Gender-Specific Risk Factors for IHD

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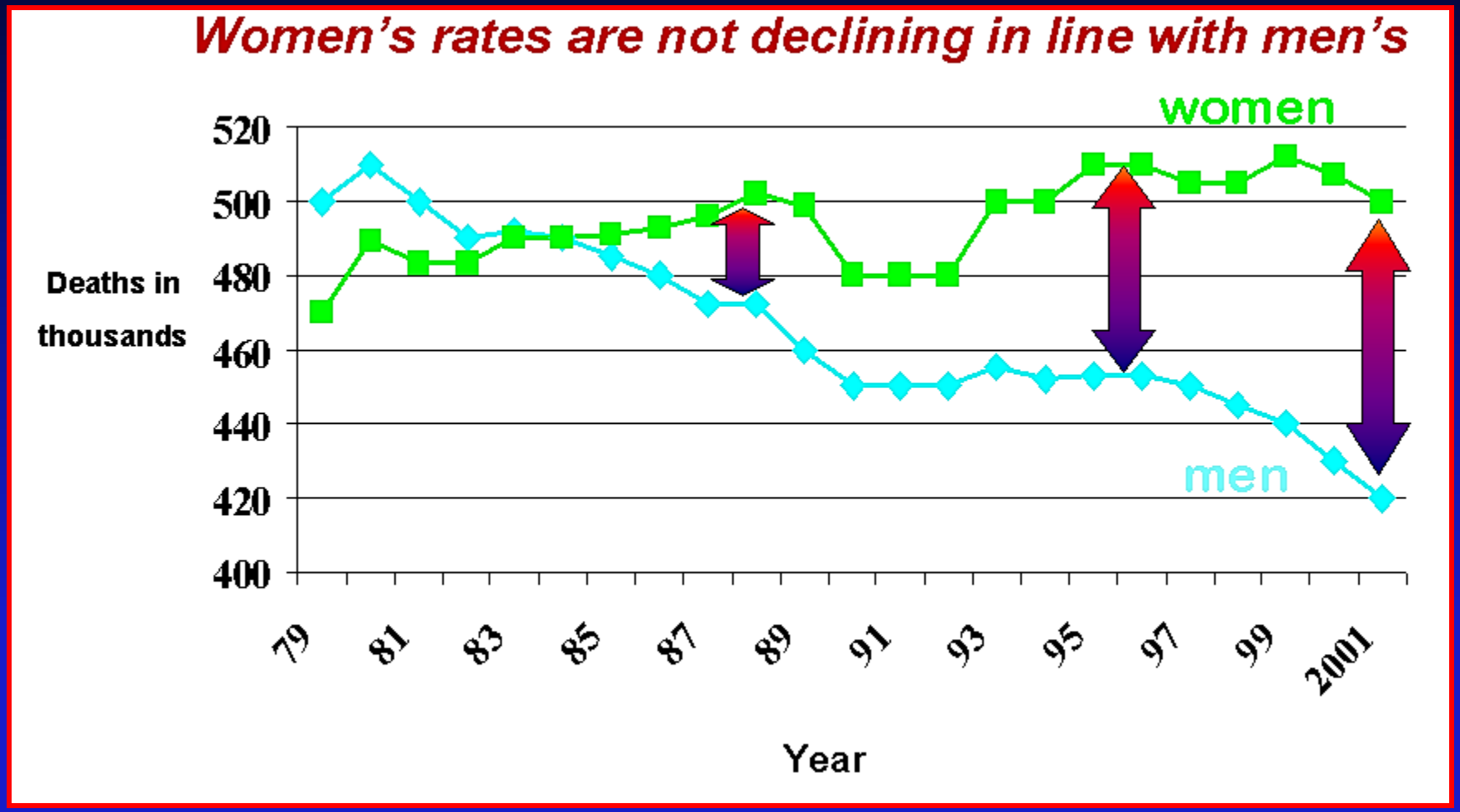
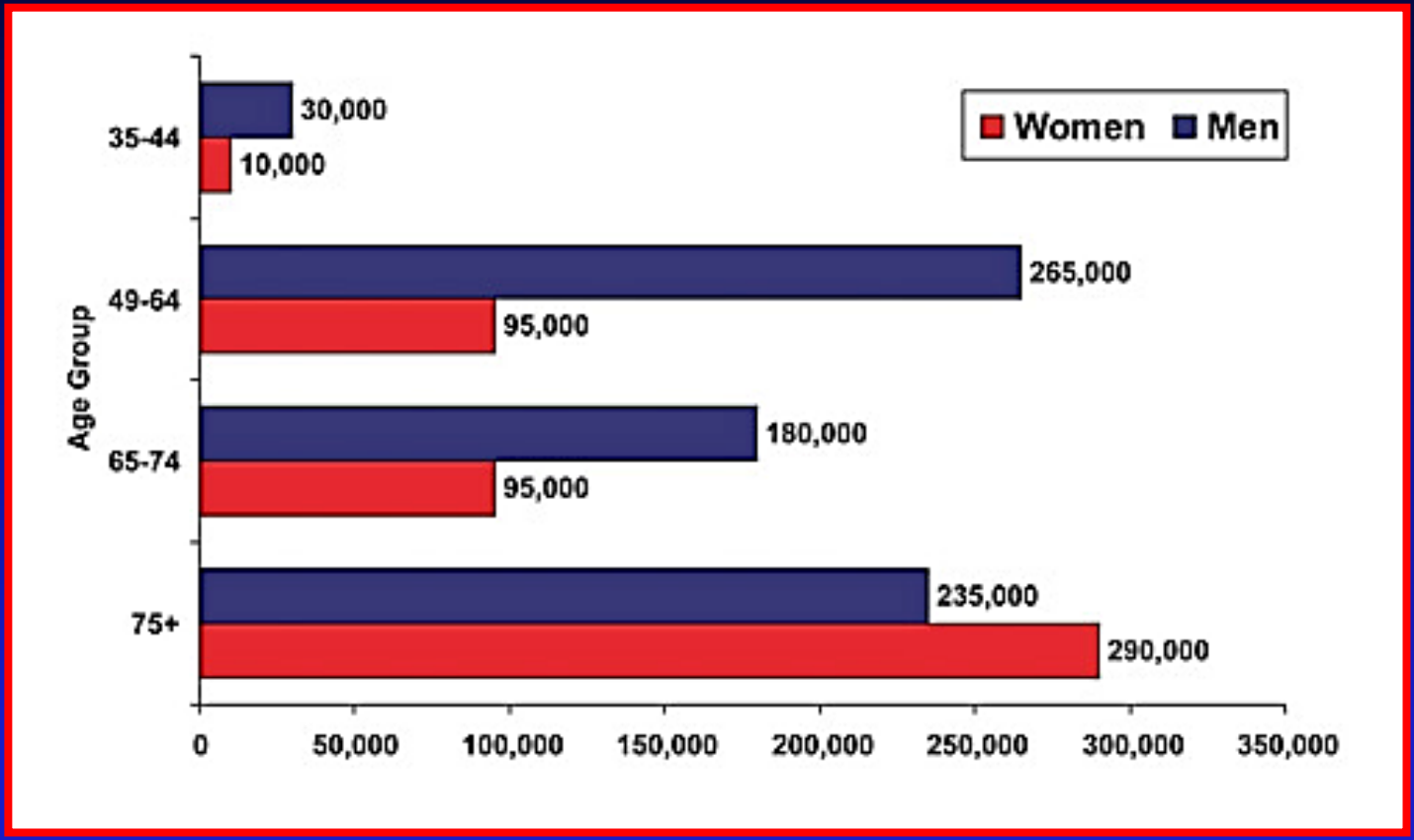
CV Mortality Trend



http://www.womensheart.org/

ACS Mortality

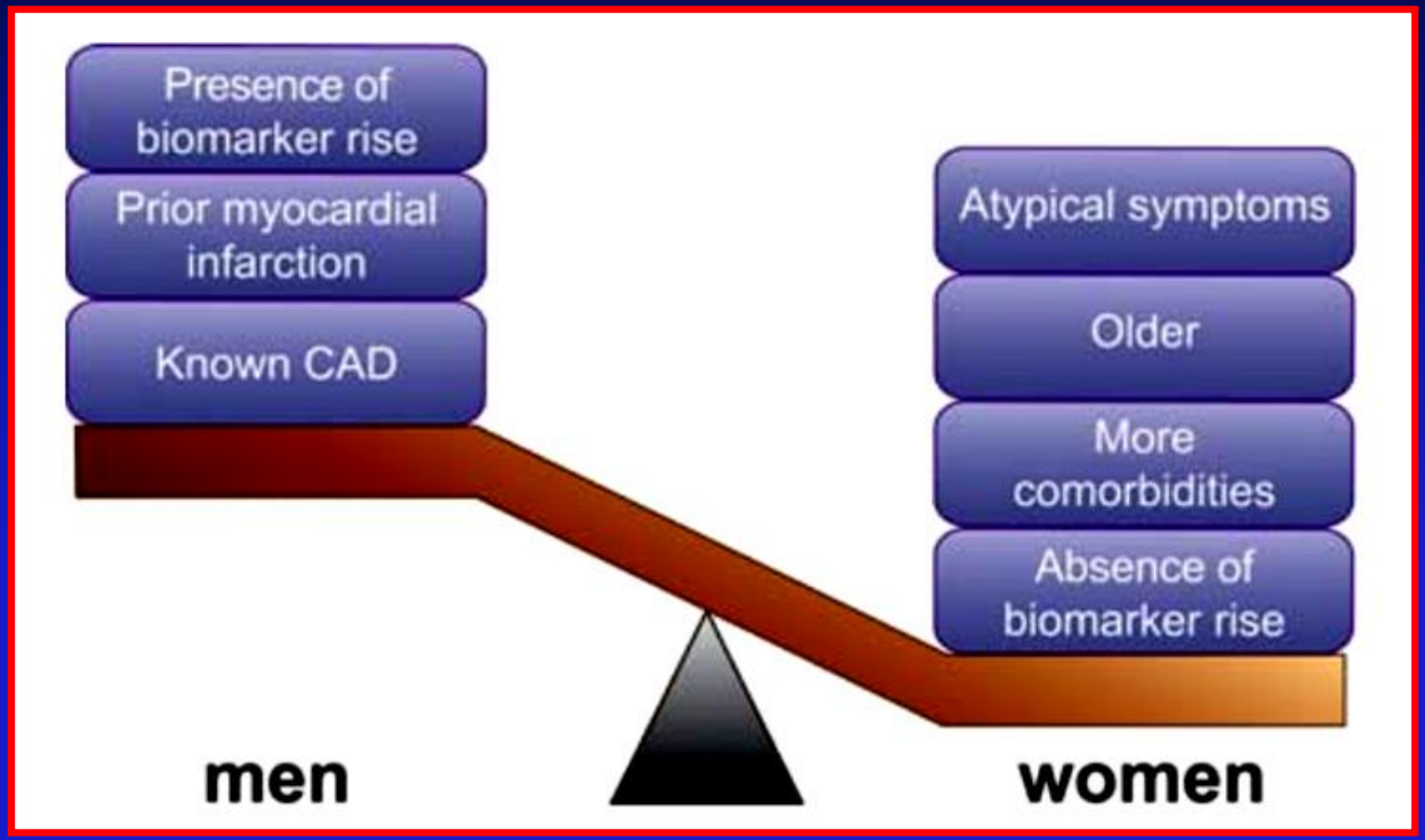


Death rates for ACS after the age of 65 are higher in women than in men in USA.

National Heart, Lung and Blood Institute

Gender Differences

Difficulties in detection of acute coronary syndromes



Moollmann et al. Eur Heart J 2011;32:3070-3072.

Gender Differences

Baseline patient characteristics

Variable	Men (n = 10,398)	Women (n = 3,725)	p Value
Age (years)	56 ± 12 (10,322)	67 ± 10 (3,693)	<0.001
Body mass index (kg/m^2)	24.1 ± 3.2 (9,511)	23.5 ± 3.5 (3,227)	<0.001
History of ischemic heart disease	11.8% (1,243)	11.2% (422)	0.301
Hypertension	41.0% (4,266)	61.2% (2,279)	<0.001
Diabetes mellitus	22.9% (2,380)	30.9% (1,150)	<0.001
Dyslipidemia	9.6% (995)	8.5% (316)	0.050
Smoking status			<0.001
Ex-smoker	17.8% (1,846)	3.0% (110)	
Current smoker	58.6% (6,098)	12.9% (479)	
Familial history of coronary heart disease	8.2% (850)	4.7% (176)	<0.001
Resuscitation before arrival	2.5% (261)	2.6% (96)	0.823
Systolic blood pressure (mm Hg)	125 ± 29 (10,130)	123 ± 32 (3,628)	<0.001
Diastolic blood pressure (mm Hg)	78 ± 21 (10,080)	75 ± 19 (3,597)	<0.001
Heart rate (per min)	77 ± 20 (10,121)	77 ± 22 (3,637)	0.091
Killip class	100.0% (9,832)	100.0% (3,530)	<0.001
I	72.5% (7,131)	61.1% (2,157)	
II	14.3% (1,403)	17.0% (601)	
III	6.3% (618)	11.3% (398)	
IV	6.9% (680)	10.6% (374)	
Ejection fraction (%)	51 ± 12 (9,245)	50 ± 12 (3,222)	0.004
Serum glucose (mg/dl)	171 ± 76 (10,118)	191 ± 92 (3,625)	<0.001
Serum creatinine (mg/d)	1.2 ± 1.9 (10,252)	1.1 ± 2.3 (3,671)	0.024
Creatine kinase-MB (mg/dl)	187 ± 302 (10,235)	168 ± 337 (3,656)	0.001
Troponin I (mg/dl)	62.3 ± 109.9 (8,255)	61.8 ± 246.3 (3,040)	0.884
Total cholesterol (mg/dl)	181 ± 43 (9,947)	186 ± 48 (3,502)	<0.001
Triglyceride (mg/dl)	130 ± 112 (9,683)	115 ± 89 (3,378)	<0.001
High-density lipoprotein cholesterol (mg/dl)	44 ± 17 (9,610)	46 ± 16 (3,335)	<0.001
Low-density lipoprotein cholesterol (mg/dl)	115 ± 38 (9,203)	120 ± 48 (3,214)	<0.001

Data are expressed as mean ± SD (number) or as percentage (number).

SH Kang et al. Am J Cardiol 2012;109:787-793.

Gender Differences

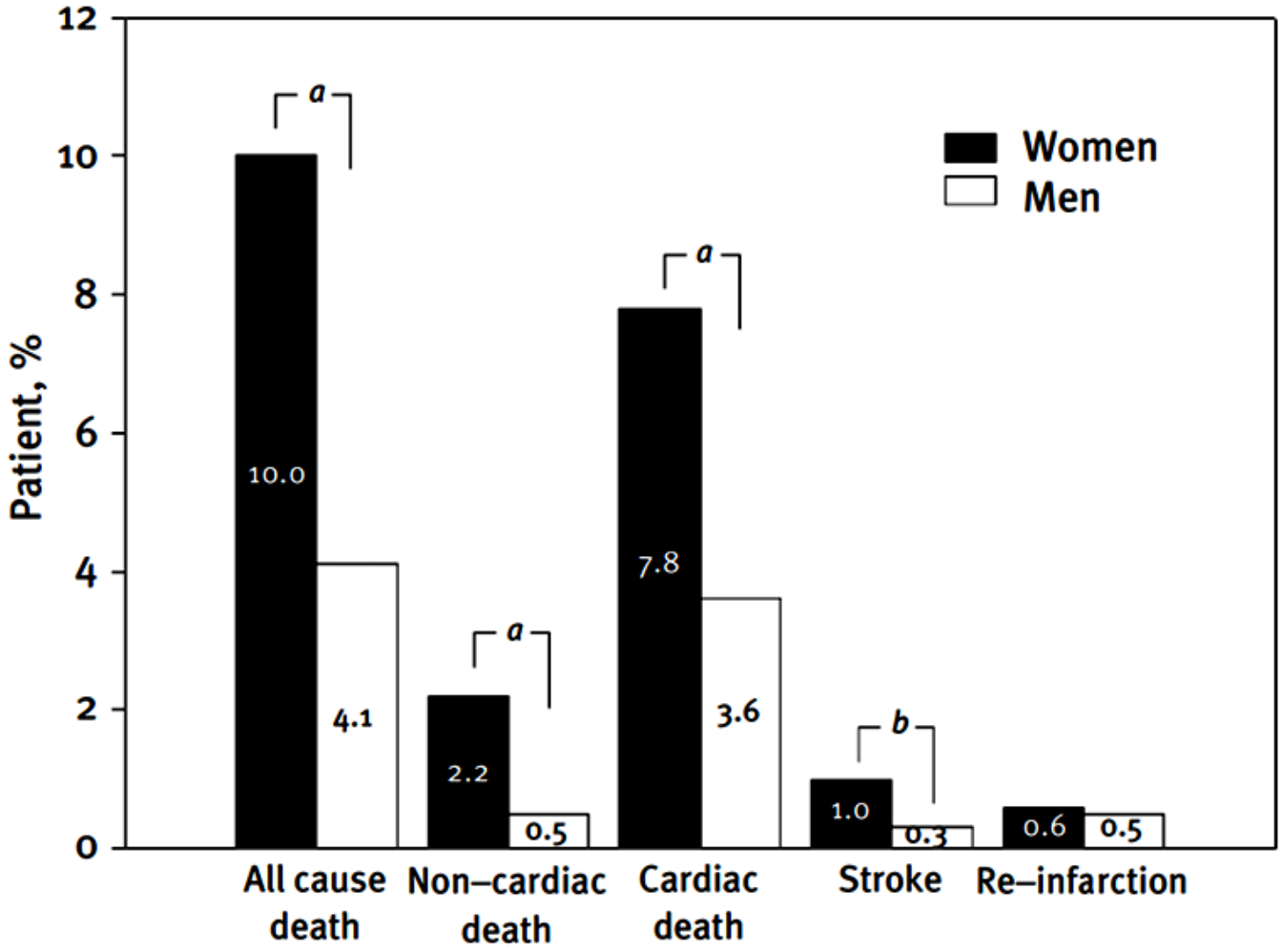


Figure 1. The rates of in-hospital cardiovascular events in women and men. $^{a}P < .001$ compared with the men. $^{b}P < .05$ compared with the men.

Park JS et al. Clin Cardiol 2010;33:E1-E6.

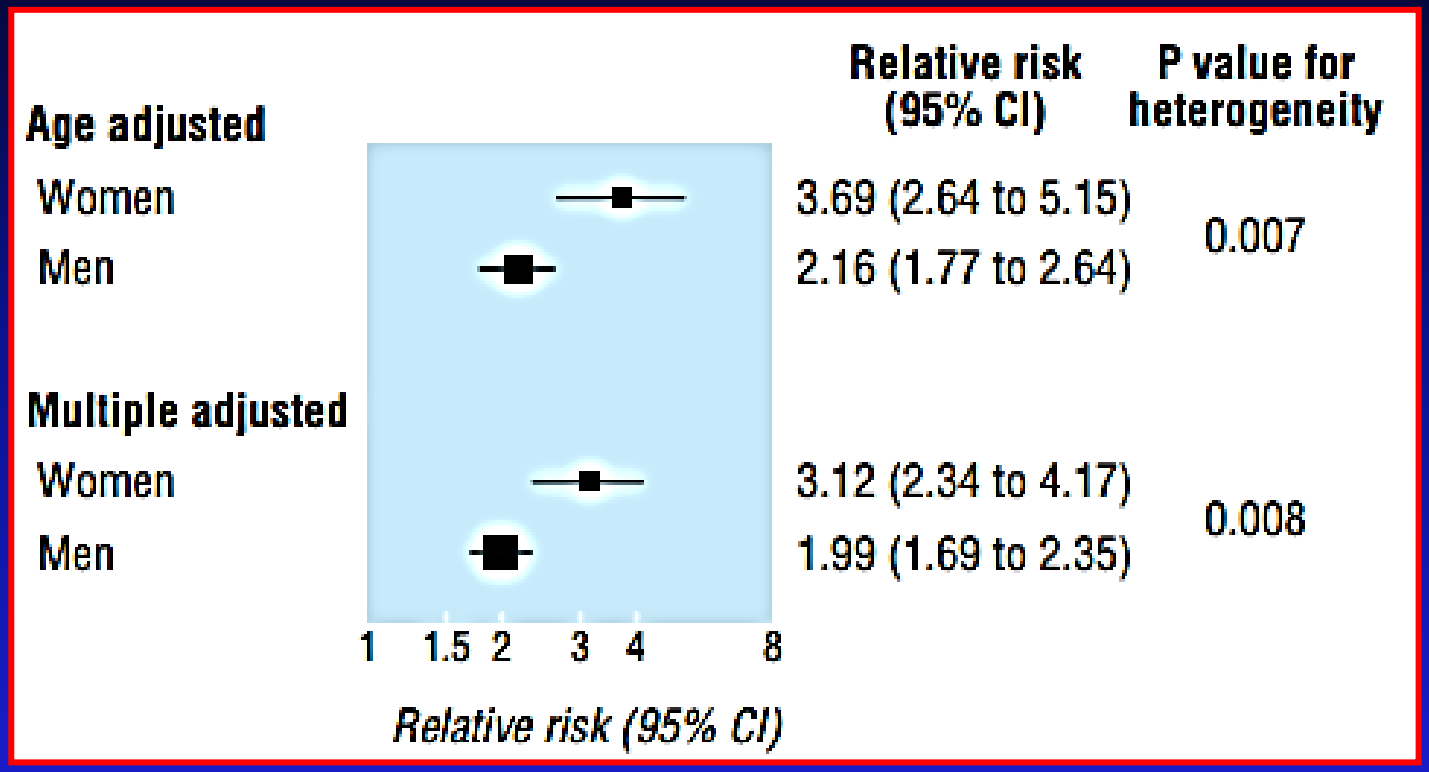
IHD: What's Different for Women

- Presentation at a later age
- Atypical presentation
- Increased risk after menopause
- High HDL, protective effect
- Higher mortality from AMI
- More long-term disability
- Have more comorbidity
- Fewer women received PCI or CABG
- Fewer women received cardiac rehabilitation
- Fewer women received medical therapy

Bedinghus et al. Am Fam Physician 2001;63:1393-1400.

Traditional Risk Factors

Diabetes Mellitus



The relative risk for fatal coronary heart disease associated with diabete mellitus is 50% higher in women than it is in men.

Huxley R et al. BMJ 2006;332:73-78.

Diabetes Mellitus

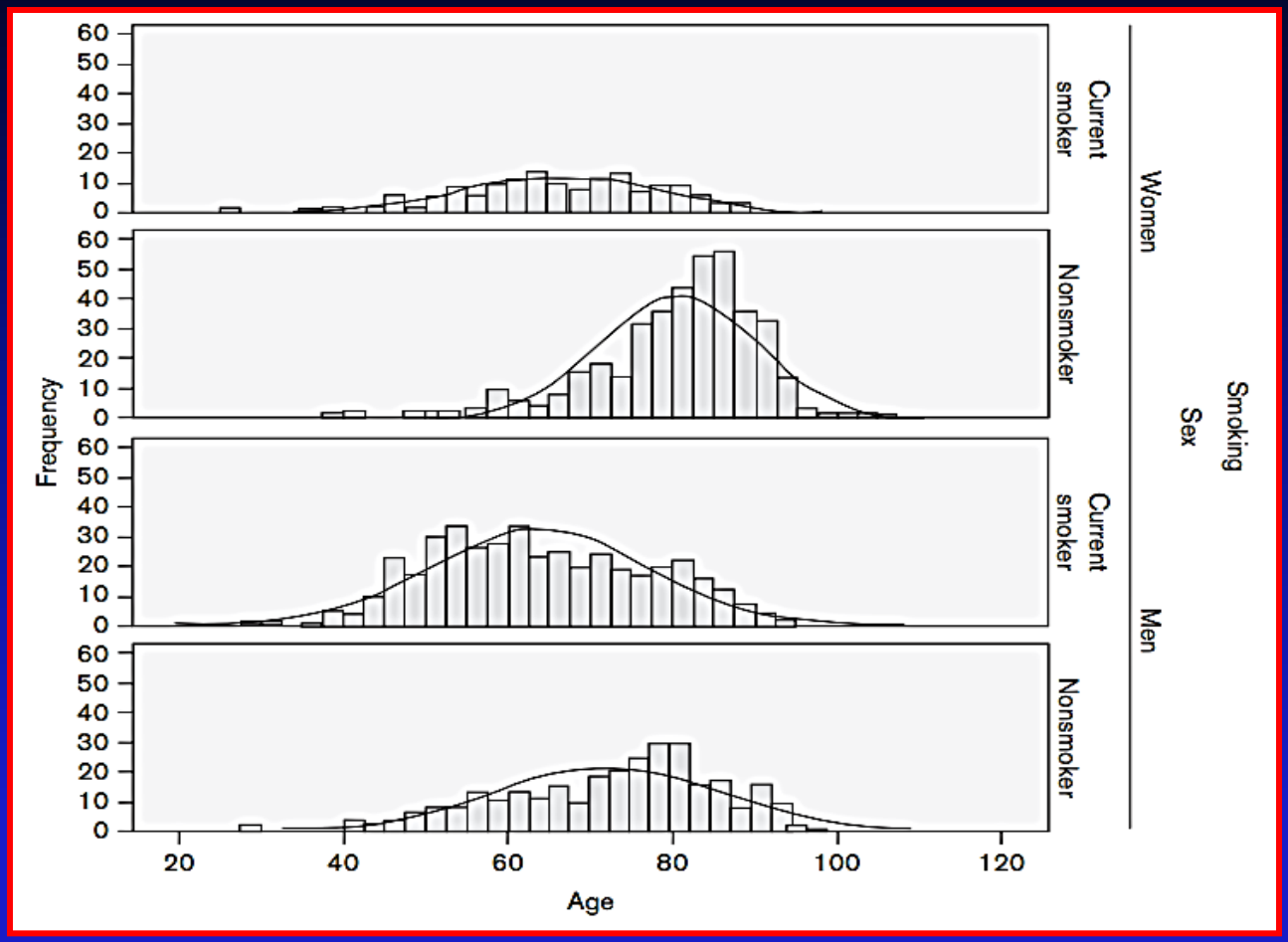
Risk factor	Difference (diabetes–no diabetes) (95% CI)	
	Men*	Women*
Systolic blood pressure (mm Hg)	7.8 (7.5 to 8.1)	12.5 (12.0 to 13.0)
Total cholesterol (mmol/l)	0.24 (0.22 to 0.26)	0.46 (0.43 to 0.49)
Triglycerides† (mmol/l)	1.53 (1.41 to 1.66)	2.01 (1.88 to 2.14)
High density lipoprotein cholesterol (mmol/l)	–0.076 (–0.1 to –0.05)	–0.13 (–0.16 to –0.1)
Body mass index (kg/m^2)	0.69 (0.65 to 0.74)	1.98 (1.87 to 2.09)

*Data from Asia Pacific Cohort Studies Collaboration.[8]
†Log transformed before analysis and subsequently transformed back.

Women with diabetes have more cardiovascular risk factors than those without diabetes, as compared to men.

Huxley R et al. BMJ 2006;332:73-78.

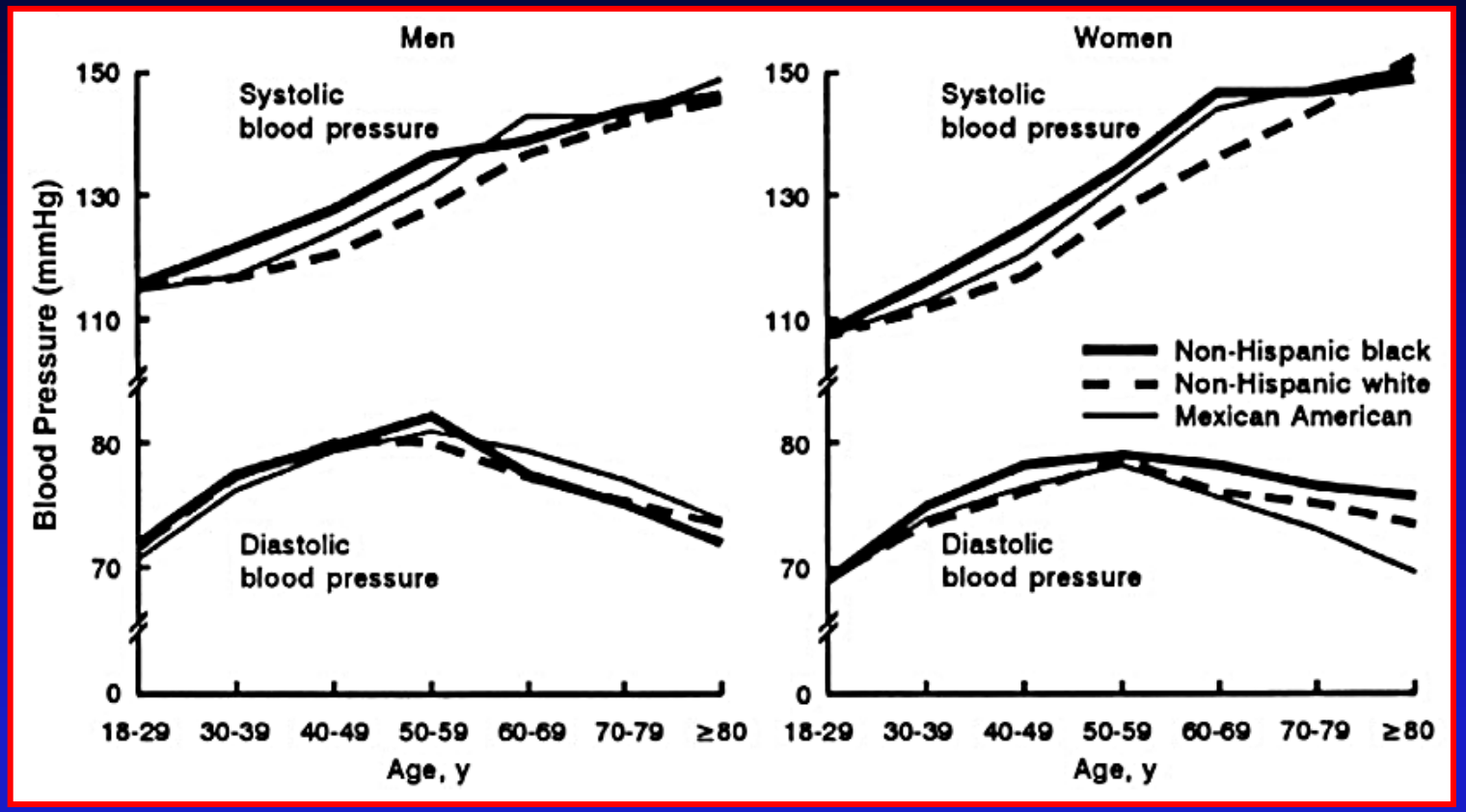
Smoking



First AMI occurred significantly more prematurely in women than in men smokers.

Grundtvig M et al. Eur J Cardiovasc Prev Rehabil 2009;16:174-179.

Hypertension



Years after menopause are associated with a continued rise in SBP, reaching that of age-matched men.

Burt VL et al. Hypertens 1995;25:305-313.

Dyslipidemia

	Men			Women		
Factor	No CVD	Yes CVD	p Value	No CVD	Yes CVD	p Value
HDL-C, mg/dl	45	42	0.001	57	51	<0.0001
LDL-C, mg/dl	134	138	0.09	126	143	<0.0001
Non–HDL-C, mg/dl	158	168	0.0002	146	170	<0.0001
LDL particle number, nmol/l	1,509	1,641	<0.0001	1,344	1,628	<0.0001

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Adapted, with permission, from Cromwell et al. [51].

Low HDL-C and high LDL-C implicate a higher coronary risk in women than in men.

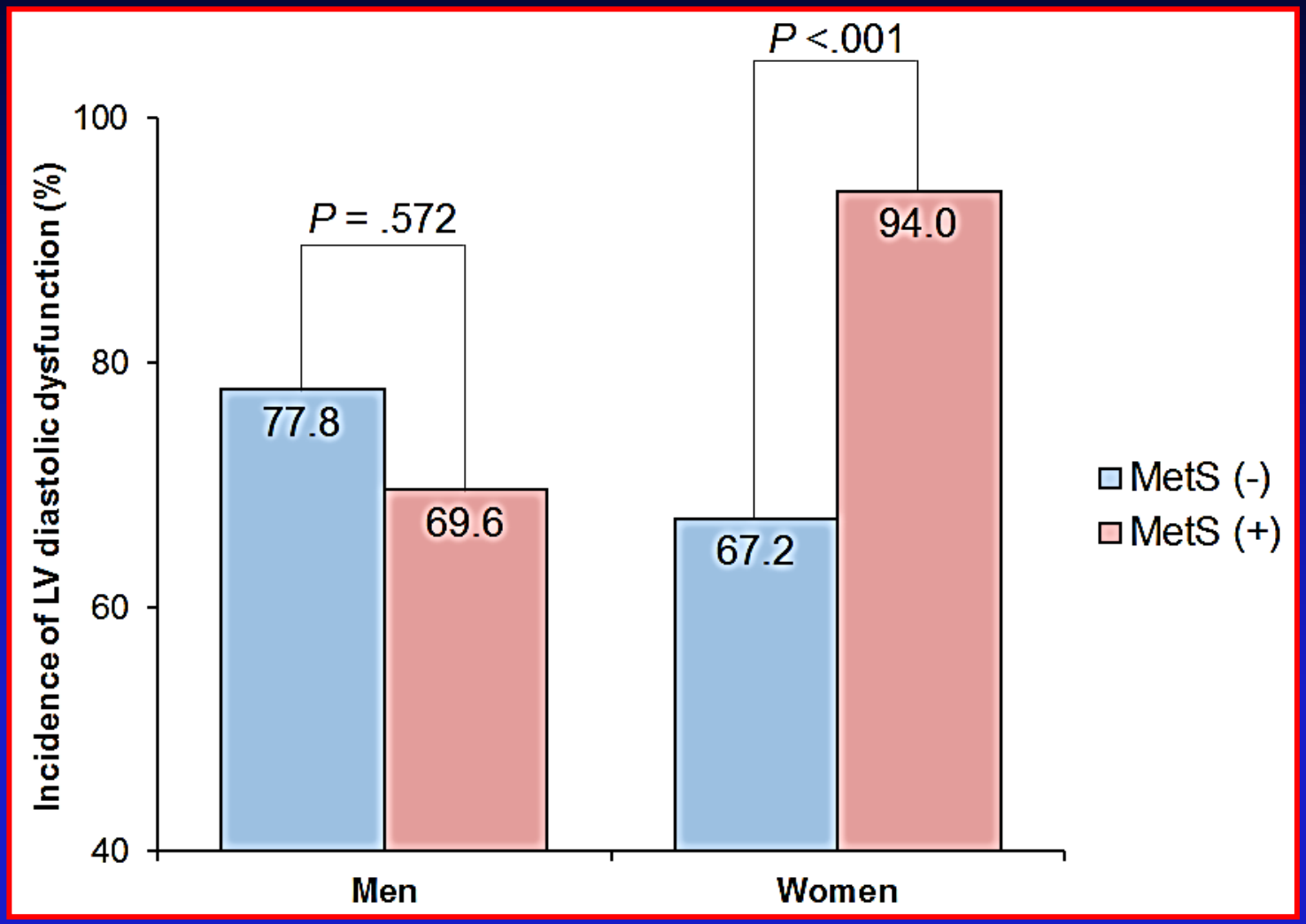
Kannel WB et al. Ann Intern Med 1971;74:1-12.

New Risk Factors in Women

- Inflammatory markers (CRP, IL-6)
- Endothelial function
- Retinal artery narrowing
- Coronary artery calcification
- Anemia
- Metabolic syndrome

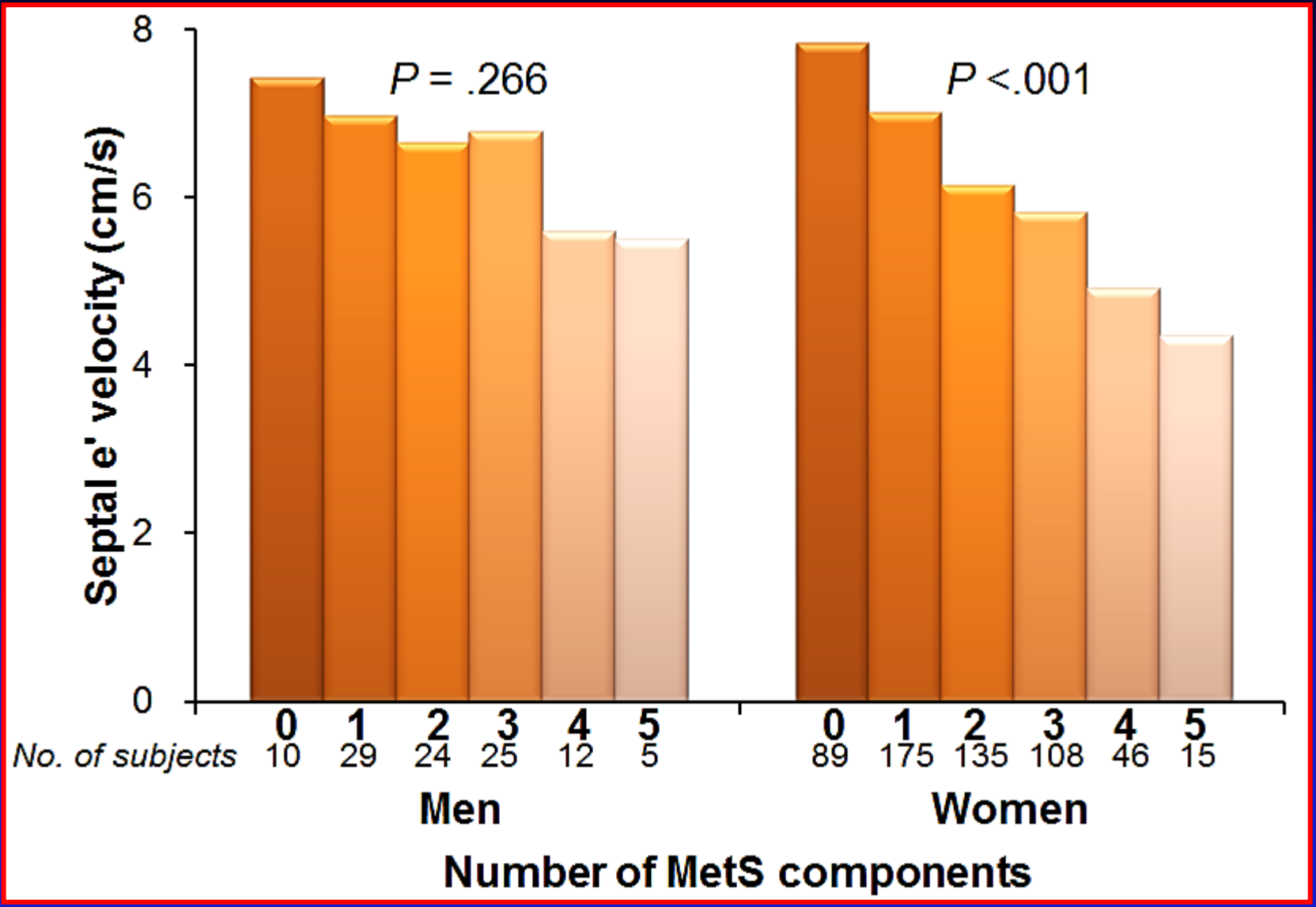
Rollinin F et al. Maturitas 2009;62:243-247.

Metabolic Syndrome



HL Kim and MA Kim et al. Submitted (Data from KoROSE registry)

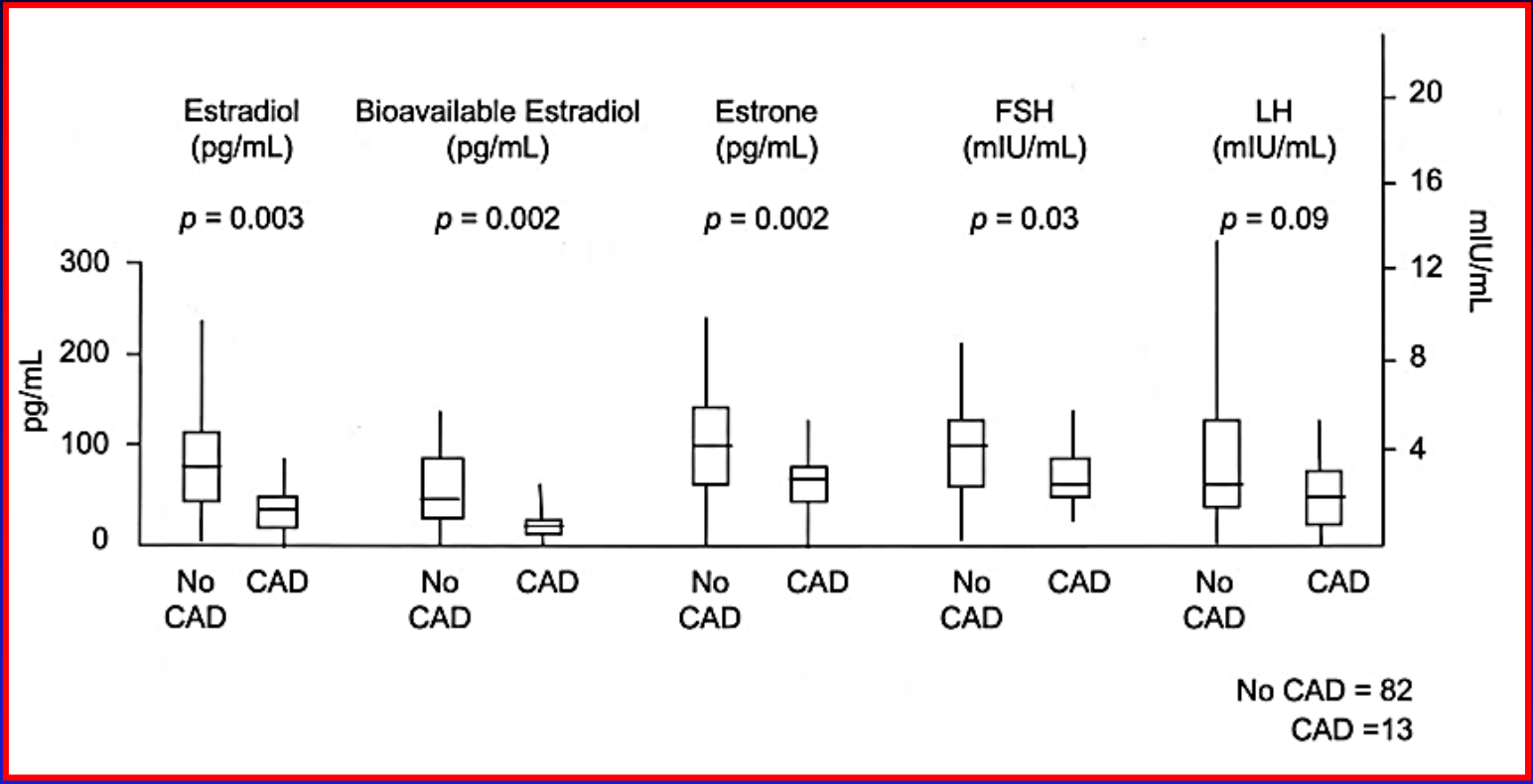
Metabolic Syndrome



HL Kim and MA Kim et al. Submitted (Data from KoROSE registry)

Women-Specific Risk Factors (Reproductive Factors)

Role of Estrogen



Premenopausal women with angiographic CAD had significantly lower estrogen and FSH than women without angiographic CAD.

Bairey Merz CN et al. J Am Coll Cardiol 2003;41:413-419.

Role of Estrogen

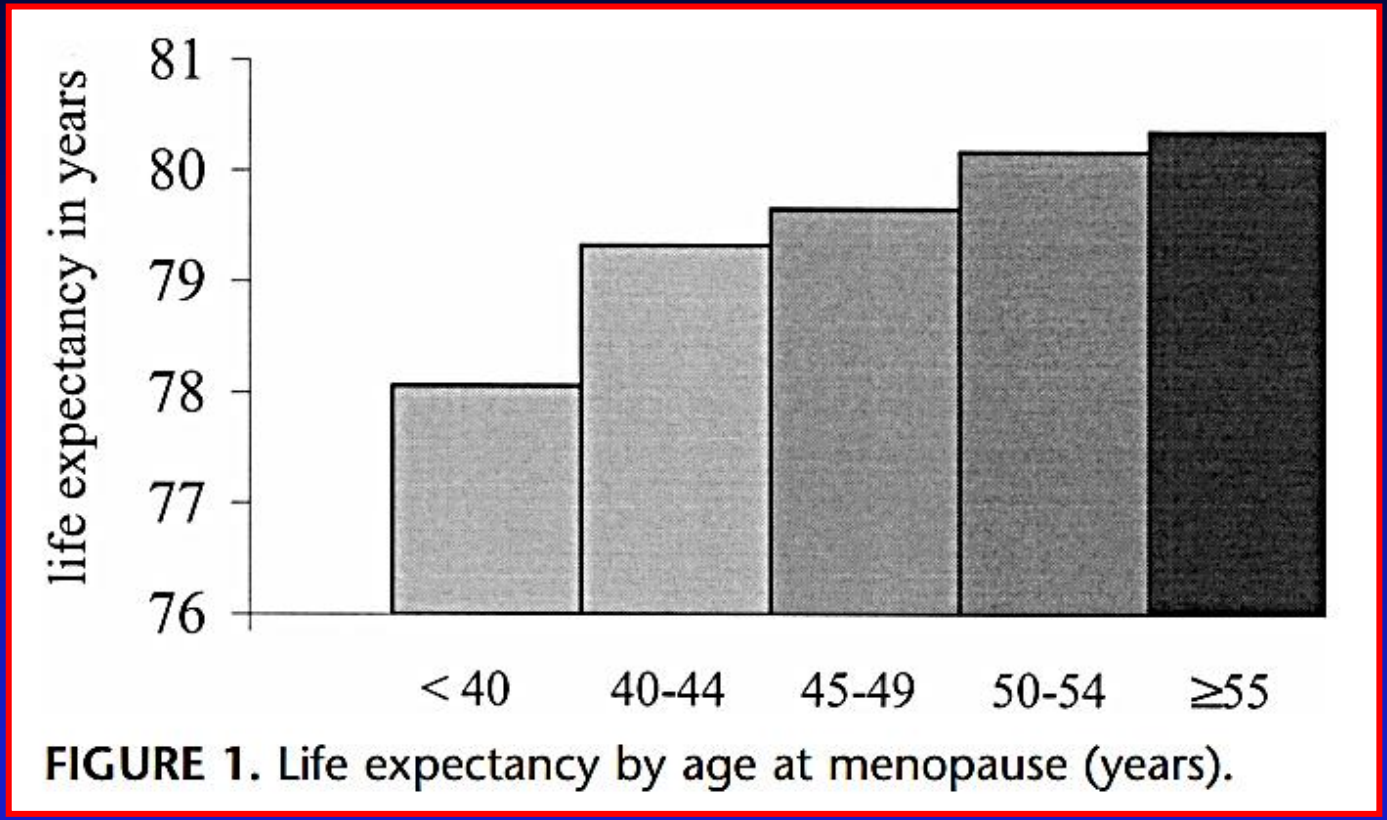
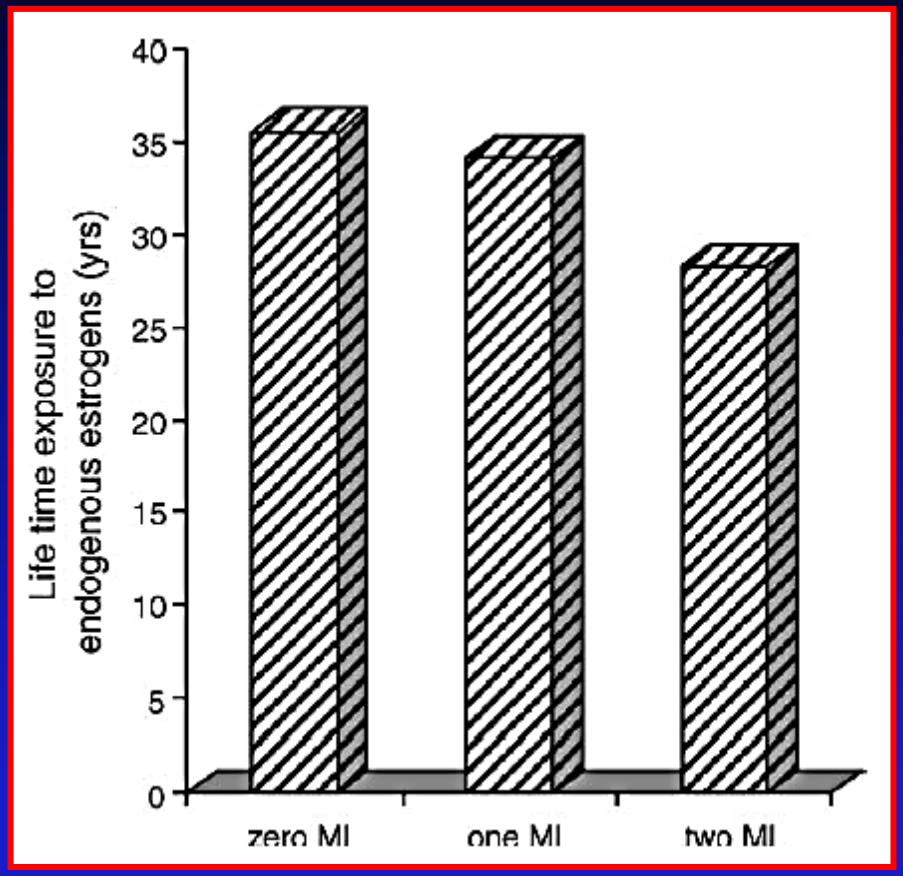


FIGURE 1. Life expectancy by age at menopause (years).

Later menopause increases life expectancy.

Ossewaarde ME et al. Epidemiology 2005;16:556-562.

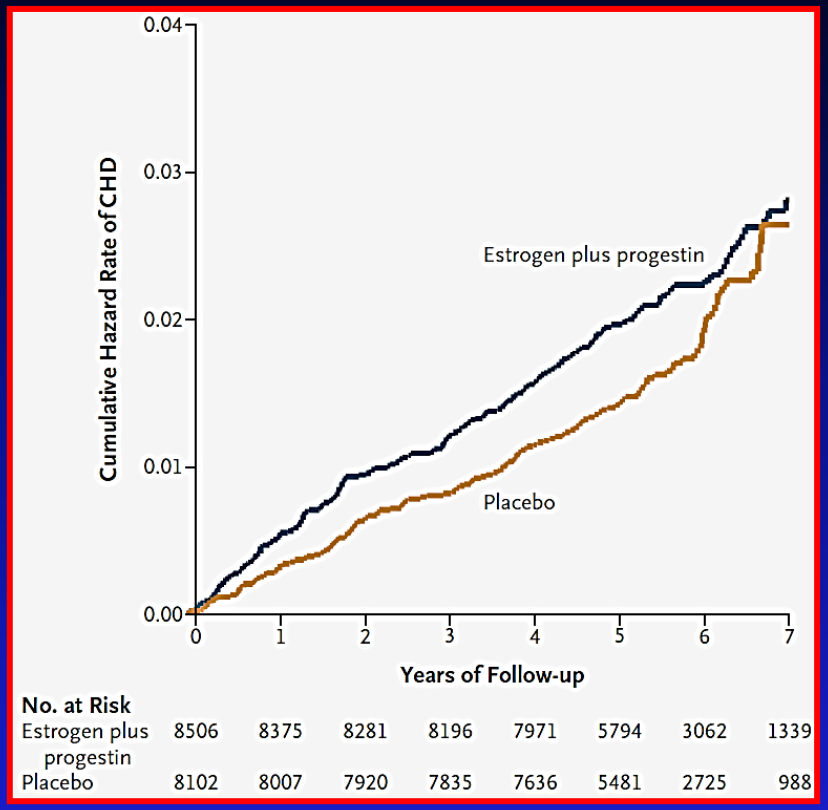
Reproductive Ages



Number of MI is negatively associated with life time exposure to endogenous estrogen.

Saltiki K et al. Maturitas 2006;55:51-57.

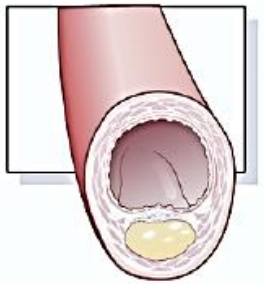
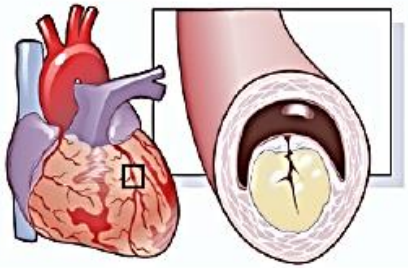
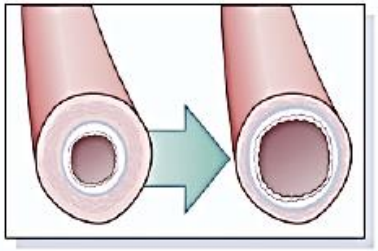
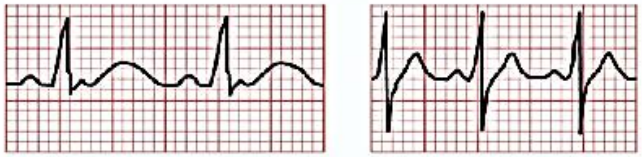
Hormone Replacement Therapy



Manson JE et al. N Engl J Med 2003;349:523-534.

HRT is not recommended in women age > 35 years with CV risk factors including hypertension, smoking, diabetes, nephropathy and other vascular disease.

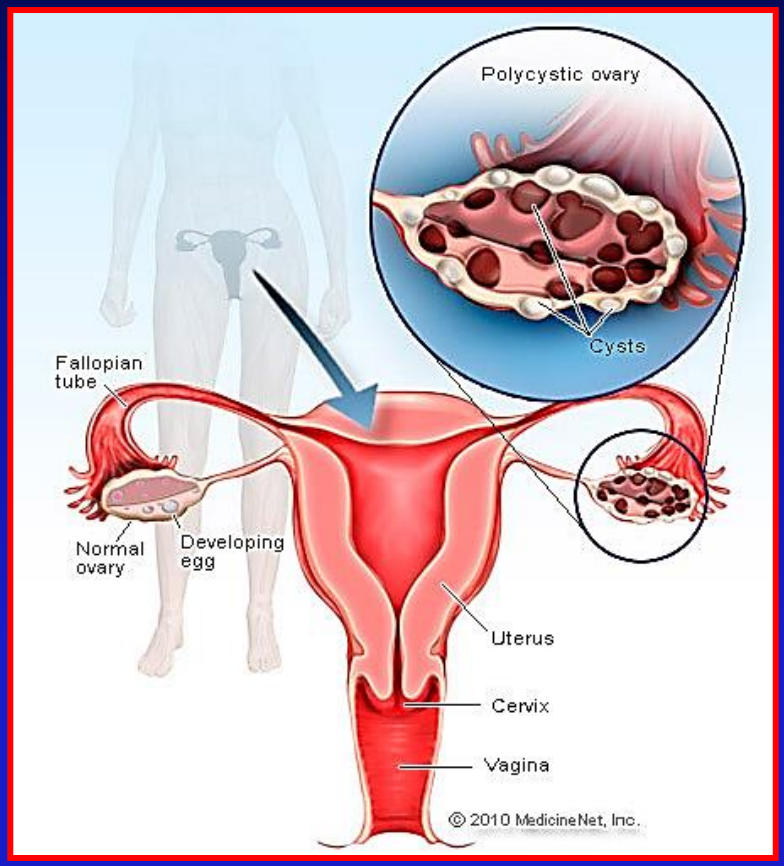
Kaunitz AM et al. N Eng J Med 2008;358:1262-1270.

Estrogens		Progestins
↓ LDL oxidation ↓ LDL binding ↑↓ lipoprotein* *** ↑ blood pressure ↓ oxidation damage ↓ VSMC proliferation ↓ glucose tolerance***	**Atherosclerosis** 	↑↓ HDL effect* ** ↑↓ blood pressure** ↑ glucose tolerance**
↑ coagulation factors ↓ platelet aggregation	**Thrombosis** 	↑ coagulation factors ↓ platelet aggregation ↓ nitric oxide**
↑ nitric oxide ↓ endothelin ↑ Cox-2 ↓ neuroendocrine response ↓ VSMC proliferation	**Vasomotion** 	↑ vasoconstriction** ↓ nitric oxide**
↑ QT prolongation	**Arrhythmogenesis** 	↓ QT prolongation

Shufelt CL and Bairey Merz CN . J Am Coll Cardiol 2009;53:221-231.

Poly Cystic Ovary Syndrome

- **Definition**
  - *Chronic anovulation*
  - *Hyperandrogenism*
  - *Polycystic ovaries*
- Highly prevalent: 1/15 women
- **Associated with**
  - *Diabetes mellitus*
  - *Hypertension*
  - *Dyslipidemia*
  - *Metabolic syndrome*



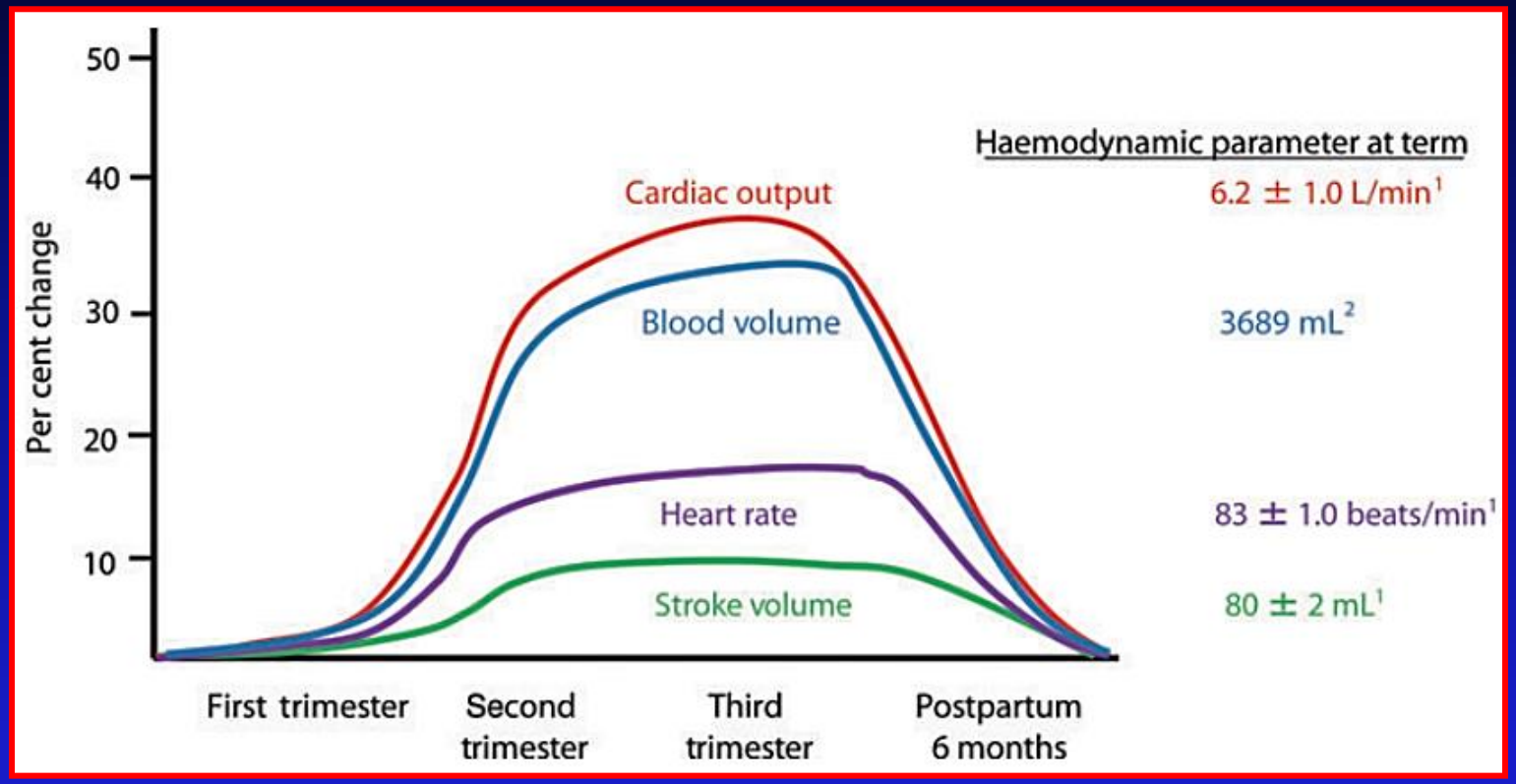
Norman RJ et al. Lancet 2007;370:685-97.

Poly Cystic Ovary Syndrome

Characteristic	PCOS (n = 11,035)	No PCOS (n = 55,175)	*P* value
Mean age in 2003 (yr)	30.7 ± 7.2	30.8 ± 7.5	
Age group in 2003, yr (N %)			1.0
15–19	850 (7.7)	4,250 (7.7)	
20–24	1,663 (15.1)	8,315 (15.1)	
25–29	2,616 (23.7)	13,080 (23.7)	
30–34	2,821 (25.6)	14,105 (25.6)	
35–39	1,856 (16.8)	9,280 (16.8)	
40–44	977 (8.9)	4,885 (8.9)	
≥ 45	252 (2.3)	1,260 (2.3)	
Race/ethnicity			<0.001
White	3,778 (34.2)	17,752 (32.2)	
Black	552 (5.0)	3,707 (6.7)	
Asian/Pacific Islander	1,117 (10.1)	5,634 (10.2)	
Hispanic	1,324 (12.0)	6,375 (11.6)	
Other	432 (3.9)	2,276 (4.1)	
Unknown	3,832 (34.7)	19,431 (35.2)	
Peak BMI (kg/m^2)			
BMI measured	6,220 (56.4)	26,622 (48.3)	<0.001
Among subjects with measured BMI:			<0.001
Normal or underweight (BMI ≤ 24)	847 (13.6)	10,549 (39.6)	
Overweight (BMI 25–29)	1,209 (19.4)	7,713 (29.0)	
Obese (BMI ≥ 30)	4,164 (67.0)	8,360 (31.4)	
Cardiovascular risk factor			
Diabetes mellitus	988 (9.0)	1,136 (1.9)	<0.001
Diagnosed hypertension	1,341 (12.2)	2,693 (4.9)	<0.001
Diagnosed hypertension and/or elevated blood pressure	2,939 (26.6)	6,466 (11.7)	<0.001
Diagnosed dyslipidemia or LDL ≥ 160 mg/dl (4.14 mmol/liter)[a]	1,610 (14.6)	3,253 (5.9)	<0.001
HDL cholesterol < 40 mg/dl (1.04 mmol/liter)[b]	2,500 (22.7)	4,125 (7.5)	<0.001
Triglyceride >200 mg/dL (2.26 mmol/liter)[c]	1,769 (16.0)	2,570 (4.7)	<0.001
Current or former smoker	2,325 (21.1)	11,761 (21.3)	0.56
Diagnosed cardiovascular disease			
Coronary heart disease	24 (0.22)	134 (0.24)	0.62
Cerebrovascular disease	27 (0.24)	104 (0.19)	0.23
Peripheral vascular disease	19 (0.17)	82 (0.15)	0.56

Lo JC et al. J Clin Endocrinol Metab 2006;91:1357-63.

Cardiovascular Changes During Pregnancy



Liu LX & Arany Z. Cardiovasc Res 2014;101:545-553.

Pregnancy Associated CV Risk

- Maternal placental syndrome
  - Preeclampsia
  - Eclampsia
  - Placental abruption
- Increased HTN, DM, dyslip. incidence
- RAAS activation
- Insulin resistance
- Endothelial dysfunction
- Peripartum cardiomyopathy
- Pregnancy resets ovarian function

Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases

Yan Feng [a], Xiumei Hong [b,c,d], Elissa Wilker [a], Zhiping Li [c], Wenbin Zhang [c], Delai Jin [c], Xue Liu [c], Tonghua Zang [c], Xiping Xu [d], Xin Xu [a,*]

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[b] *School of Life Science, University of Science and Technology of China, Hefei, Anhui, China*
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Available online 6 August 2007

Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese Health Study

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[a] *Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN*
[b] *National University of Singapore, Saw Swee Hock School of Public Health, Singapore*
[c] *Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA*

Severity of cardiovascular disease in women: Relation with exposure to endogenous estrogen

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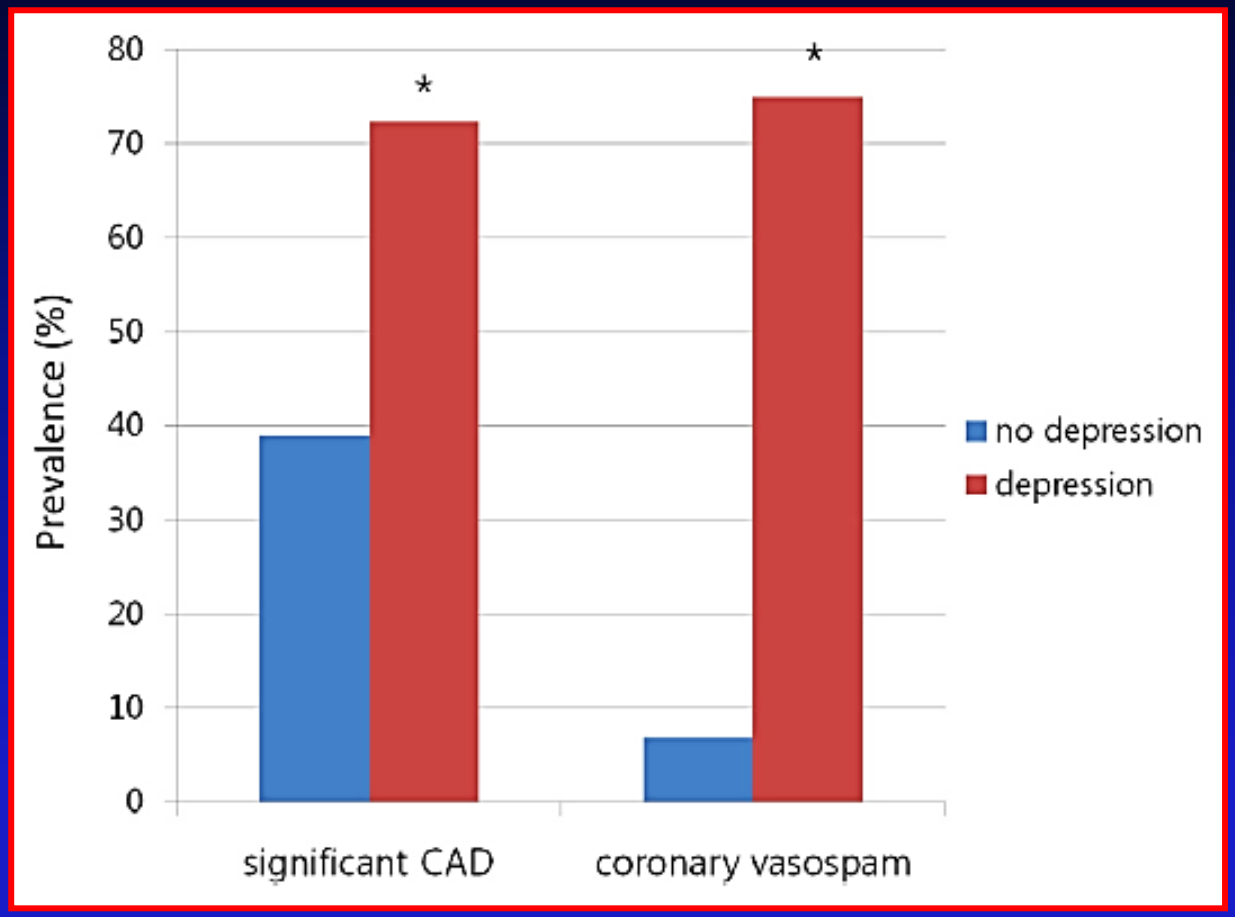
Endocrine Unit, Evgenidion Hospital and Dept Medical Therapeutics, ALEXANDRA Hospital, Athens University School of Medicine, Athens, Greece

Received 20 September 2005; received in revised form 26 December 2005; accepted 29 December 2005

Whether reproductive factors are associated with ischemic heart disease is still debated.

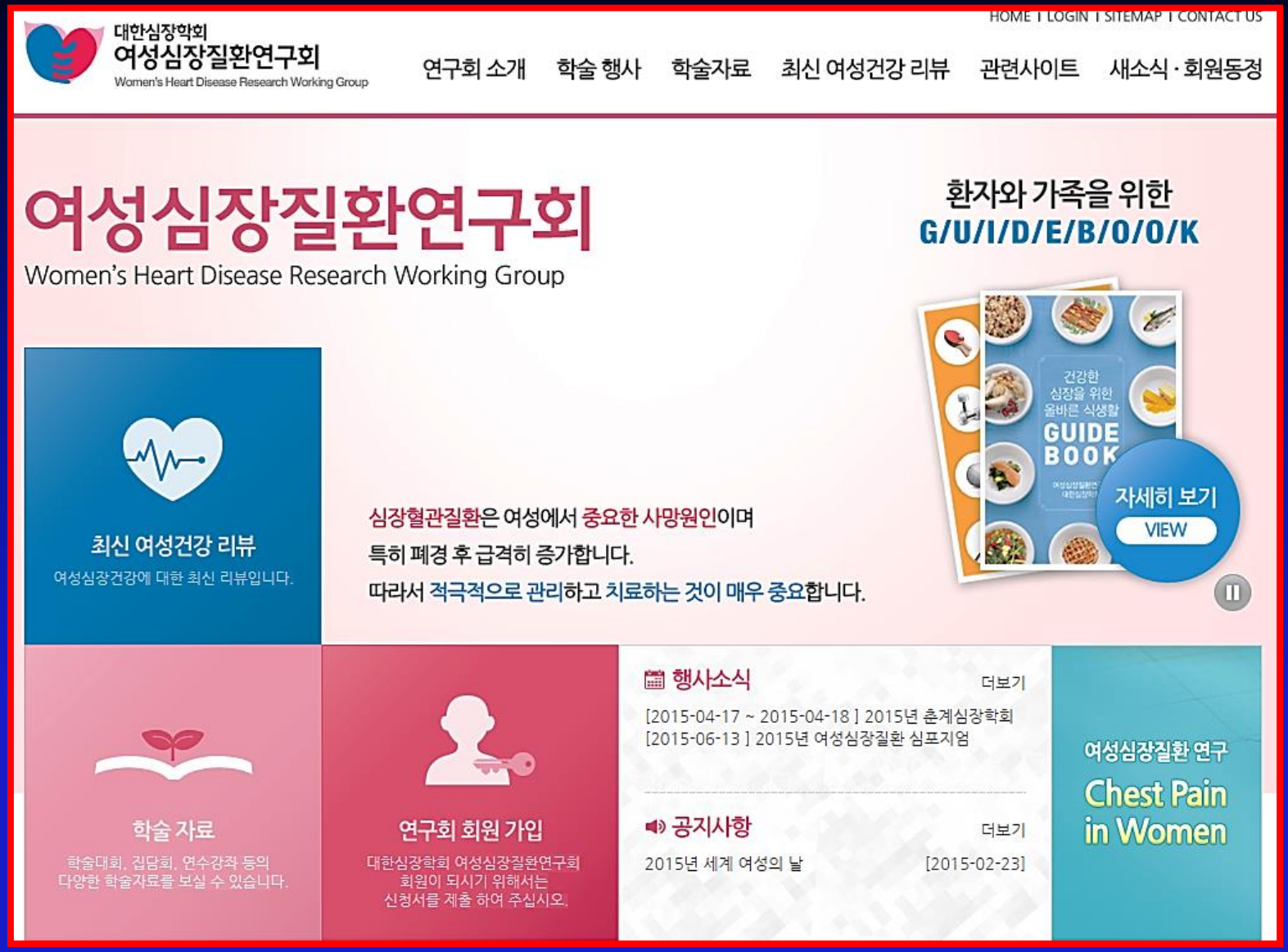
Depression



Patients in the depressed group exhibited a significantly higher prevalence of significant CAD and coronary vasospasm than non-depressed patients.

Cho KI et al. Physiol Behav 2015;143:45-50.

The KoRean wOmen'S chest pain rEgistry (KoROSE)



http://www.womensheart.or.kr/

Women Specific Predictors of Obstructive Coronary Artery Diesease in Symptomatic Women:

Chest Pain in Korean Women's Registry

Hack-Lyoung Kim[1], Myung-A Kim[1], Wan Joo Shim[2], Seong Mi Park[2], Yong Hyun Kim[2], Jin Oh Na[2], Mi Seung Shin[3], Yong-Jin Kim[4], Kyung-Hee Kim[5], Hyun Ju Yoon[6], Gil Ja Shin[7], Yoon-Kyung Cho[8], Sung-Eun Kim[9], Kyung-Soon Hong[9], Hyun-Sook Kim[9], Kyoung Im Cho[10]

[1]Seoul National University Boramae Medical Center, Seoul, [2]Korea University Hospital, Seoul, [3]Gachon Medical School Gil Medical Center, Incheon, [4]Seoul National University Hospital, Seoul, [5]Sejong general Hospital, Bucheon, [6]Chonnam National University Hospital, Gwangju, [7]Ewha Womans University Hospital, Seoul, [8]Kangnam CHA Hospital, Seoul, [9]Hallym University Medical Center, Seoul, Chuncheon and Anyang, [10]Kosin University Gospel Hospital, Pusan, Korea

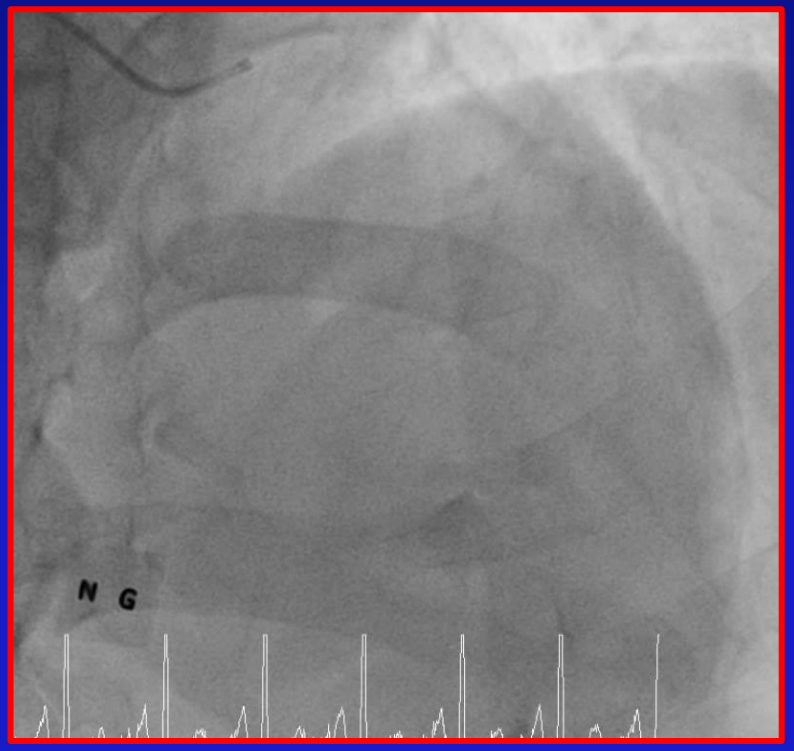
Study Methods

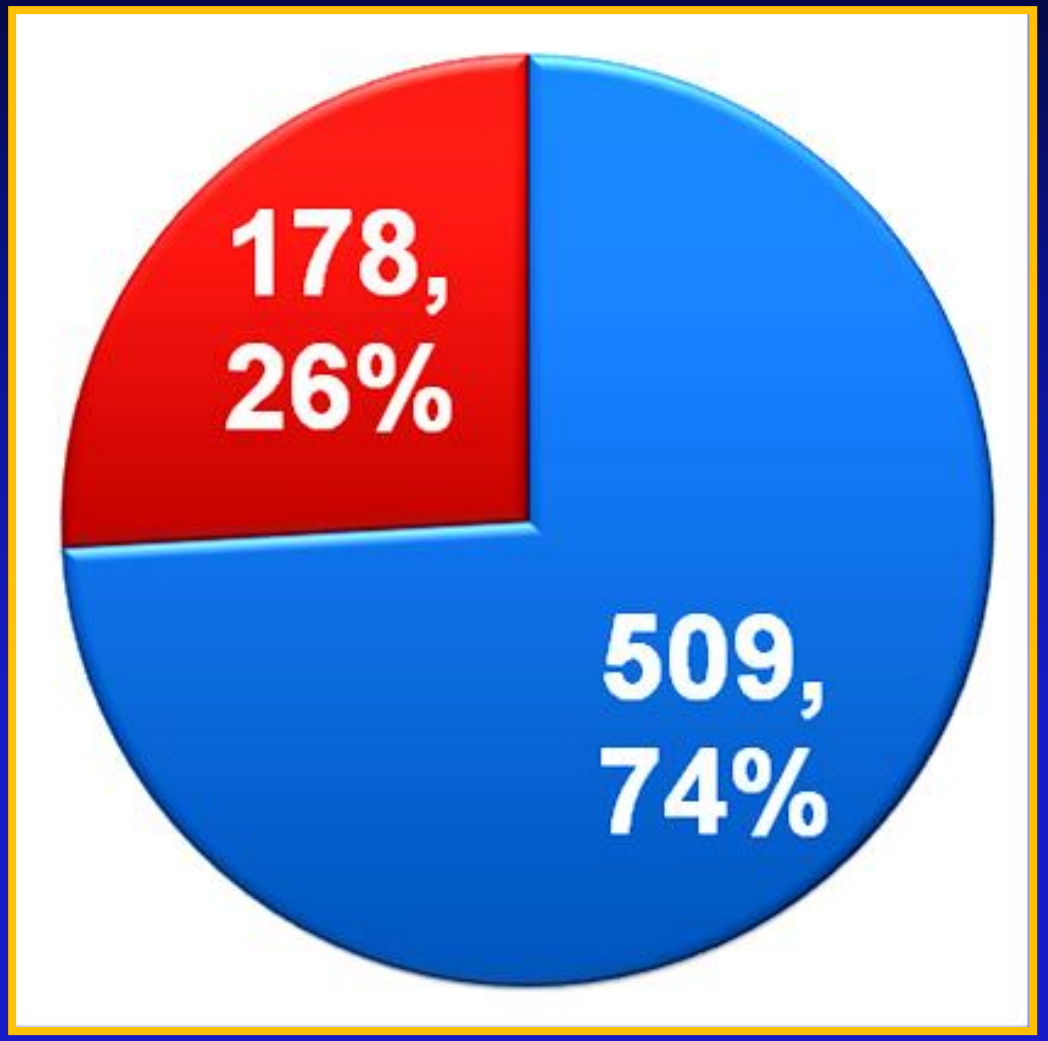
- Between 2/18/2011~8/1/2013
- 29 cardiac centers were particiapted.
- ***Chest pain in Korean Women's registry***
- **687** women with chest discomfort undergoing evaluation for CAD and referred for CAG
- **Obstructive CAD: ≥ 50% luminal stenosis** of one or more epicardial coronary artery.
- Information on women-specific risk factors was obtained using a standardized questionnaire.
- Multiple logistic regression analysis

Prevalence of Obstructive CAD

Obstructive

Non-obstructive





Baseline Characteristics

Characteristic	CAD (+) (n = 178)	CAD (-) (n = 509)	*P* value
Age, years	65.7 ± 9.2	57.9 ± 11.4	< 0.001
Body mass index, kg/m^2	24.6 ± 2.8	24.8 ± 3.4	0.564
Medical illness, n (%)			
Diabetes mellitus	58 (32.9)	59 (13.7)	< 0.001
Hypertension	115 (64.6)	204 (40.1)	< 0.001
Dyslipidemia	40 (22.5)	116 (22.8)	0.423
Medications, n (%)			
Statin	102 (57.3)	174 (34.2)	< 0.001
Aspirin	111 (62.3)	168 (33.0)	< 0.001
Beta-blocker	78 (42.6)	87 (17.1)	< 0.001
RAS blocker	65 (36.5)	90 (17.6)	< 0.001
Statin	102 (57.3)	174 (34.2)	< 0.001
Laboratory findings			
Hemoglobin, g/dL	12.4 ± 1.2	12.8 ± 1.1	< 0.001
WBC, per μL	5,030 ± 3,856	3,868 ± 3,571	< 0.001
eGFR, mL/min/1.73m^2	81.7 ± 28.4	87.3 ± 23.5	0.022
Fasting glucose, mg/dL	123 ± 51	107 ± 50	0.001
HbA1c, %	6.94 ± 1.15	6.42 ± 1.42	0.013
Total cholesterol, mg/dL	180 ± 49	184 ± 40	0.389
LDL cholesterol, mg/dL	105 ± 36	108 ± 36	0.375
HDL cholesterol, mg/dL	48.1 ± 13.1	52.1 ± 13.7	0.003
Triglyceride, mg/dL	137 ± 111	119 ± 74	0.028
BNP, pg/mL	197 ± 261	242 ± 485	0.756
CRP, mg/dL	1.08 ± 3.35	1.27 ± 3.88	0.641
Echocardiography			
LV mass index, g/m^2	99 ± 25	101 ± 31	0.648
LA diameter, mm	38.7 ± 5.9	36.3 ± 5.5	< 0.001
E/e'	13.0 ± 6.6	10.3 ± 3.8	< 0.001

CAD, coronary artery disease; RAS, renin-angiotensin system; WBC, white blood cell; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, brain natriuretic peptide; CRP, C-reactive protein; LV, left ventricular; LA, left atrial.

Reproductive Characteristics

Characteristic	Available information	CAD (+) (n = 178)	CAD (-) (n = 509)	*P* value
Age at menarche, years	n = 423	16.2 ± 1.8	15.7 ± 2.2	0.025
Age at menopause, years	n = 333	50.6 ± 4.9	49.0 ± 6.4	0.028
Reproductive duration, years	n = 318	34.5 ± 5.6	34.7 ± 7.7	0.843
Number of pregnancy	n = 451	4.06 ± 1.75	3.26 ± 1.80	< 0.001
HRT, yes, n (%)	n= 560	16 (11.0)	106 (25.5)	0.007
HRT duration, years	n = 51	6.50 ± 3.45	6.31 ± 9.52	0.962
Preeclampsia, yes, n (%)	n = 505	2 (1.5)	15 (4.0)	0.387
Twin pregnancy, yes, n (%)	n = 505	2 (1.5)	11 (3.0)	0.744
PCOS, n (%)	n = 619	3 (1.9)	7 (1.5)	0.657

CAD, coronary artery disease; HRT, hormonal replacement therapy; PCOS, polycystic ovarian syndrome.

Independent Predictors

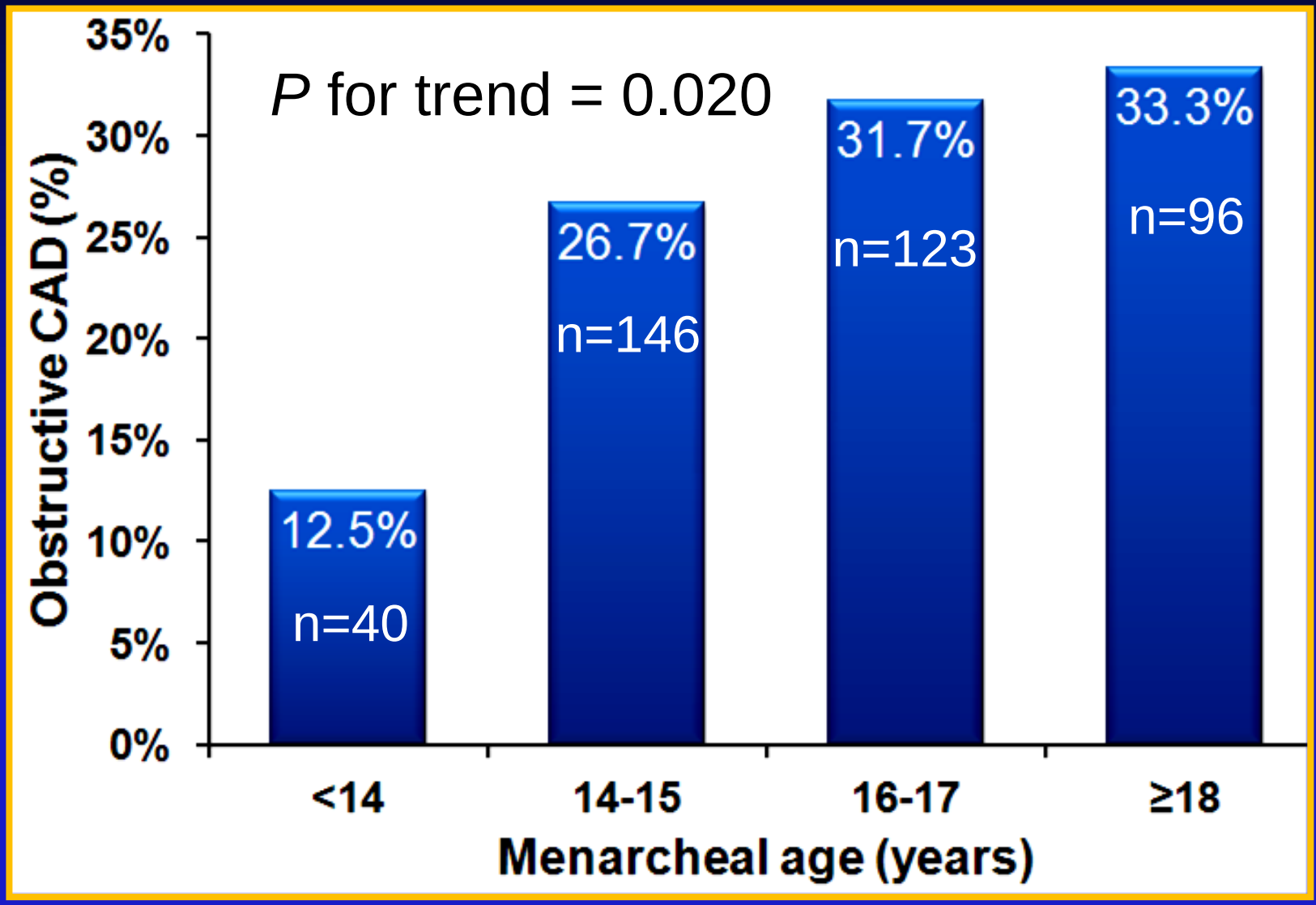
Multiple logistic regression analyses

Variable	OR	95% CI	*P* value
Age at menarche, per one year	1.292	1.082-1.530	0.005
Age at menopause, per one year	1.062	0.9433-1.107	0.783
Number of pregnancy, per one pregnancy	1.252	1.052-1.523	0.017
Hormonal replacement therapy, yes	0.347	0.128-1.012	0.053

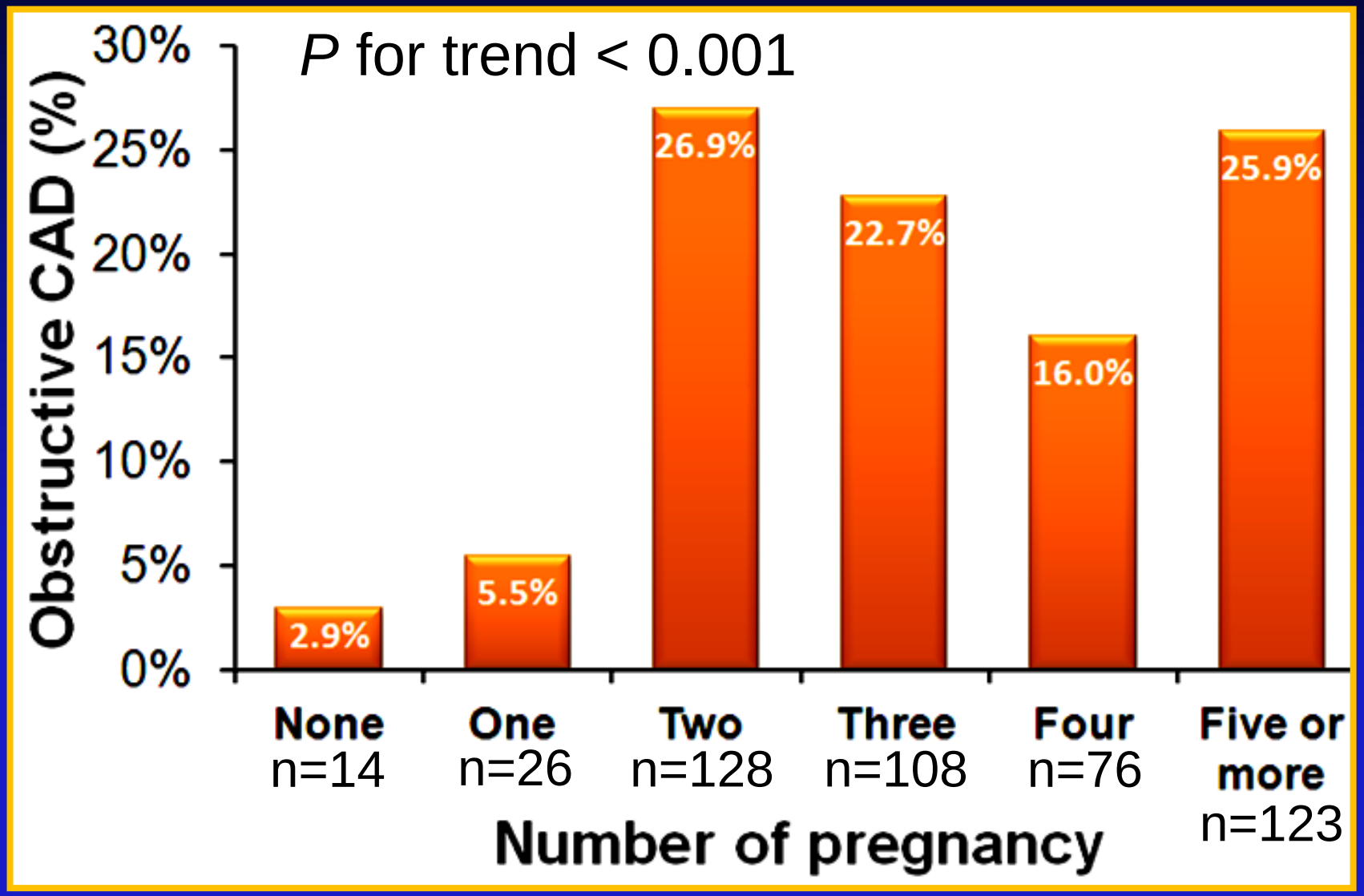
Each variable entered in binary logistic regression analysis separately. Age, diabetes mellitus, hypertension, dyslipidemia, estimated glomerular filtration rate, high density lipoprotein cholesterol, white blood cell count, hemoglobin and E/e' were adjusted in each multivariable model.

OR, odds ratio; IC, confidence interval.

Menarcheal Age



Number of Pregnancy



Summary

- Risk factors for obstructive CAD in women are similar to those of men in respect of traditional risk factors such as old age, diabetes mellitus and low HDL cholesterol level.
- ***Later age at menarche and number of pregnancy*** are identified as a women-specific risk factor suggesting the important role of hormonal status on the development of CAD.

Conclusions

- IHD is the leading cause of death in women, but is still under-recognised and undertreated.
- There are marked gender differences in the impact of traditional risk factors for IHD.
- Reproductive factors are not yet clarified as a risk factor of IHD, and further researchs are needed.
- A greater awareness of this differences are necessary to miprove therapeutic strategy and ouctomes in women.

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감사합니다!

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