# Cardiovascular Disease Risk in Women – Do Hormones Matter?

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Cardiovascular Disease Mortality Trends for Males and Females United States: 1979-2002
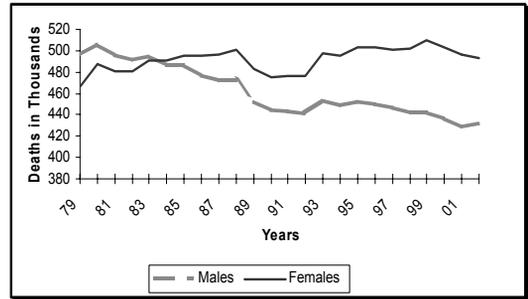
Source: CDC/NCHS.

Leading Causes of Death for All Males and Females- United States: 2002

Deaths in Thousands
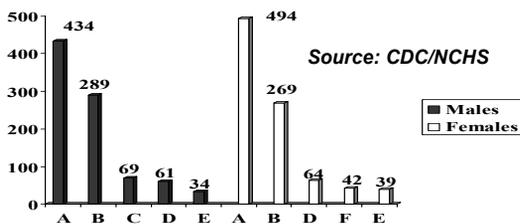
Source: CDC/NCHS

A Total CVD (Preliminary)
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease

Leading Causes of Death for White Males and Females - United States: 2002
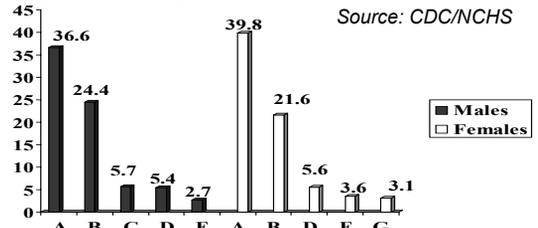
Percent of Total Deaths

Source: CDC/NCHS

A Total CVD (Preliminary)
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease
G Influenza and Pneumonia

Leading Causes of Death for Black or African-American Males and Females - United States: 2002

Percent of Total Deaths
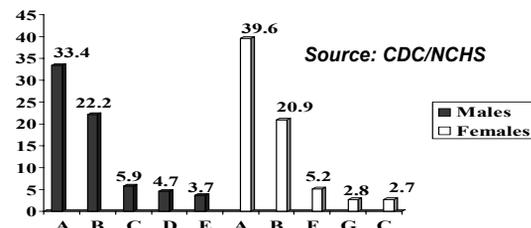
Source: CDC/NCHS

A Total CVD (Preliminary)
B Cancer
C Accidents
D Assault (Homicide)
E HIV(AIDS)
F Diabetes Mellitus
G Nephritis, Nephrotic Syndrome and Nephrosis

Age Adjusted Death Rates for Coronary Heart Disease, Stroke, and Lung and Breast Cancer for White and Black Females – United States: 2002
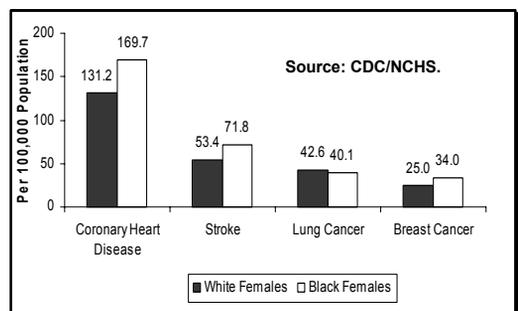
Source: CDC/NCHS.

Prevalence of Cardiovascular Diseases in Americans Age 20 and Older by Age and Sex NHANES: 1999-2002

Ages	Males	Females
20-34	11.2	6.2
35-44	22.9	17.6
45-54	36.2	36.6
55-64	52.9	56.5
65-74	68.5	75.0
75+	77.8	86.4
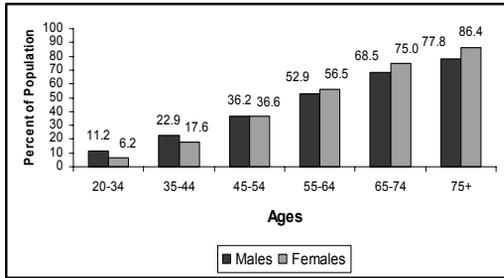
Source: CDC/NCHS and NHLBI. These data include coronary heart disease, congestive heart failure, stroke and hypertension.

Prevalence of Coronary Heart Diseases by Age and Sex
NHANES :1999-2002

Ages	Men	Women
20-34	0.0	0.3
35-44	1.4	0.2
45-54	3.0	1.6
55-64	11.6	3.6
65-74	11.5	6.3
75+	16.8	10.3
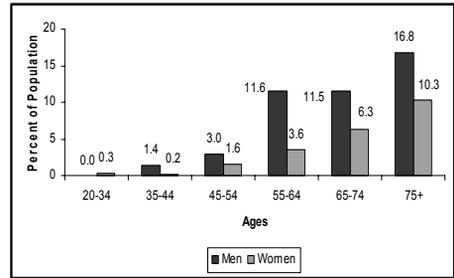
Source: CDC/NCHS and NHLBI.

Annual Number of Americans Having Diagnosed Heart Attack by Age and Sex
ARIC: 1987-2000

Ages	Men	Women
29-44	34,000	10,000
45-64	250,000	88,000
65+	410,000	372,000
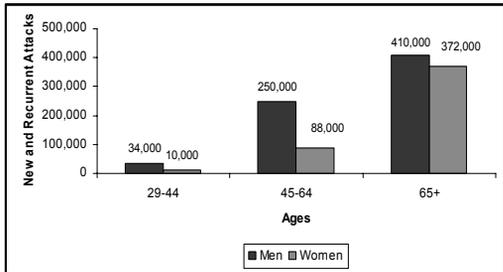
Source: Extrapolated from rates in the NHLBI's ARIC surveillance study, 1987-2000. These data don't include silent MIs.

Annual Rate of First Heart Attacks by Age, Sex and Race
ARIC: 1987-2000

White Men ● Black Men ■ White Women △ Black Women ✕
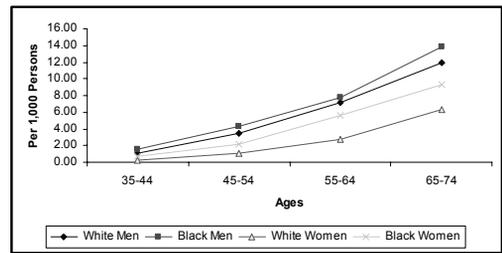
Source: NHLBI's ARIC surveillance study, 1987-2000.

Prevalence of Stroke by Age and Sex

NHANES: 1999-2002

Ages	Men	Women
20-34	0.4	0.3
35-44	1.1	0.8
45-54	1.2	2.1
55-64	3.1	3.0
65-74	6.6	6.3
75+	12.0	11.5
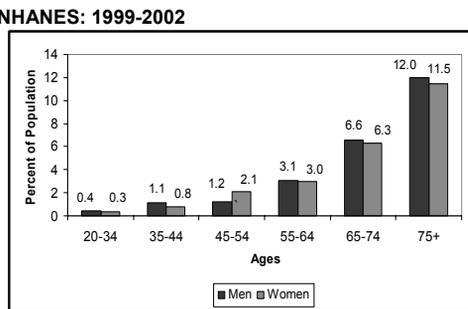
Source: CDC/NCHS and NHLBI.

Risk of Stroke in Women in the Third Trimester, Peri- and Post-Partum Period Versus Risk of Nonpregnant Women and Women in the First 2 Trimesters

Pregnancy Duration	Ischemic Stroke	Intracerebral Hemorrhage	Subarachnoid Hemorrhage
Third Trimester	2.2	0.3	0.8
Around Delivery	33.8	95.0	46.9
Puerperium	8.3	11.7	1.8
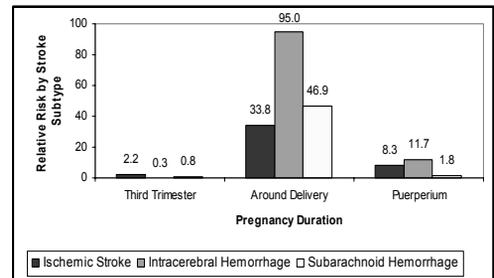
Source: Epidemiology 2001;12:456-60

Prevalence of Congestive Heart Failure by Age and Sex
NHANES: 1999-2002

Percent of Population by Ages:

Ages	Men	Women
20-34	0.3	0.3
35-44	0.5	0.4
45-54	1.8	1.5
55-64	5.8	2.3
65-74	6.2	4.1
75+	9.8	10.9
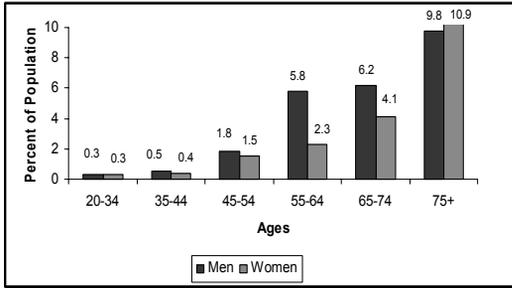
Source: CDC/NCHS and NHLBI.

Hospital Discharges for Congestive Heart Failure by Sex
United States: 1970-2002

Discharges in Thousands, Years 70–02 (Males, Females)
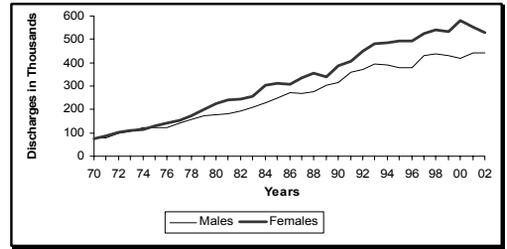
Note: Hospital discharges include people living and dead.

Source: CDC/NCHS.

Estimated 10-Year CHD Risk in 55-Year-Old Adults According to Levels of Various Risk Factors
Framingham Heart Study

Estimated 10-Year Rate (%):

	A	B	C	D
Men	5	13	25	37
Women	5	8	20	27
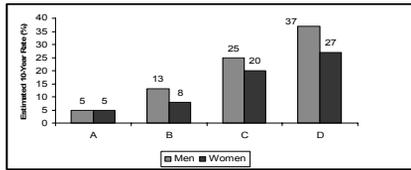
	A	B	C	D
Blood Pressure (mm Hg)	120/80	140/90	140/90	140/90
Total Cholesterol (mg/dL)	200	240	240	240
HDL Cholesterol (mg/dL)	50	50	40	40
Diabetes	No	No	Yes	Yes
Cigarettes	No	No	No	Yes

mm Hg = millimeters of mercury
mg/dL = milligrams per deciliter of blood

Source: Wilson PWF, et al. Circulation 1998;97:1837-1847.

Estimated 10-Year Stroke Risk in 55-Year-Old Adults According to Levels of Various Risk Factors - Framingham Heart Study

Estimated 10-Year Rate (%):

	A	B	C	D	E	F
Men	2.6	4.0	5.4	8.4	14.8	22.4
Women	1.1	2.0	3.5	6.3	19.1	27.0
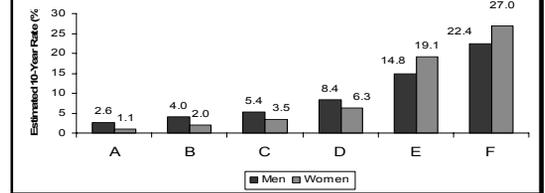
	A	B	C	D	E	F
Systolic BP	95-105	130-148	130-148	130-148	130-148	130-148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarettes	No	No	No	Yes	Yes	Yes
Prior Atrial Fib.	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

Source: Stroke 1991;22:312-318.

Prevalence of High Blood Pressure in Americans by Age and Sex
NHANES: 1999-2002

Percent of Population by Ages:

Ages	Men	Women
20-34	11.1	5.8
35-44	21.3	18.1
45-54	34.1	34.0
55-64	46.6	55.5
65-74	60.9	74.0
75+	69.2	83.4
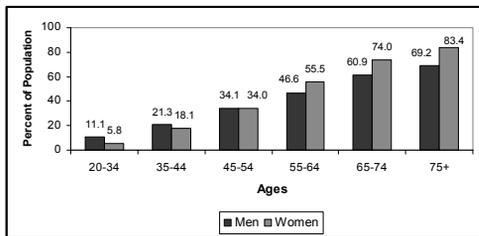
Source: CDC/NCHS and NHLBI.

Age-Adjusted Prevalence of Physician-Diagnosed Diabetes in Americans Age 20 and Older by Sex and Race/Ethnicity

NHANES: 1999-2002

Percent of Population:

|	Non-Hispanic Whites	Non-Hispanic Blacks	Mexican Americans
Men	6.2	10.3	10.4
Women	4.7	12.6	11.3
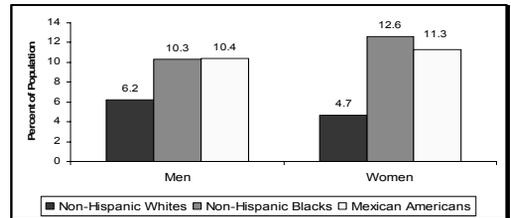
Source: CDC/NCHS and NHLBI.

Prevalence of Non-Insulin-Dependent

(Type 2) Diabetes in Women* Ages 25-64 by Race/Ethnicity and Education

NHANES III: 1988-94

Percent of Population (y-axis 0–20)

Years of Education	Whites	Blacks	Mexican Americans
<9	4.5	20	11.5
9-11	9.3	11.3	6.8
12	4.6	5.1	6.1
>12	2.9	5.4	6.4

Whites ■ Blacks ☐ Mexican Americans
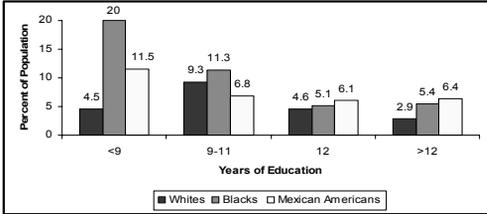
* Findings for men are similar but of lower magnitude. See Pathways by which SES and ethnicity influence CVD risk factors. Annals NY Academy of Science. 1999;896:191-209

Source: JAMA. 1998;280:356-62.

Age-Adjusted Prevalence of Obesity in Americans Ages 20-74 by Sex and Survey

NHES, 1960-62; NHANES, 1971-74, 1976-80, 1988-94 and 1999-2002

Percent of Population (y-axis 0–40)

	1960-62	1971-74	1976-80	1988-94	1999-2002
Men	10.7	12.1	12.7	20.6	27.6
Women	15.8	16.6	17.0	25.9	33.2
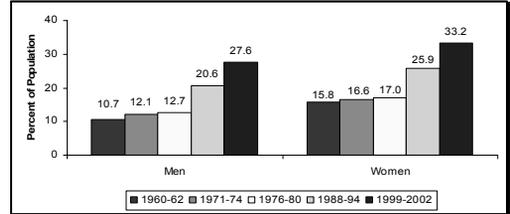
Note: Obesity is defined as a BMI of 30.0 or higher.

Source: CDC/NCHS.

Prevalence of Students in Grades 9-12 Who Participated in Sufficient Vigorous or Moderate Physical Activity During the Past 7 Days by Race/Ethnicity and Sex

YRBS: 2003

Percent of Population (y-axis 0–80)

	Vigorous	Moderate
Non-Hispanic White Males	71.9	28.9
Non-Hispanic White Females	58.1	23.3
Non-Hispanic Black Males	65	25.8
Non-Hispanic Black Females	44.9	17.5
Hispanic Males	66.7	23.3
Hispanic Females	51.8	20.6
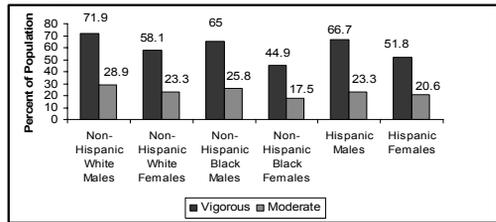
■ Vigorous ■ Moderate

Note: "Vigorous activity" is defined as activity causing sweating and hard breathing for at least 20 minutes on 3 or more of the 7 days. "Moderate activity" is defined as activities such as walking or bicycling lasting for at least 30 minutes on 5 or more of the 7 days.

Source: MMWR, Vol. 53, No. SS-2, May 21, 2004, CDC/NCHS.

Prevalence of Moderate or Vigorous Physical Activity in Americans Age 20 and Older by Sex, Race/Ethnicity and BMI

NHANES III: 1988-94

Percent of Population (y-axis 0–50)

	BMI <25	BMI 25-29.9	BMI 30+
Non-Hispanic White Men	46.6	48.8	37.3
Non-Hispanic Black Men	47.3	41.8	44.5
Mexican-American Men	35.4	39.5	26.4
Non-Hispanic White Women	44.2	30.6	28.8
Non-Hispanic Black Women	29.4	30.3	26.8
Mexican-American Women	29.5	28.7	20

■ BMI <25 ■ BMI 25-29.9 ☐ BMI 30+
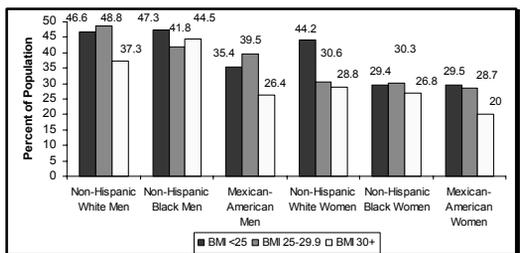
Note: BMI indicates body mass index: weight in kilograms divided by height in meters squared (kg/m2).

Source: CDC/NCHS.

Observational Studies of HRT and CVD

Relative Risk

Stampfer et al,1985
Wilson et al, 1985
Bush et al, 1987
Petitti et al, 1987
Boysen et al, 1988
Criqui et al,1988
Henderson et al, 1988
van der Giezen et al, 1990
Wolf et al, 1991
Falkeborn et al, 1992
Psaty et al, 1994
Folsom et al,1995
Meta-analysis

0   0.5   1.0   2.0   10
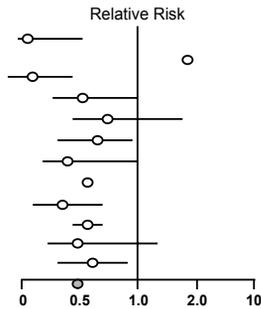
NURSES' HEALTH STUDY

- Observational Study – NIH Funded
- 121,700 female nurses 30-55 yo enrolled in 1976
- 70,553 postmenopausal without previous CVD – 20 yr F/U
- Biennial follow-up questionnaire

  ? Menopausal
  ? HRT
  ? What kind of HRT
  ? What dose of HRT
  ? CVD events

- nonfatal MI
- fatal CAD
- fatal and nonfatal stroke
- >98% mortality F/U

Grodstein et al. Ann Intern Med 2000;133:933-41

NURSES' HEALTH STUDY 1976-96

Risk for Major CHD

HRT Use	Person-Years of Follow-up	Cases n	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	662	1.0 (referent)
Past	185 497	337	0.82 (0.72-0.94)
Current	265 203	259	0.61 (0.52-0.71)
<1 y	20 091	9	0.40 (0.21-0.77)
1-1.9 y	19 155	9	0.41 (0.21-0.80)
2-4.9 y	79 928	60	0.53 (0.41-0.70)
5-9.9 y	77 435	74	0.58 (0.45-0.74)
≥10 y	69 594	107	0.74 (0.59-0.91)

Grodstein et al. Ann Intern Med 2000;133:933-41

PROBLEMS WITH OBSERVATIONAL STUDIES

- Differences (measured and unmeasured) between groups being compared
- Women who take HRT
  - Healthier
  - Wealthier
  - More health care
    Rx for HRT
    Fill Rx for HRT
    20-40% adherence to HRT for >1 yr.

Barrett-Connor Ann Intern Med 1991;115:455-6
Ettinger & Pressman Am J Manag Care 1999;5:779-85

RELATIVE RISK OR ODDS RATIO FOR CARDIOVASCULAR DISEASE INCIDENCE
Pooled Estimates

Pooled Estimate
  Current HRT Use
  Past HRT Use
  Ever HRT Use
  Any HRT Use
Pooled Estimate
  Current HRT Use
  Past HRT Use
  Ever HRT Use
  Any HRT Use

●— Not adjusted for Socioeconomic Status
○— Adjusted for Socioeconomic Status

0.2   HRT Better   1.0   Placebo Better   5.0

Relative Risk or Odds Ratio
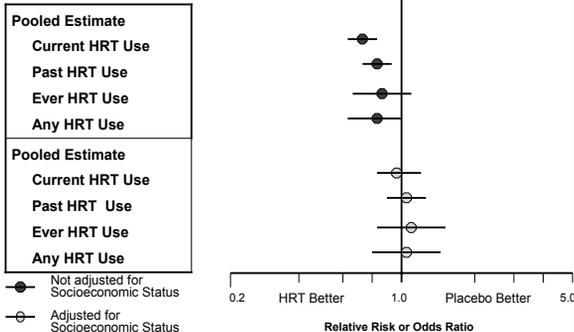
Humphrey et al. Ann Intern Med 2002; 137:273-284

Randomized controlled Trials of HRT and CVD

| Trial	Design	Findings
PEPI	effect on lipids	improved profile
CAVEAT	angiographic	↓ restenosis
ERA	angiographic	no Δ in CAD progression
HERS	2° prevention	↑ early events ↓ late events
HERS II	2° prevention	no Δ events
WHI	1° prevention	stopped early due to ↑ breast Ca
WISDOM	1° prevention	stopped early due to futility of finding benefit

WHI
HRT Component of WHI Clinical Trial

– Average duration of follow-up = 5.2 years
– Regimens: CEE 0.625 mg/d + MPA 2.5 mg/d (n = 8,506) or placebo (n = 8,102)
– Primary outcome: coronary heart disease (nonfatal MI and CHD death)
– Primary adverse outcome: invasive breast cancer
– Global index: a summary measure of the overall balance of risks and benefits

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI
Disease Rates for Women on Combination HRT or Placebo
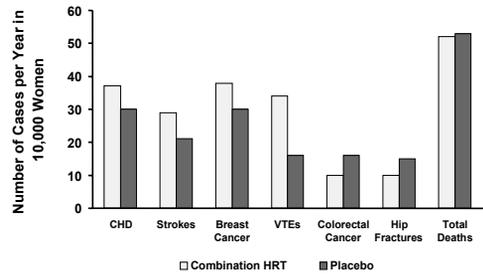
Adapted from *WHI HRT Update*, June 2002.

ESTROGEN PLUS PROGESTIN AND THE RISK OF CHD IN VARIOUS SUBGROUPS

SUBGROUP	ESTROGEN-PLUS-PROGESTIN GROUP	PLACEBO GROUP	P VALUE FOR INTERACTION	Hazard Ratio for CHD
	NO. CASES OF CHD (ANNUALIZED PERCENTAGE)			
AGE			0.36	
50-59 YRS	37 (0.22)	27 (0.17)		1.27
60-69 YRS	75 (0.35)	68 (0.34)		1.05
70-79 YRS	76 (0.78)	52 (0.55)		1.44
YRS SINCE MENOPAUSE			0.33	
<10	31 (0.19)	34 (0.22)		0.89
10-19	63 (0.38)	51 (0.32)		1.22
>20	74 (0.75)	44 (0.46)		1.71
ASPIRIN USE (≥80mg/day)			0.71	
YES	48 (0.53)	41 (0.46)		1.14
NO	140 (0.36)	106 (0.29)		1.22
STATIN USE			0.44	
YES	24 (0.78)	23 (0.80)		0.99
NO	164 (0.63)	124 (0.29)		1.22

Manson et al. N Engl J Med 2003;349;523-34.

WHI
ERT COMPONENT
11,000 PARTICIPANTS

• Average duration of follow-up ≈ 7 years
• Regimen: CEE 0.625 mg/d or placebo
• Stopped in February 2, 2004 by NHLBI (DSBM was divided)
  – **Increased stroke risk (8/yr/10,000 women)**
  – No effect on heart disease
  – No effect on breast cancer
  – Decreased hip fracture risk

KAPLAN-MEIER ESTIMATES OF CUMULATIVE HAZARDS FOR HEART DISEASE AND STROKE

CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.
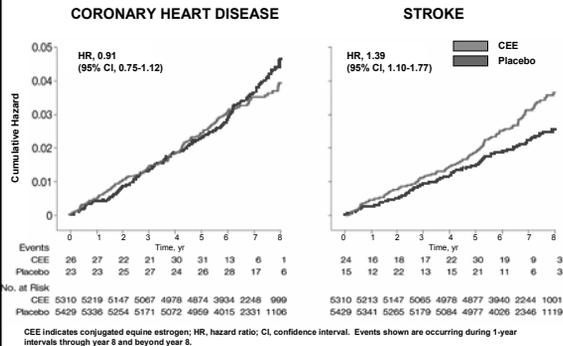
WHI Steering Committee. JAMA 2004;291:1701-1712

KAPLAN-MEIER ESTIMATES OF CUMULATIVE HAZARDS FOR INVASIVE BREAST CANCER AND HIP FRACTURE

CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.

WHI Steering Committee. JAMA 2004;291:1701-1712

	No. of Cases (Annualized %)		Hazard Ratio (95% CI)	P Value	Favors CEE	Favors Placebo	
Outcomes by Age, y	CEE	Placebo					
Coronary Heart Disease							50-59 yrs
50-59	16 (0.14)	29 (0.24)	0.56 (0.30-1.03)				60-69 yrs
60-69	87 (0.54)	96 (0.59)	0.92 (0.69-1.23)	.14			70-79 yrs
70-79	74 (0.88)	72 (0.84)	1.04 (0.75-1.44)				
Stroke							
50-59	19 (0.16)	19 (0.16)	1.06 (0.57-2.04)				
60-69	79 (0.48)	50 (0.30)	1.65 (1.16-2.36)	.59			
70-79	70 (0.83)	49 (0.57)	1.25 (0.85-1.82)				
Venous Thromboembolism							
50-59	16 (0.15)	13 (0.13)	1.22 (0.62-2.42)				
60-69	49 (0.31)	39 (0.23)	1.31 (0.86-2.00)	.39			
70-79	34 (0.40)	24 (0.28)	1.44 (0.86-2.44)				
Invasive Breast Cancer							
50-59	25 (0.21)	35 (0.29)	0.72 (0.43-1.21)				
60-69	42 (0.26)	60 (0.36)	0.72 (0.49-1.07)	.51			
70-79	27 (0.32)	29 (0.34)	0.94 (0.56-1.60)				
Colorectal Cancer							
50-59	8 (0.07)	14 (0.12)	0.59 (0.25-1.41)				
60-69	26 (0.16)	31 (0.19)	0.88 (0.52-1.48)	.048			
70-79	27 (0.32)	13 (0.15)	2.09 (1.08-4.04)				
Hip Fracture							
50-59	5 (0.04)	1 (0.01)	5.04 (0.59-43.17)				
60-69	6 (0.04)	19 (0.11)	0.30 (0.13-0.80)	.39			
70-79	27 (0.30)	44 (0.52)	0.62 (0.38-1.00)				
Total Death							
50-59	34 (0.29)	47 (0.39)	0.73 (0.47-1.13)				
60-69	127 (0.79)	124 (0.76)	1.01 (0.79-1.29)	.19			
70-79	130 (1.54)	111 (1.30)	1.20 (0.90-1.54)				
Global Index							
50-59	104 (0.89)	132 (1.11)	0.80 (0.62-1.03)				
60-69	312 (1.96)	327 (1.97)	0.99 (0.84-1.15)	.08			
70-79	276 (3.29)	246 (2.88)	1.16 (0.97-1.37)				

Hazard Ratio
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0

CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval.
Data are plotted as hazard ratios with errors bars showing 95% CIs.

|	No. of Cases (Annualized %)		Hazard Ratio (95% CI)	P Value	Favors CEE	Favors Placebo	
Outcomes by Age, y	CEE	Placebo					
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60-69	87 (0.54)	96 (0.59)	0.92 (0.69-1.23)	.14			70-79 yrs
70-79	74 (0.88)	72 (0.84)	1.04 (0.75-1.44)				
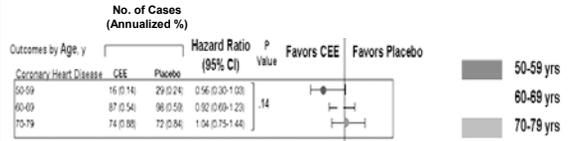
LIMITATIONS OF WHI

HRT and ERT were begun at an advanced age – after many hormone-free years.

—? Integrity of ERs, other response mechanisms.

The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition

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CHARACTERISTICS OF WOMEN IN THE 50-59 YEAR OLD WHI HRT AND PLACEBO GROUPS

PARAMETER	E+P	PLACEBO
Age 50-59 y(% total group)	2839 (33.4)	2868 (33.1)
Menopausal age (y)[a]		
<5	1315 (17.1)	1224 (16.3)
5 to <10	1467 (19.1)	1488 (19.8)
10 to <15	1611 (21.0)	1566 (20.9)
≥15	3286 (42.8)	3231 (43.0)

a= Average, 12.0 y

Unmet Needs

- **Controlled studies of HRT begun in perimenopausal period.**
- **Studies of other estrogens, progestins.**
- **Mechanistic studies.**
- **Identification of biomarkers for susceptibility to adverse effects of HRT.**
  - **Proinflammatory factors**
  - **Genetic factors**