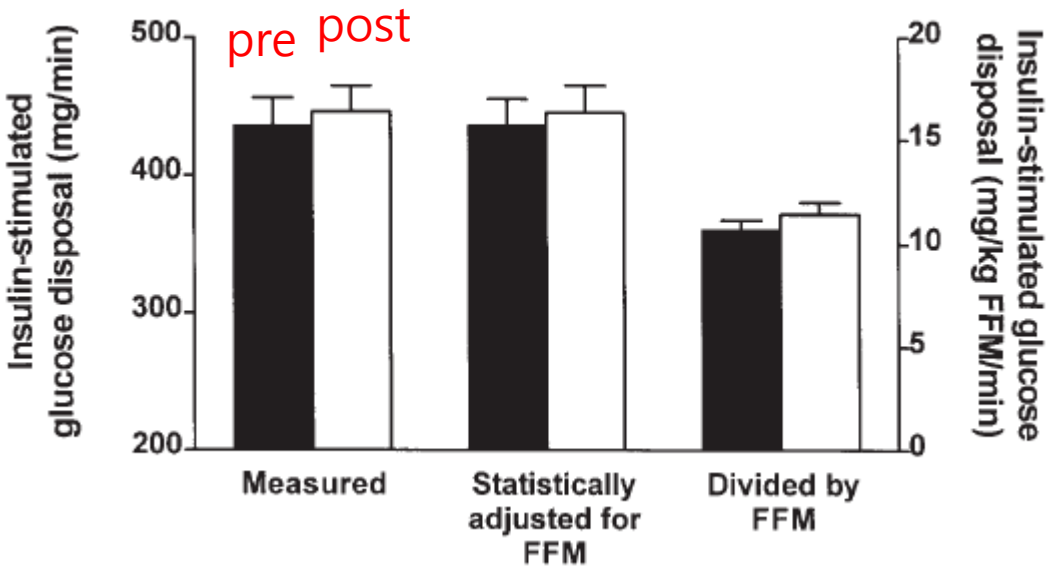
- Total cholesterol, LDL-C, apoB showed substantial increases during menopausal transition

- Monitoring lipids in peri-M women should enhance primary prevention of CHD

Changes of glucose homeostasis

Effect of menopausal status on insulin mediated glucose disposal

Variable	Premenopausal	Postmenopausal
n	43	40
Age (years)	47 ± 3	51 ± 4*
Height (cm)	165 ± 5	162 ± 5†
Weight (kg)	61 ± 8	66 ± 9†
Fat mass (kg)	17 ± 8	23 ± 6*
FFM (kg)	41 ± 4	40 ± 4
Intra-abdominal fat (cm^2)	56 ± 29	88 ± 34*
Subcutaneous abdominal fat (cm^2)	224 ± 112	276 ± 80†



Diabetes Care 23:801–806, 2000

Change of menopausal status and diabetes

- Longitudinal cohort of 475 women
- Glucose tolerance status were evaluated at 6 yrs later

	Pre-M⇒ Pre-M	Pre-M⇒ Post-M	Post-M at baseline	P crude	P adjusted
Mean age	36.9	52.2	64.1	<.001	
IFG, %	7.5	7.9	5.8	0.55	0.15
IGT, %	6.6	17.5	20.9	<.001	0.46
DM, %	6.3	23.8	30.2	<.001	0.21

Although there is no association between diabetes and menopause, the changes in body composition during menopausal transition is linked to impaired insulin sensitivity

Menopause, Vol. 16, No. 4, 2009

Changes of blood pressure

Menopause associated with HTN

Author, year	Population	Menopausal status	Design	Results
Weiss, 1972	897 women Age 40-51	Pre-M post-M	Cross-Sectional	Increasing DBP is related to menopause, independent of age
Zanchetti, 2005	18,326 women Age 46-59	Pre-M Peri-M post-M	Cross-Sectional	SBP and DBP are higher in post-M, evident only in younger age (46-49)
Staessen, 1997	315 W, age, BMI matched 315 men, Age 30-70	166 pre-M 44 peri-M 105 post-M	Prospective	SBP rose 5mmHg per decade more in peri-M, post-M than pre-M
Scuteri, 2001	226 women Mean age 64 ± 10	Pre-M,Peri-M post-M with HRT	Prospective	Post-M with HRT have a smaller increase in SBP over time

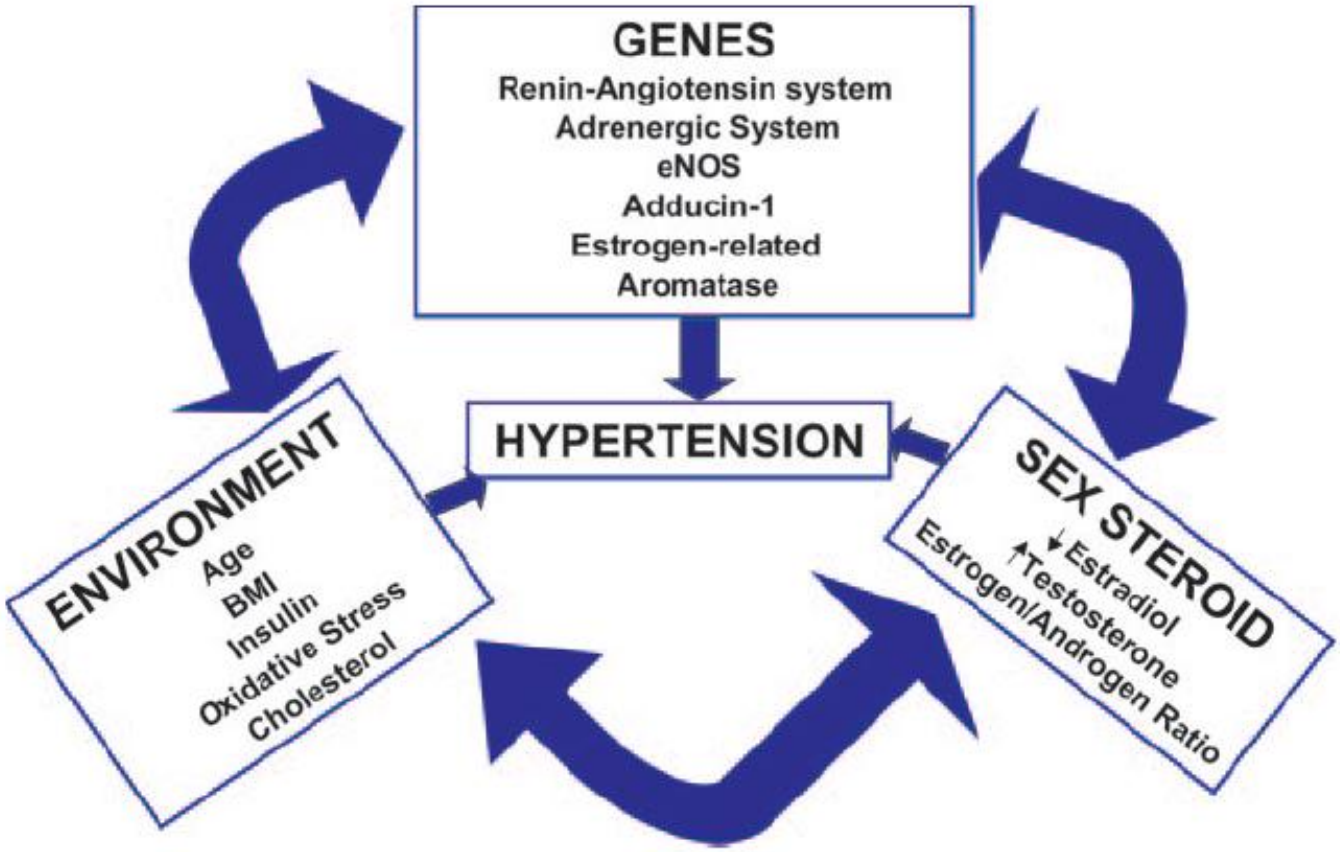
Hypertension 2008;51: 952

No association between menopause and HTN or CVD

Author, year	Population	Menopausal status	Design	Results
Casiglia, 1996	568 women At f/u, pre-M: 40±4 post-M; 61±8	Pre-M post-M	Prospective	No HTN or CVD risk difference between pre- and post-M after controlling for age
Luoto, 2000	3800 women Age 45-64	Peri-M post-M	Prospective	Looking specifically peri-M, SBP did not differ from post-M
Pearson, 1997	M: 1307, Age 17-97 W: 333, Age 18-93	166 pre-M 44 peri-M 105 post-M	Prospective	No greater increase in BP rise over time compared to men
Colditz, 1987	121,700 women 30-55	Pre-M, post-M	Prospective	Natural menopause: no greater risk for coronary heart disease Surgical menopause: 2.2 fold increased risk

Hypertension 2008;51: 952

Factors contributing to HTN in post-M women

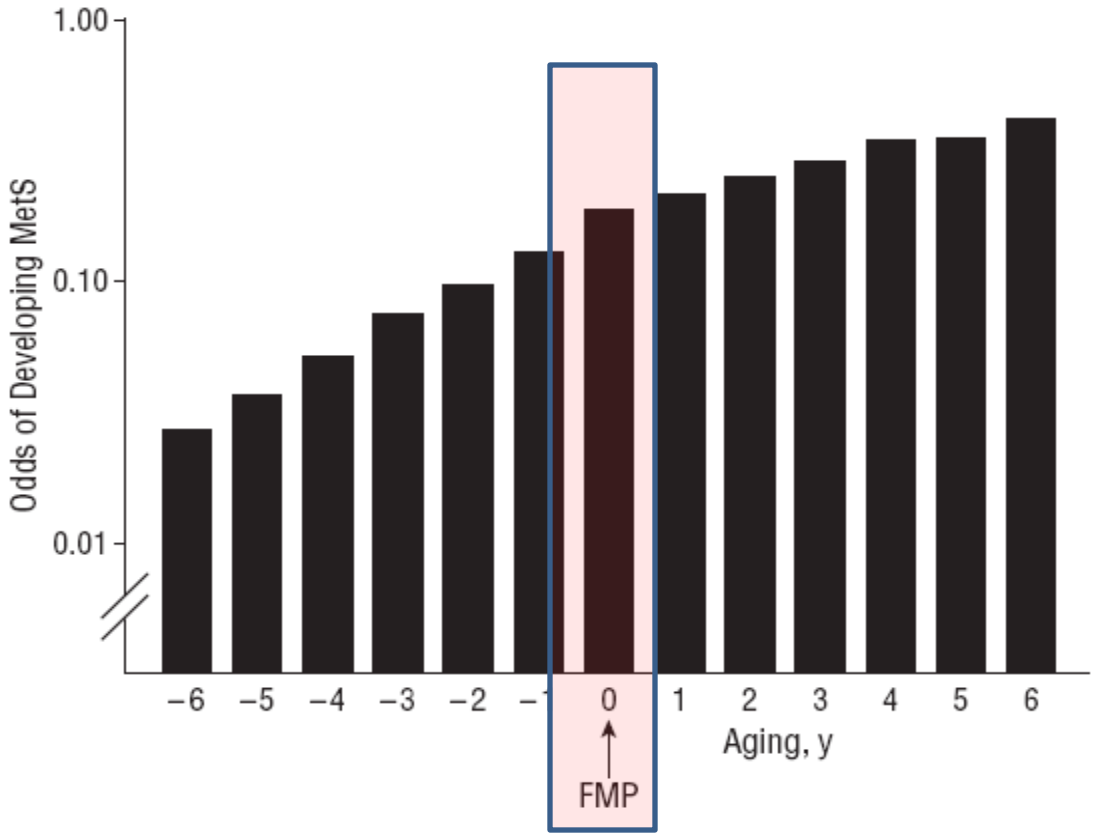


Hypertension 2008;51: 952

Metabolic syndrome

Menopause and MetS

SWAN: longitudinal, 9-yr study of 949 subjects with pre or early periM at baseline



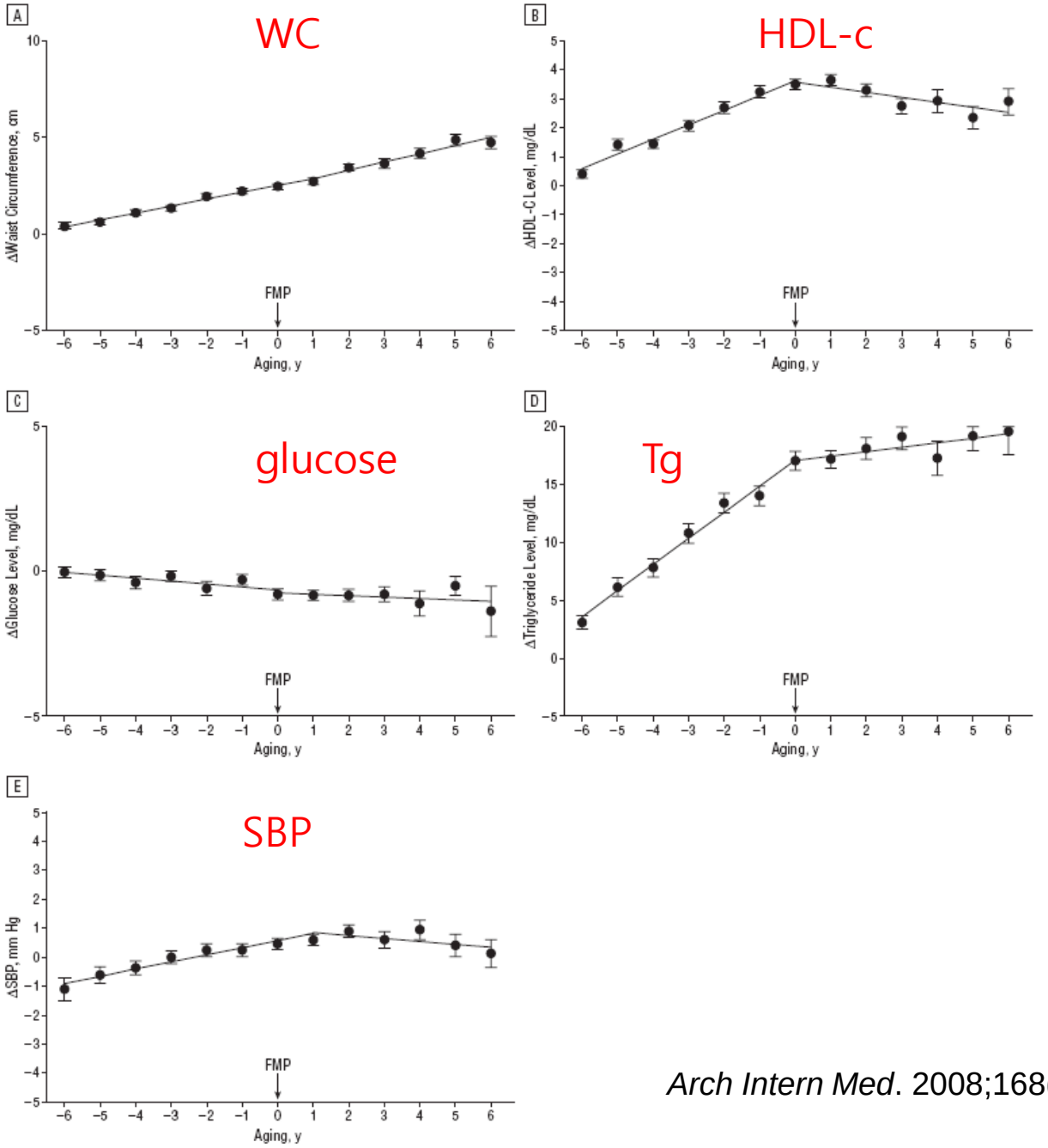
Adjusted for age at final menstrual period, ethnicity, study site, education, marital status, smoking, BMI, change in BMI

Arch Intern Med. 2008;168(14):1568-1575

Multivariate predictors of the development of Mets

Baseline BMI[b]	3.34 (2.72-4.10)	<.001
Δ BMI[b]	1.49 (1.32-1.67)	<.001
Smoking	2.44 (1.52-3.89)	<.001
Education of ≤high school	1.70 (1.10-2.64)	.02
Unmarried	1.46 (0.95-2.24)	.08
Age at final menstrual period	1.17 (1.09-1.25)	<.001
Perimenopausal aging	1.45 (1.35-1.56)	<.001
Postmenopausal aging	1.24 (1.18-1.30)	<.001

Arch Intern Med. 2008;168(14):1568-1575



Arch Intern Med. 2008;168(14):1568-1575

Relative androgen excess predicts MetS

Hormone Measure	OR (95% CI)	*P* Value	Log-Likelihood
Bioavailable testosterone level			
Δ	1.10 (1.01-1.20)	.02	−1430.6
Baseline	1.34 (1.11-1.62)	.002	
SHBG level			
Δ	0.87 (0.81-0.93)	<.001	−1427.5
Baseline	0.82 (0.69-0.98)	.03	
Estradiol level			
Δ	0.97 (0.88-1.06)	.49	−1437.2
Baseline	0.92 (0.75-1.12)	.40	
Testosterone level			
Δ	0.96 (0.86-1.06)	.40	−1442.5
Baseline	1.16 (0.94-1.42)	.16	

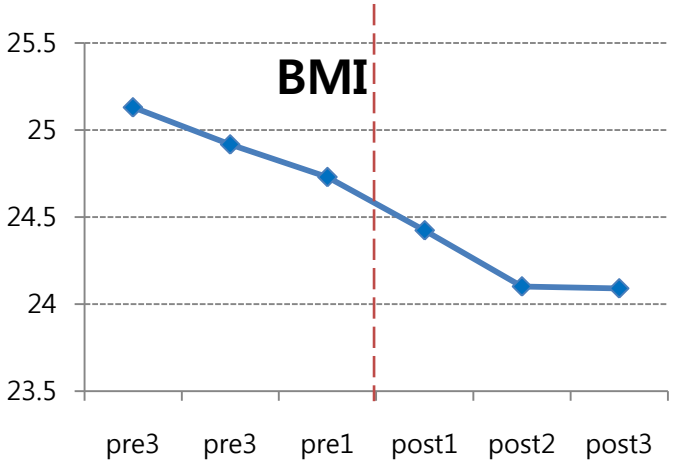
Arch Intern Med. 2008;168(14):1568-1575

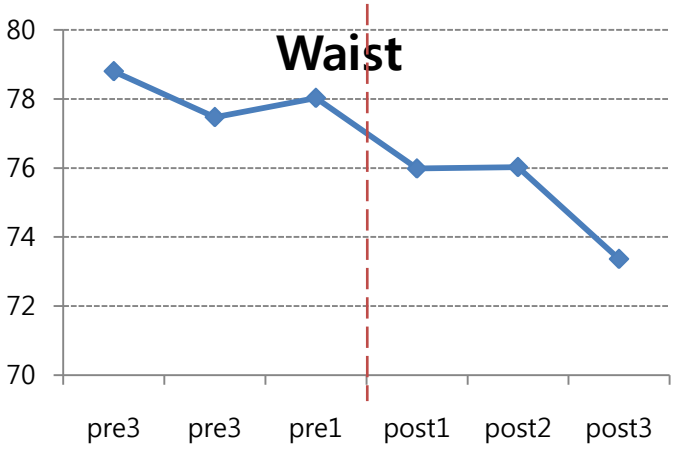
Results from Human Genomic Study in Ansan

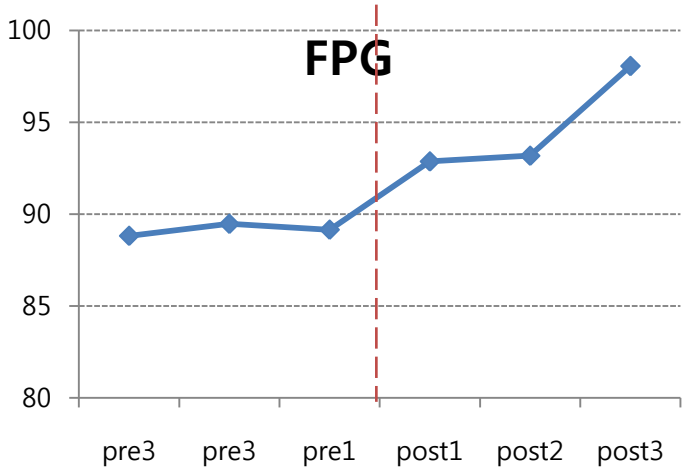
Changes of metabolic risk factors in middle-aged Koreans

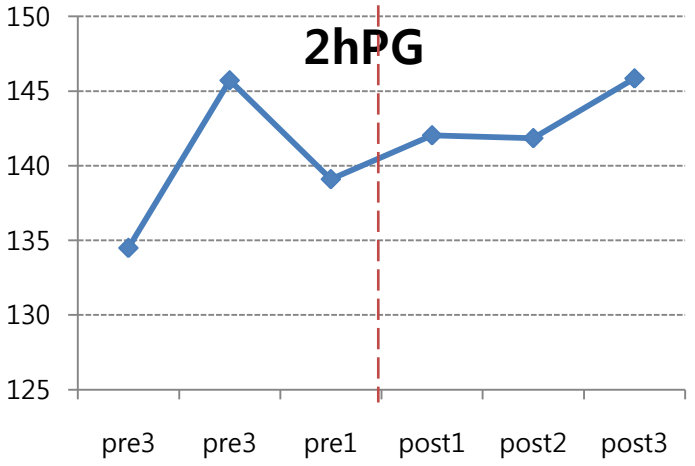
- Participants of Human Genomic Study in Ansan
- Ongoing prospective population-based study from 2001
- Until now, 4th biennial exam was finished.
- For the present study: Include women who were pre-menopause at baseline and post-menopause at 4th exam.
- Exclude who got hysterectomy, ovariectomy, hormone therapy, final data (n=355, baseline age= 47±3.4)
- To examine the sequential changes of metabolic risk factors during menopausal transition

Changes of metabolic risk factors in menopausal transition (1)

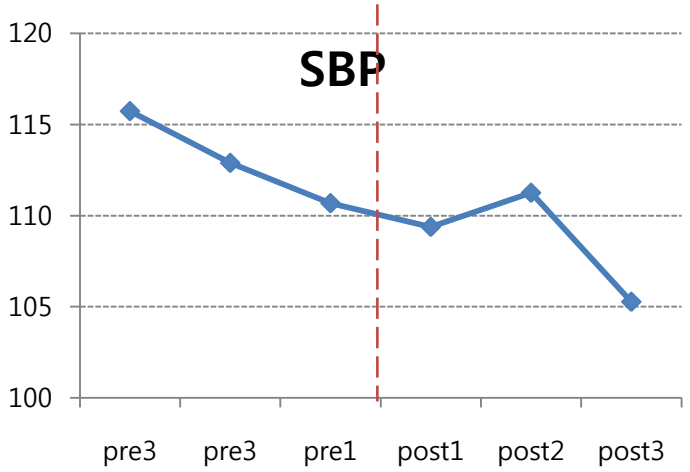


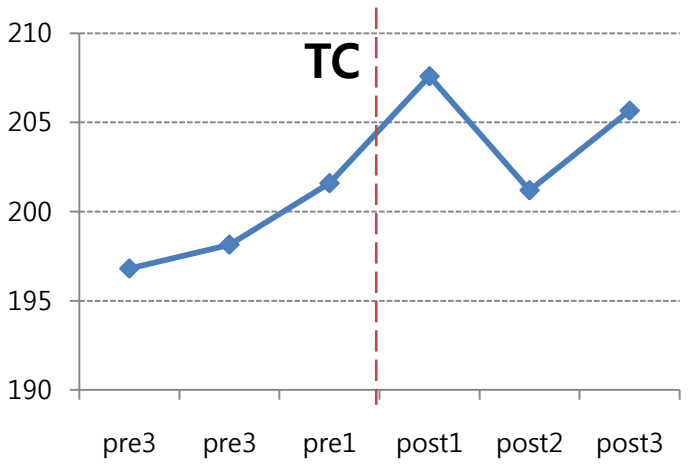


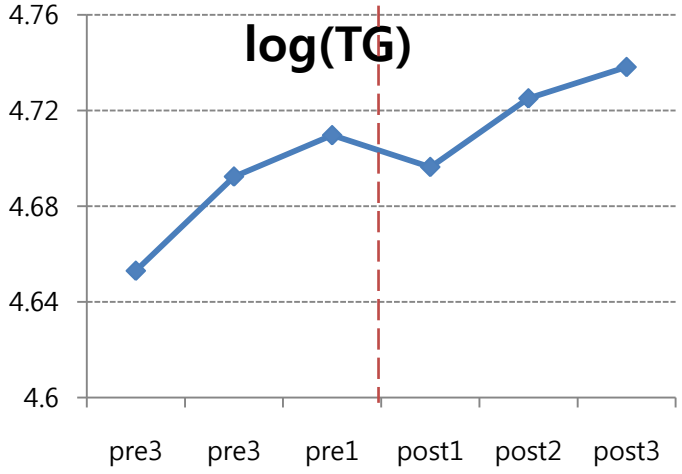


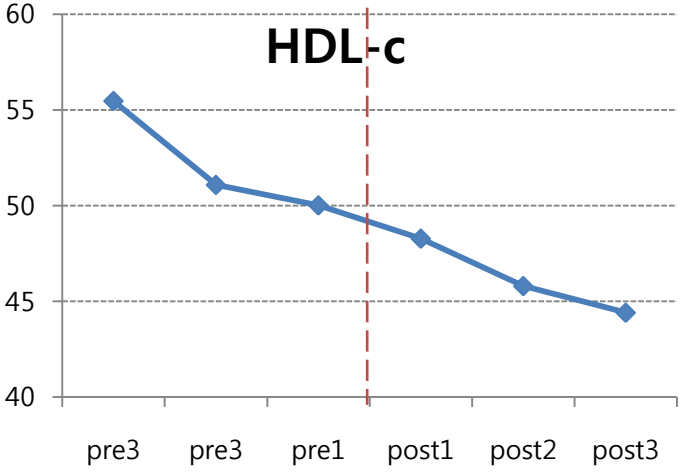


Changes of metabolic risk factors in menopausal transition (2)









Conclusion

- It is evident that risk of CVD and death increases in post-M women

- Menopause is associated with increases in total cholesterol, LDL-C and central obesity, whereas increases in BP and weight during midlife are more linear and appear to reflect chronological aging, mostly in Caucasian studies.

Conclusion

- Complex interplay between testosterone and estradiol may be a cause of increased CV risk in women at midlife

- It is prudent to increase the frequency of risk factor monitoring during this time to identify women timely who may benefit from pharmacologic management of their risk factors

Thank you for your attention!