Menopause and Hormone Replacement Therapy

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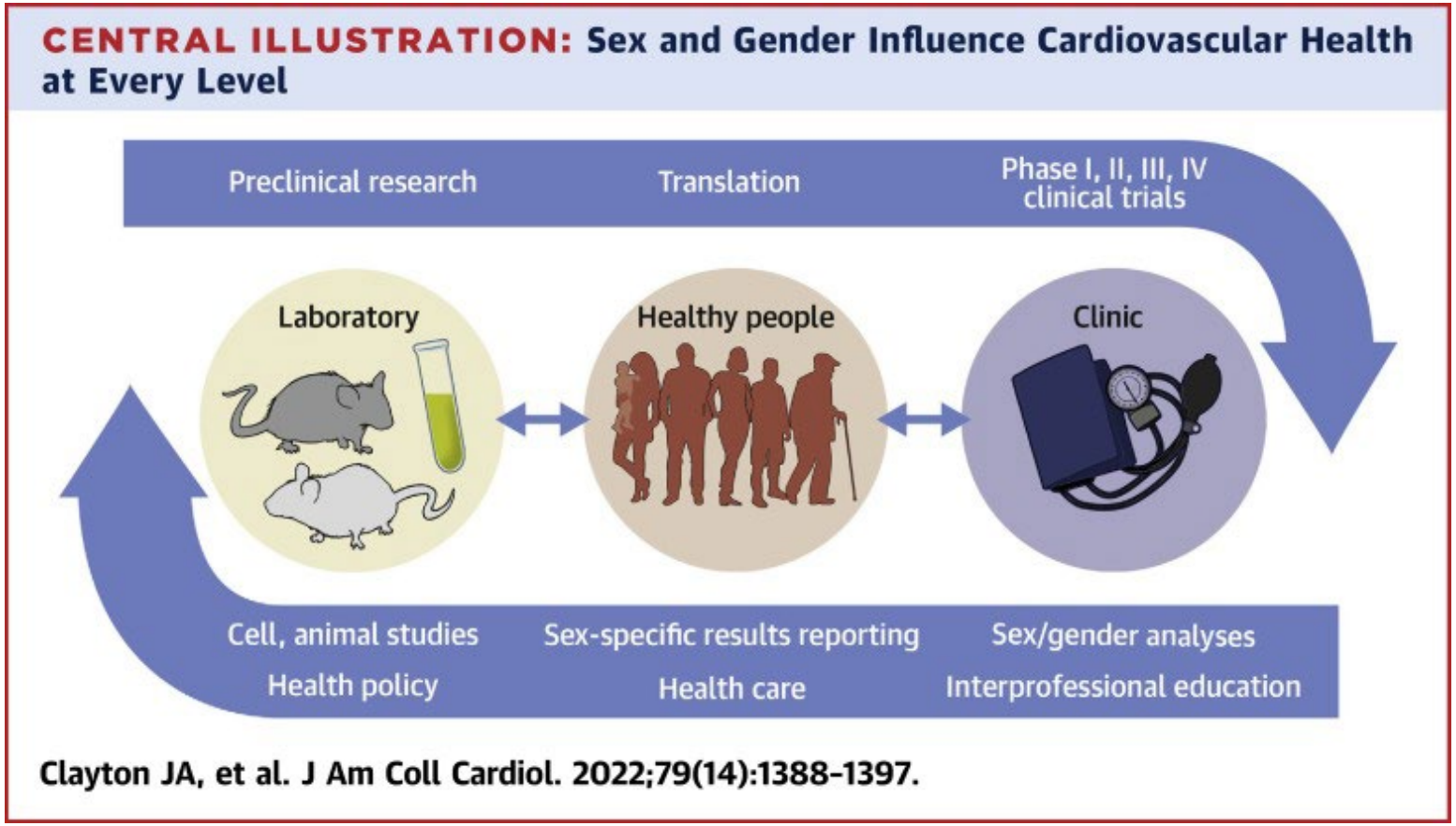
Sex as a biological variable

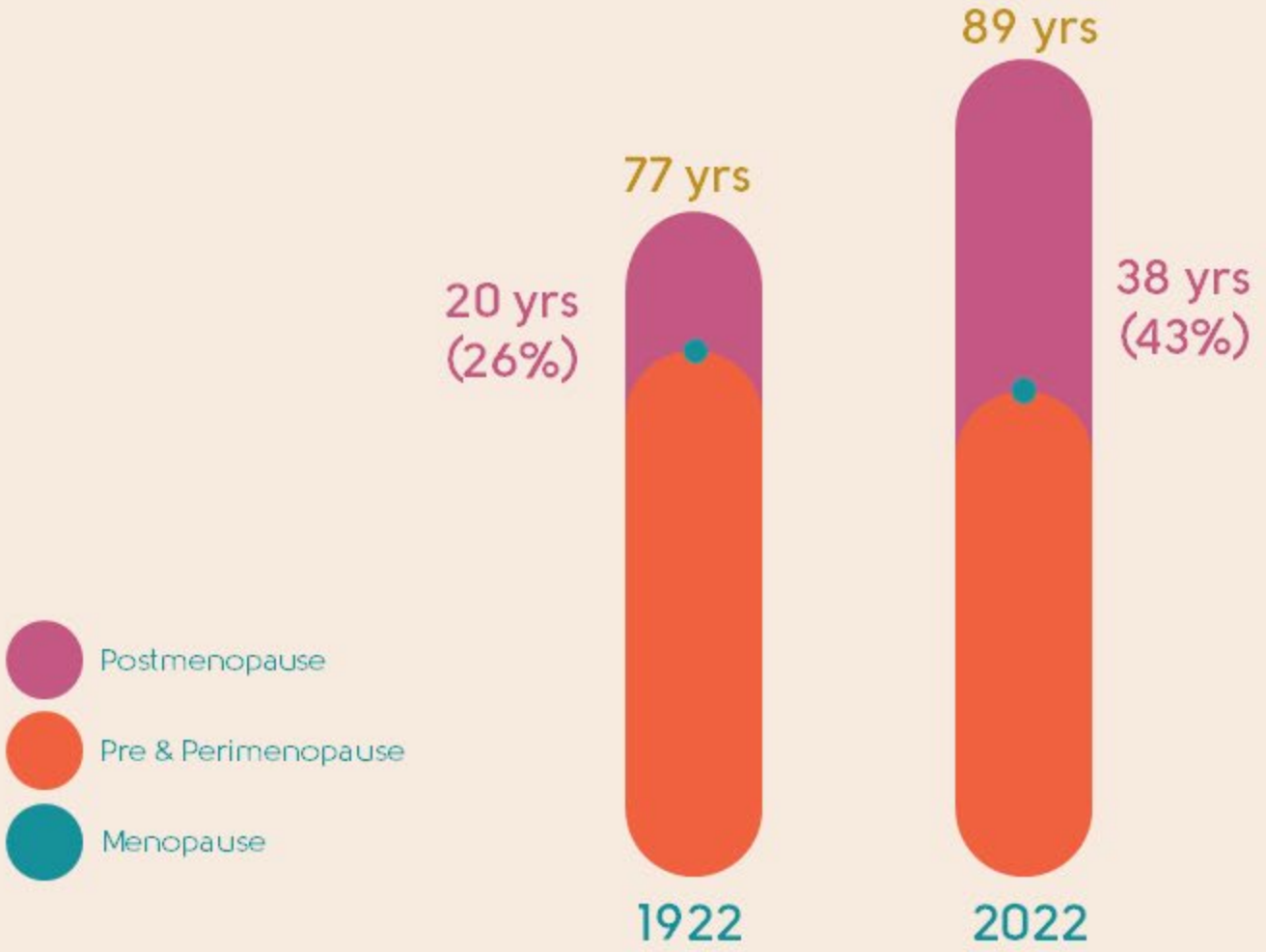


Life expectancy is increasing

Today postmenstrual life is approx.

40%

of your whole life



https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/mortalityinenglandandwales/2012-12-17
Using modal age at death 1922/77 yrs 2022/89 yrs; Menopause 1922 57 yrs, 2022 51 yrs; postmenopausal life 1922 26%/20 yrs, 2022 43%/38 yrs

Menopause definition

- Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause. It occurs at a median age of 51.4 years and is a reflection of complete, or near complete, ovarian follicular depletion, with resulting hypoestrogenemia and high follicle-stimulating hormone (FSH) concentrations.

Menopause Facts

>63 million women in the US >50 years of age;

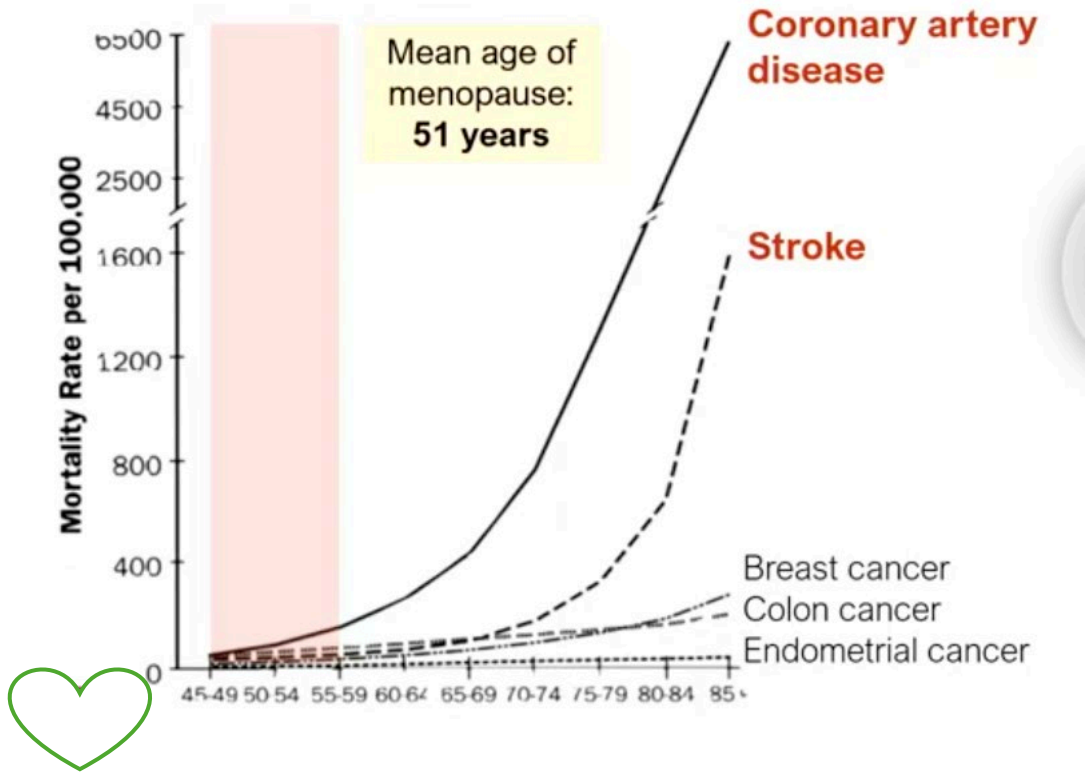
Around 6000 women enter menopause each day;

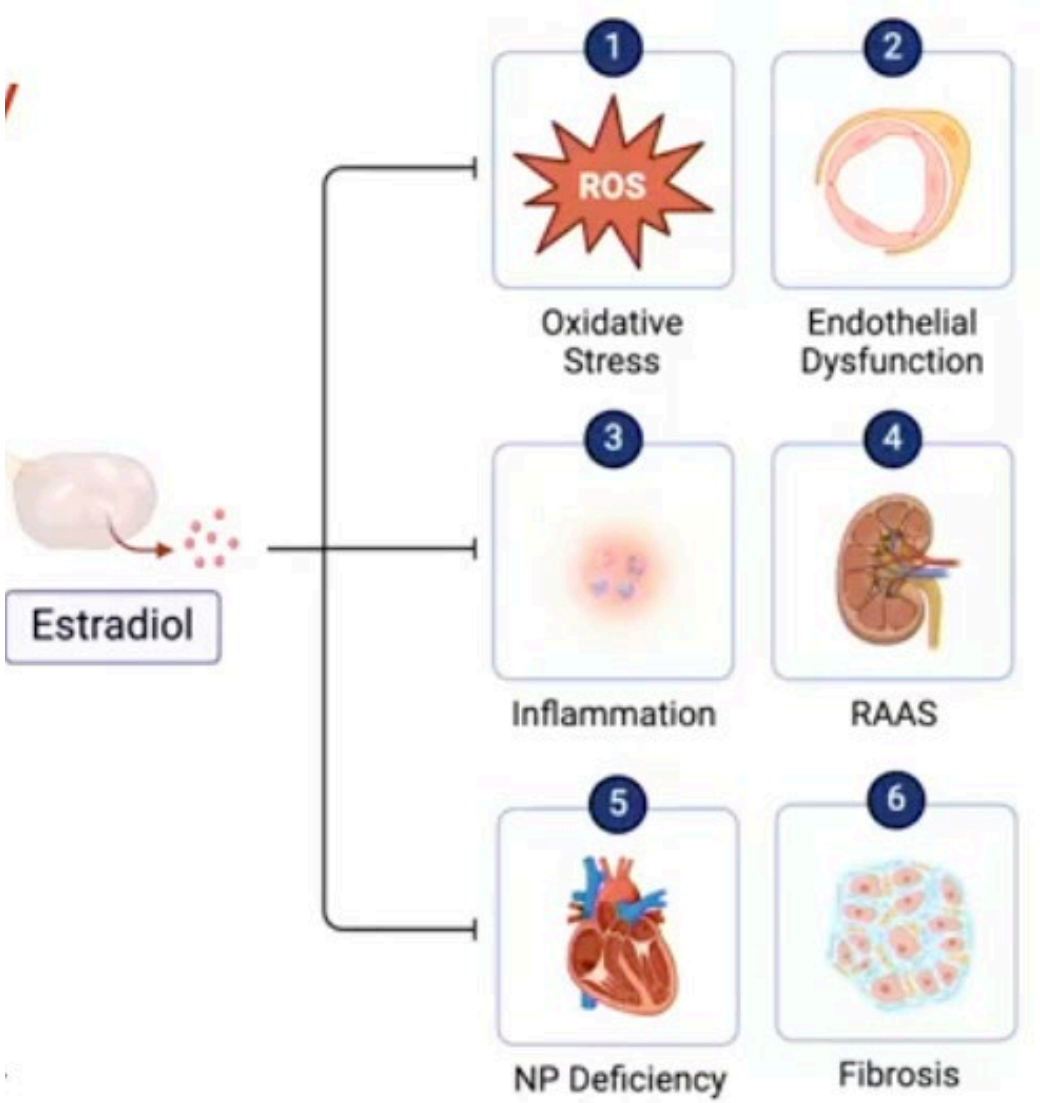
Vasomotor symptoms are the most common symptoms;

About 75% of women experience vasomotor symptoms;

VMS are more common in Black/African women and smokers;

Cardiometabolic changes





Zhao Z, Wang H, Jessup JA, Lindsey SH, Chappell MC, Groban L. Role of estrogen in diastolic dysfunction. Am J Physiol Heart Circ Physiol. 2014 Mar 1;306(5):H628-40. doi: 10.1152/ajpheart.00859.2013. Epub 2014 Jan 10. PMID: 24414072; PMCID: PMC3949059.

Changes with menopause

- Higher blood pressure
- Increase in visceral adiposity
- Increase in LDL
- Increase in apo lipoprotein B

More vasomotor symptoms are associated with increased CVD and CVD mortality.

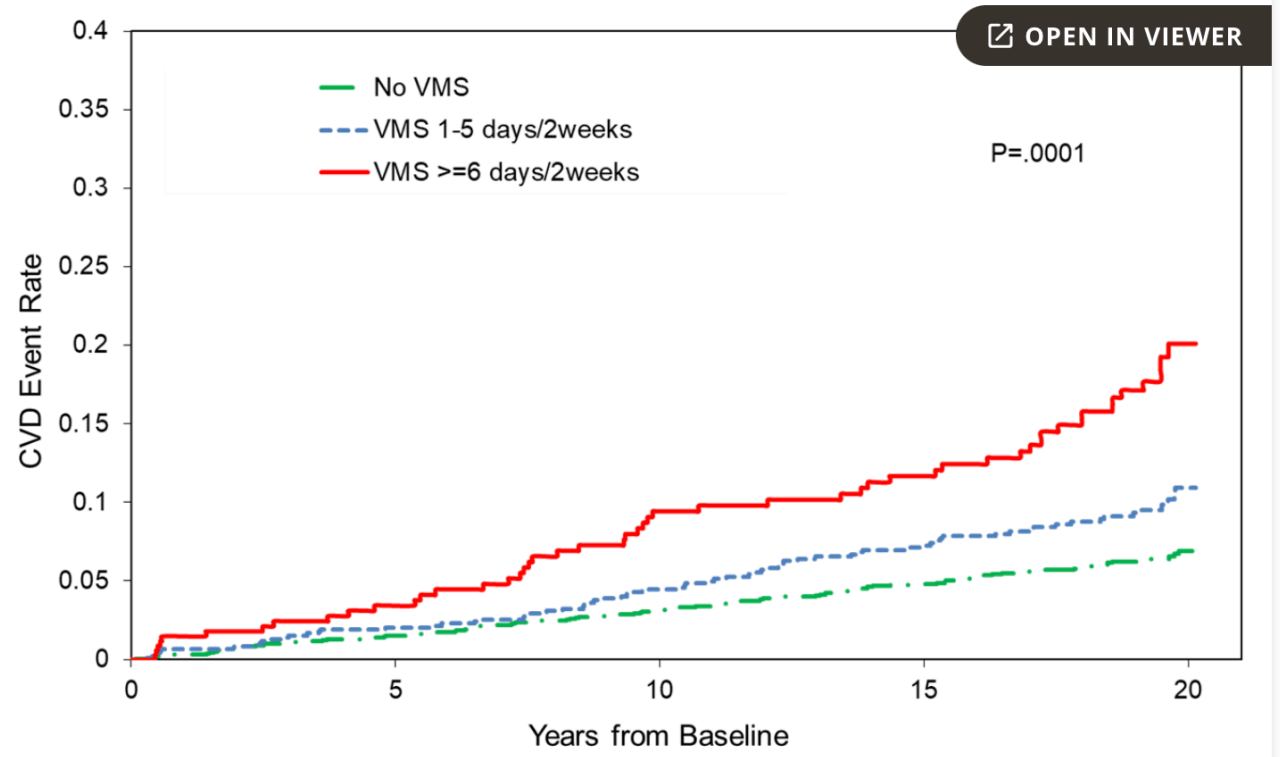


Figure 1. Baseline vasomotor symptoms (VMS) in relation to fatal and nonfatal cardiovascular disease (CVD) events, N=3083, 231 events.

Thurston et al., JAHA, 2021;10(3):e017416

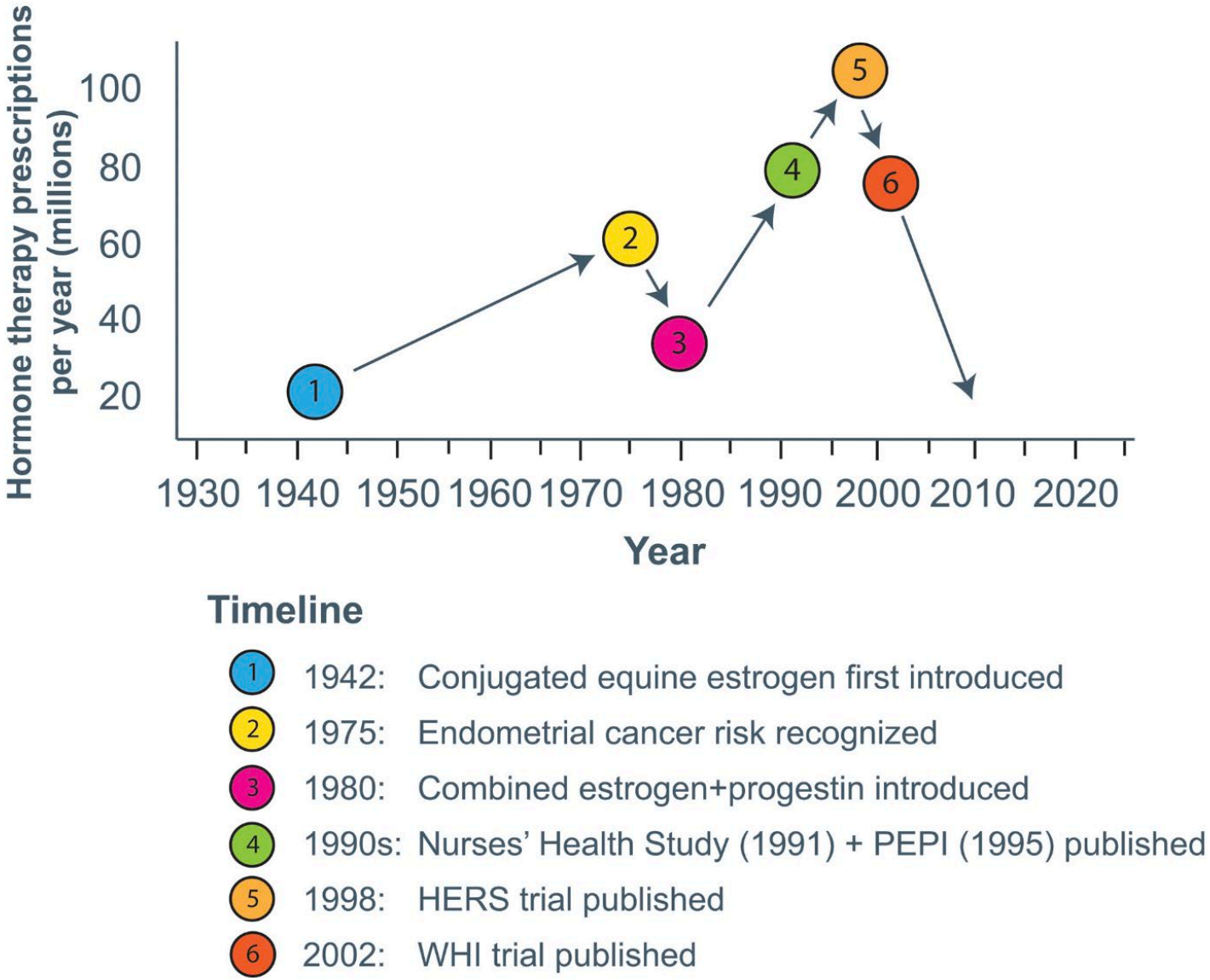


Figure 1. Timeline of hormone therapy use in the United States. HERS indicates Heart and Estrogen/progestin Replacement Study; PEPI, Postmenopausal Estrogen/Progestins Interventions; and WHI, Women's Health Initiative.

August 19, 1998

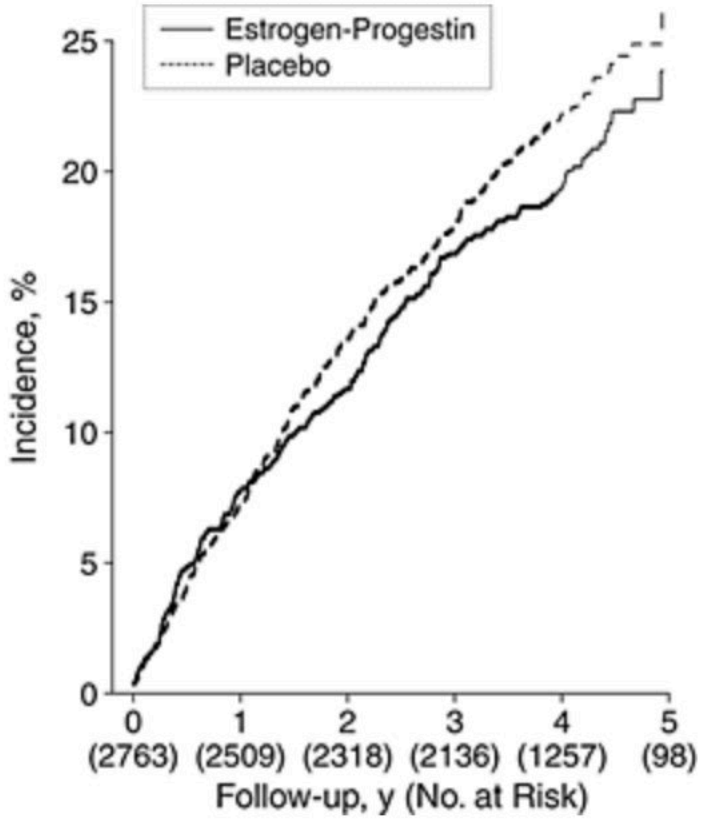
Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; et al

» Author Affiliations

JAMA. 1998;280(7):605-613. doi:10.1001/jama.280.7.605

HERS Trial 1998



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

More on the Women's Health Initiative

Published June 2, 1994 | N Engl J Med 1994;330:1619-1620 | DOI: 10.1056/NEJM199406023302220

VOL. 330 NO. 22

WHI 1994

Table 7. Risk With Hormone Therapy in Primary and Secondary Prevention From Meta-Analysis of 19 Randomized Control Trials[18]

	Primary prevention	Secondary prevention
Death all-cause	RR, 1.00 (95% CI, 0.89–1.12)	RR, 1.04 (95% CI, 0.87–1.24)
Death from cardiovascular disease	RR, 0.81 (95% CI, 0.47–1.40)	RR, 1.00 (95% CI, 0.78–1.29)
Myocardial infarction	RR, 1.02 (95% CI, 0.80–1.31)	RR, 0.98 (95% CI, 0.81–1.18)
Angina	RR, 0.90 (95% CI, 0.74–1.08)	RR, 0.91 (95% CI, 0.74–1.12)
Revascularization	RR, 0.96 (95% CI, 0.85–1.09)	RR, 0.98 (95% CI, 0.63–1.53)
Venous thromboembolism	RR, 1.92 (95% CI, 1.24–2.99) Absolute risk increase, 0.008, with NNTH 118	RR, 2.02 (95% CI, 1.13–3.62) Absolute risk increase, 0.014, with NNTH 71
Stroke	RR, 1.32 (95% CI, 1.12–1.56) Absolute risk increase 0.006 with NNTH of 165	RR, 1.09 (95% CI, 0.89–1.33)
Pulmonary embolism	RR, 1.89 (95% CI, 1.17–3.04) Absolute risk increase, 0.004, with NNTH 242	RR, 2.48 (95% CI, 0.92–6.70)

NNTH indicates number needed to harm; and RR, risk ratio.[18]

Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long?

Leslie Cho, MD, Andrew M. Kaunitz, MD, Stephanie S. Faubion, MD, MBA, Sharonne N. Hayes, MD, Emily S. Lau, MD, MPH,

No recommendation to give HRT for prevention of cardiovascular disease

Table 1. Recommendations for Hormone Therapy From 4 Different Medical Societies

Aspect of treatment	American College of Obstetricians and Gynecologists[10]	North American Menopause Society[13]	American Association of Clinical Endocrinology and American College of Endocrinology[11]	Endocrine Society[12]
Principal indication	Menopause symptoms	Menopause symptoms	Menopause symptoms	Menopause symptoms
Prevention of coronary heart disease	Not recommended	Not recommended	Not recommended	Not recommended
Special considerations	None	Consideration of age and time from menopause onset	Consideration of age, time from menopause onset, and risk of cardiovascular disease, with lipid profile, smoking history	Consideration of age, time from menopause onset, and baseline risks of cardiovascular disease and breast cancer
Dose and route of administration	Lowest effective dose	Appropriate dose to manage symptoms with consideration of route	Lowest effective dose	Shared decision-making to determine formulation, dose, and route
Duration of use	Shortest period based on risk-benefit analysis, with recommendation against routine discontinuation in patient ≥65 y of age	May be extended for persistent vasomotor symptoms, prevention of bone loss, or quality of life after attempt at stopping; reassess benefits and risks regularly	Recommended for ≤5 y with reduction of dose if continuing	Shortest total duration consistent with the treatment goals and evolving risk assessment of the individual woman

FDA- approved indications and types of hormone replacement therapy

FDA- approved indications
Vasomotor symptoms: hot flashes and night sweats
Osteoporosis
Premature hypoestrogenism
Vulvovaginal atrophy

Formulations	Oral	Transdermal	Vaginal
Administration	Pills	Patches, Gels, Implants	Creams, Pessaries
Estrogen type	Estradiol conjugated estrogen	Estradiol	Estradiol conjugated estrogen
Medications	Estrogen only Combined estrogen and progesterone Progesterone only	Estrogen only Combined estrogen and progesterone	Estrogen only low-dose

Cardiologist's approach to hormone replacement therapy

- **Higher Risk/Avoid MHT**
  - Known ASCVD/ CAD/ PAD
  - Known venous thrombosis or pulmonary embolism
  - Known Stroke/TIA or MI
  - Known Clotting Disorder
  - Known Breast Cancer
  - 10 year ASCVD Risk ≥7.5%
- **Definite Risk for CVD/Caution with MHT**
  - Diabetes
  - Smoking
  - Uncontrolled HTN
  - Obesity/ Sedentary/ Limited mobility
  - SLE/RA/Migraine with Aura
  - High TG or uncontrolled Cholesterol levels
  - 10 year ASCVD Risk ≥5-7.4%
- **Lower Risk/Acceptable for MHT**
  - Recent menopause, normal weight, normal blood pressure, active female
  - 10 year ASCVD Risk <5%

ASCVD risk	<10 year	>10 years
Low <5%	Hormone replacement therapy can be used	Shared decision making
Intermediate >5-7.5%	hormone replacement therapy can be used, but transdermal preferred	Avoid systemic hormone replacement therapy. Shared decision making.
High >7.5%	Avoid hormone replacement therapy Shared decision making if severe vasomotor symptoms	Avoid hormone replacement therapy

Obesity and Hormone replacement therapy

- About 50% of women age 40-59 are obese
- There is an increase risk of venous thromboembolism:
    1. 3x increase in VTE BMI 25-30n vs BMI <25
    2. 6x increase in VTE BMI >30

Estrogen Plus Progestin and Risk of Venous Thrombosis

Mary Cushman, MD, MSc; Lewis H. Kuller, MD; Ross Prentice, PhD; et al

» Author Affiliations | Article Information

JAMA. 2004;292(13):1573-1580. doi:10.1001/jama.292.13.1573

HTN and Hormone replacement therapy

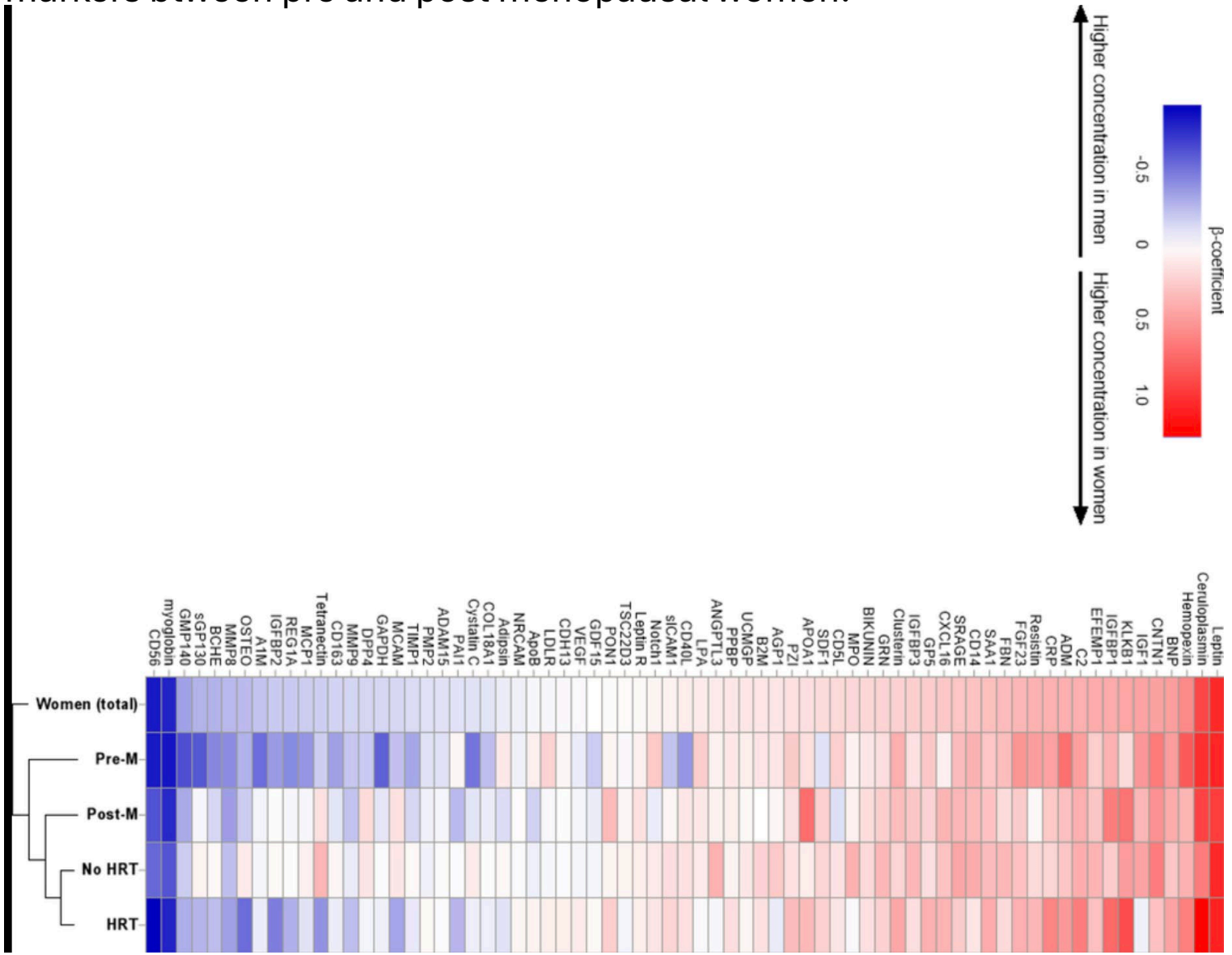
- From WHI: SBP increase of around 0.8 mmHg – 1 mmHg

High risk patients that should not receive HT

- History of CAD – MI, PCI, CABG
- History of VTE
- Congenital heart disease
- History of ischemic stroke
- Spontaneous coronary artery dissection (SCAD)

Emerging data

Menopause and hormone status influence circulating levels of CVD protein biomarkers btween pre and post menopausal women.



Lau ES, Paniagua SM, Guseh JS, Bhambhani V, Zanni MV, Courchesne P, Lyass A, Larson MG, Levy D, Ho JE. Sex Differences in Circulating Biomarkers of Cardiovascular Disease. J Am Coll Cardiol. 2019 Sep 24;74(12):1543-1553. doi: 10.1016/j.jacc.2019.06.077. PMID: 31537263; PMCID: PMC6756178.

Take home points

- Once a woman enters menopause, she is at risk of accelerating cardiovascular risk.
- Better understanding of the mechanisms that increase cardiovascular disease susceptibility in women with early menopause may enhance the prevention and management of cardiovascular disease in women.
- Menopause hormonal therapy increased risk of cardiovascular disease in large RCTs, but may be safe in women <60 years of age and < 10 years post menopause.
- Menopause hormonal therapy is approved for vasomotor symptoms, premature hypoestrogenism, vaginal atrophy and osteoporosis. Not for CVD prevention.
- The importance of team approach and shared decision making

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Thank you!