

2° CONGRESSO NAZIONALE
Verso la medicina genere specifica

LA DONNA
LA COPPIA DOPO
L'ETÀ FERTILE

19 - 20 settembre 2018

HOTEL MICHELANGELO • MILANO

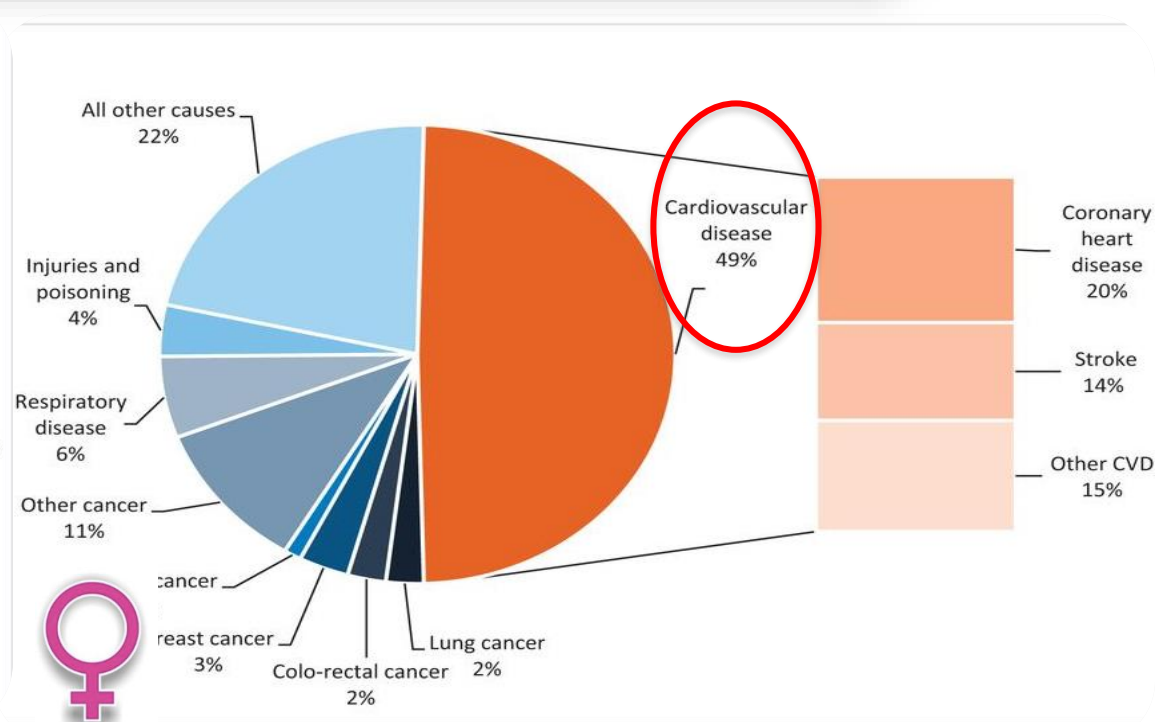
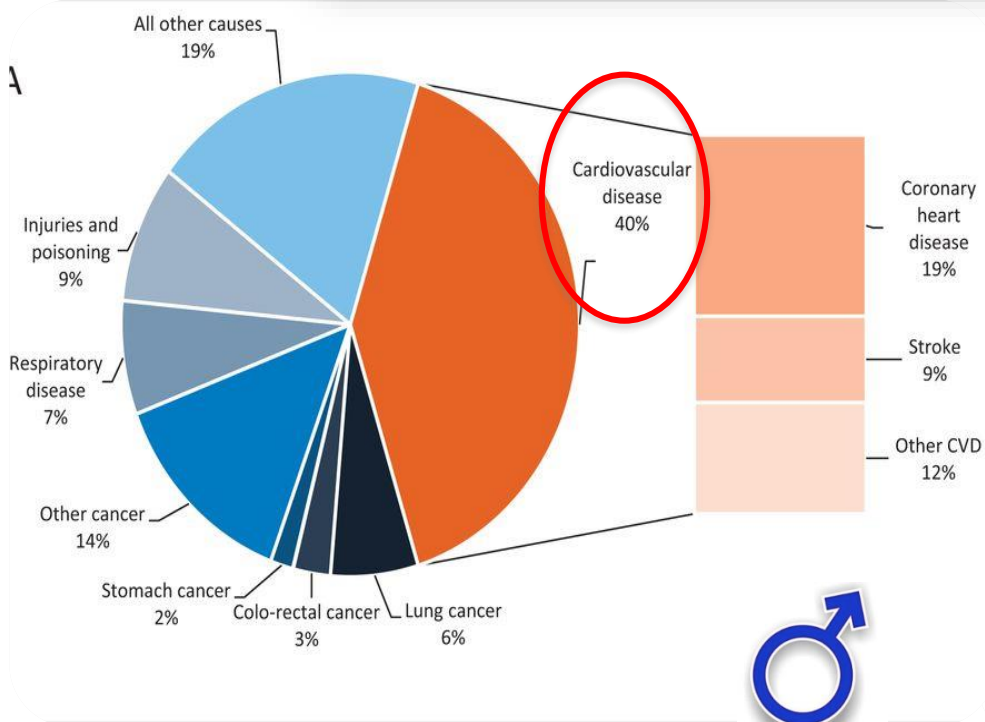


RISCHIO CARDIOVASCOLARE E MENOPAUSA

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Cardiovascular disease in Europe: epidemiological update 2016

Nick Townsend^{1*}, Lauren Wilson¹, Prachi Bhatnagar¹, Kremlin Wickramasinghe¹,
Mike Rayner¹, and Melanie Nichols^{1,2}

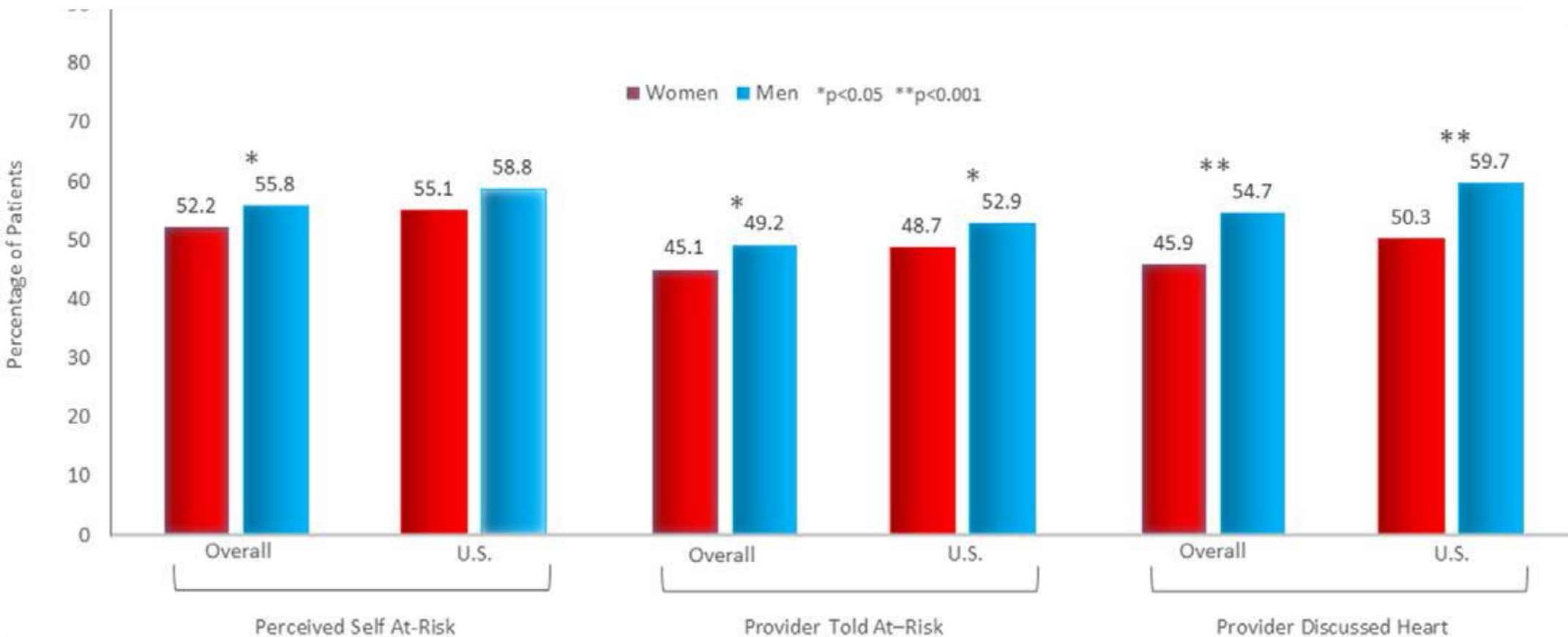


Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women

The Women's Heart Alliance

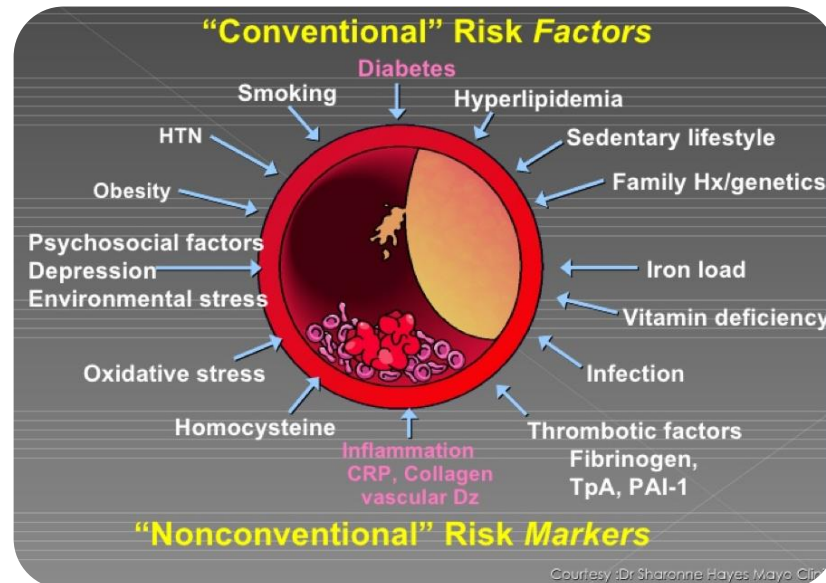
C. Noel Bairey Merz, MD,^a Holly Andersen, MD,^b Emily Sprague, MA,^c Adam Burns, MPP,^c Mark Keida, PhD,^c
Mary Norine Walsh, MD,^d Phyllis Greenberger, MSW,^e Susan Campbell, MPH,^f Irene Pollin, MSW, PhD(Hon),^g
Cassandra McCullough, MBA,^h Nancy Brown, BA,ⁱ Marjorie Jenkins, MD,^j Rita Redberg, MD,^k Paula Johnson, MD,^l
British Robinson, MA, JD(HON)^m

*Solo il 22% dei Medici di Base e solo il 42 %
dei Cardiologi era adeguatamente preparato*



Differenze di Genere Rischio Cardiovascolare

- F. R. Tradizionali
- F. R. Emergenti
- F. R. Specifici di Genere



Frequenza F.R.

Fattori Etnici-Geografici
Abitudini connesse con il ruolo sociale

- Comorbidità
Disordini
Autoimmuni

Inappropriata percezione Rischio Cardiovascolare

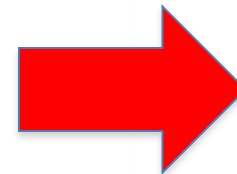
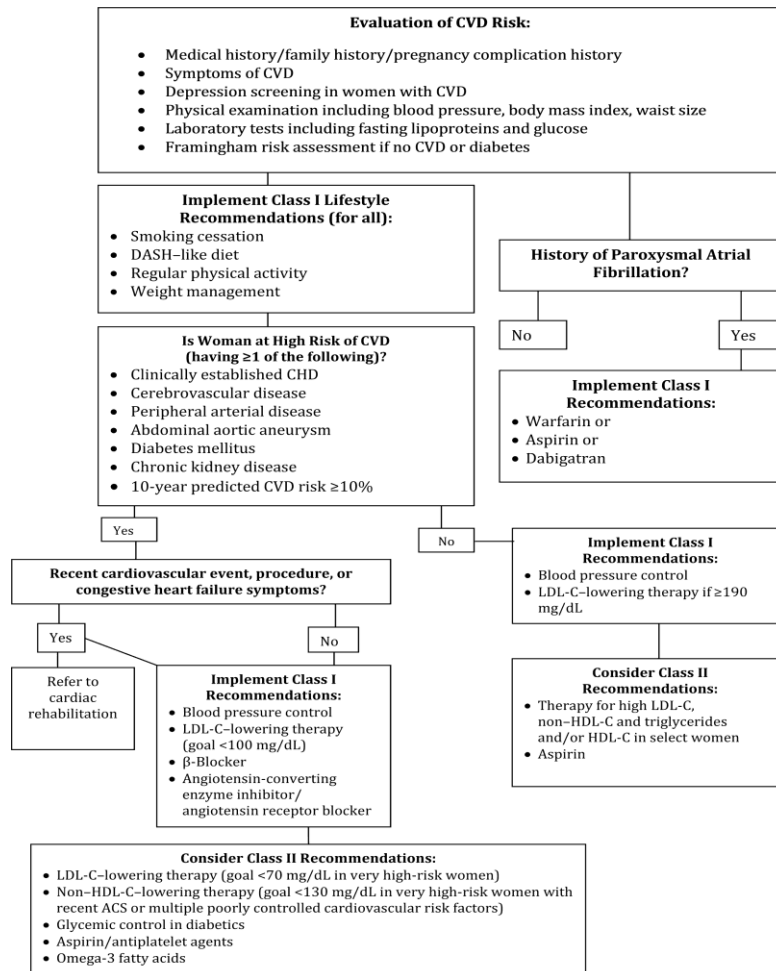
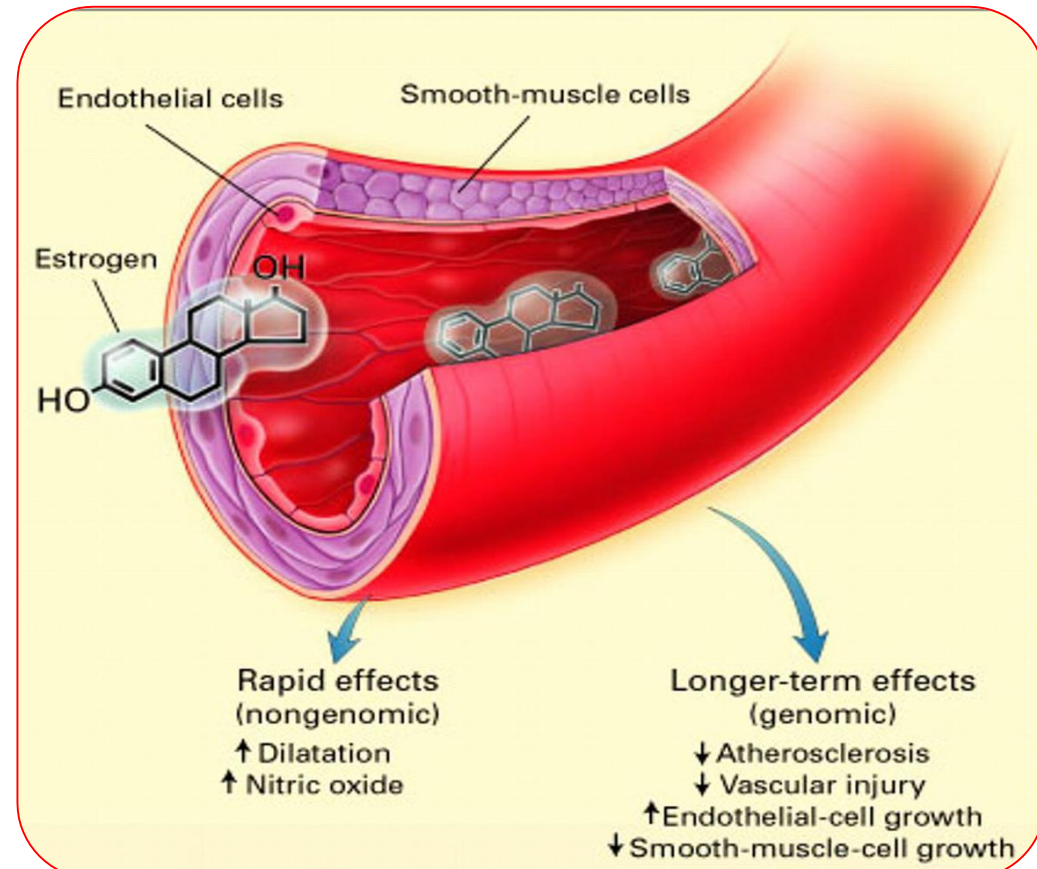
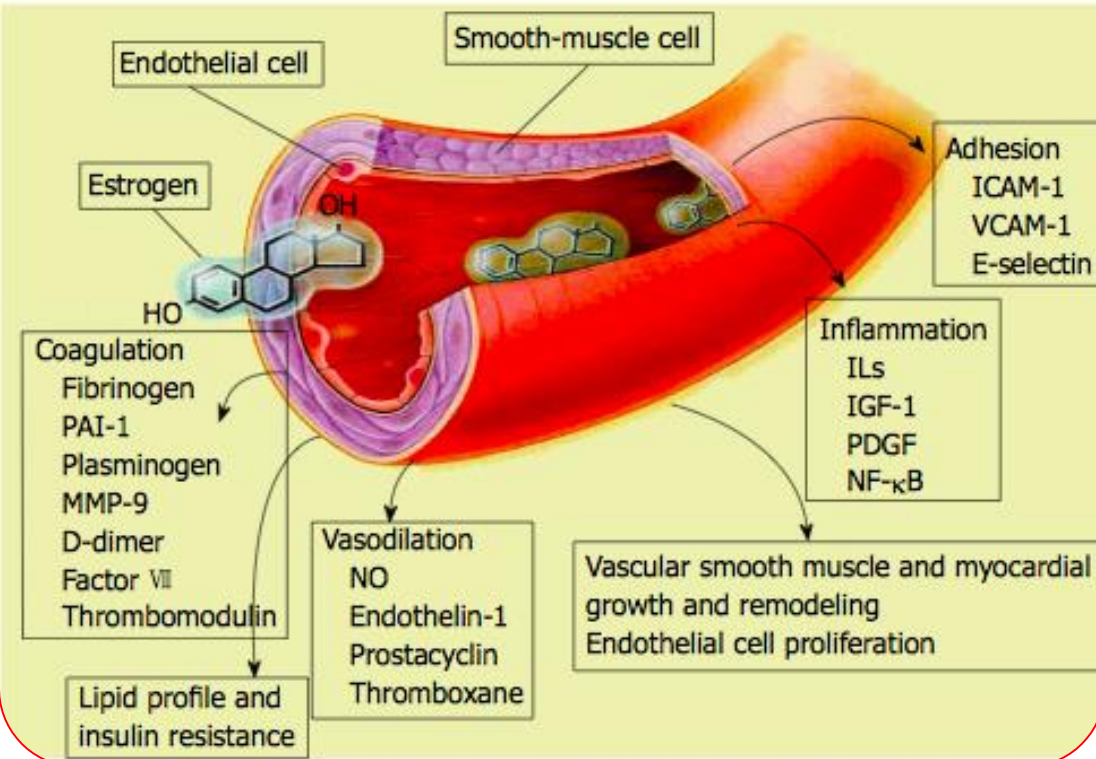


Table 2. Classification of CVD Risk in Women

| Risk Status | Criteria |
|---|---|
| High risk (≥ 1 high-risk states) | Clinically manifest CHD Clinically manifest cerebrovascular disease Clinically manifest peripheral arterial disease Abdominal aortic aneurysm End-stage or chronic kidney disease Diabetes mellitus 10-y Predicted CVD risk $\geq 10\%$ |
| At risk (≥ 1 major risk factor[s]) | Cigarette smoking SBP ≥ 120 mm Hg, DBP ≥ 80 mm Hg, or treated hypertension Total cholesterol ≥ 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia Obesity, particularly central adiposity Poor diet Physical inactivity Family history of premature CVD occurring in first-degree relatives in men < 55 y of age or in women < 65 y of age Metabolic syndrome Evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened IMT) Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise Systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis) History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension |
| Ideal cardiovascular health (all of these) | Total cholesterol < 200 mg/dL (untreated) BP $< 120/ < 80$ mm Hg (untreated) Fasting blood glucose < 100 mg/dL (untreated) Body mass index < 25 kg/m ² Abstinence from smoking Physical activity at goal for adults > 20 y of age: ≥ 150 min/wk moderate intensity, ≥ 75 min/wk vigorous intensity, or combination Healthy (DASH-like) diet (see Appendix) |

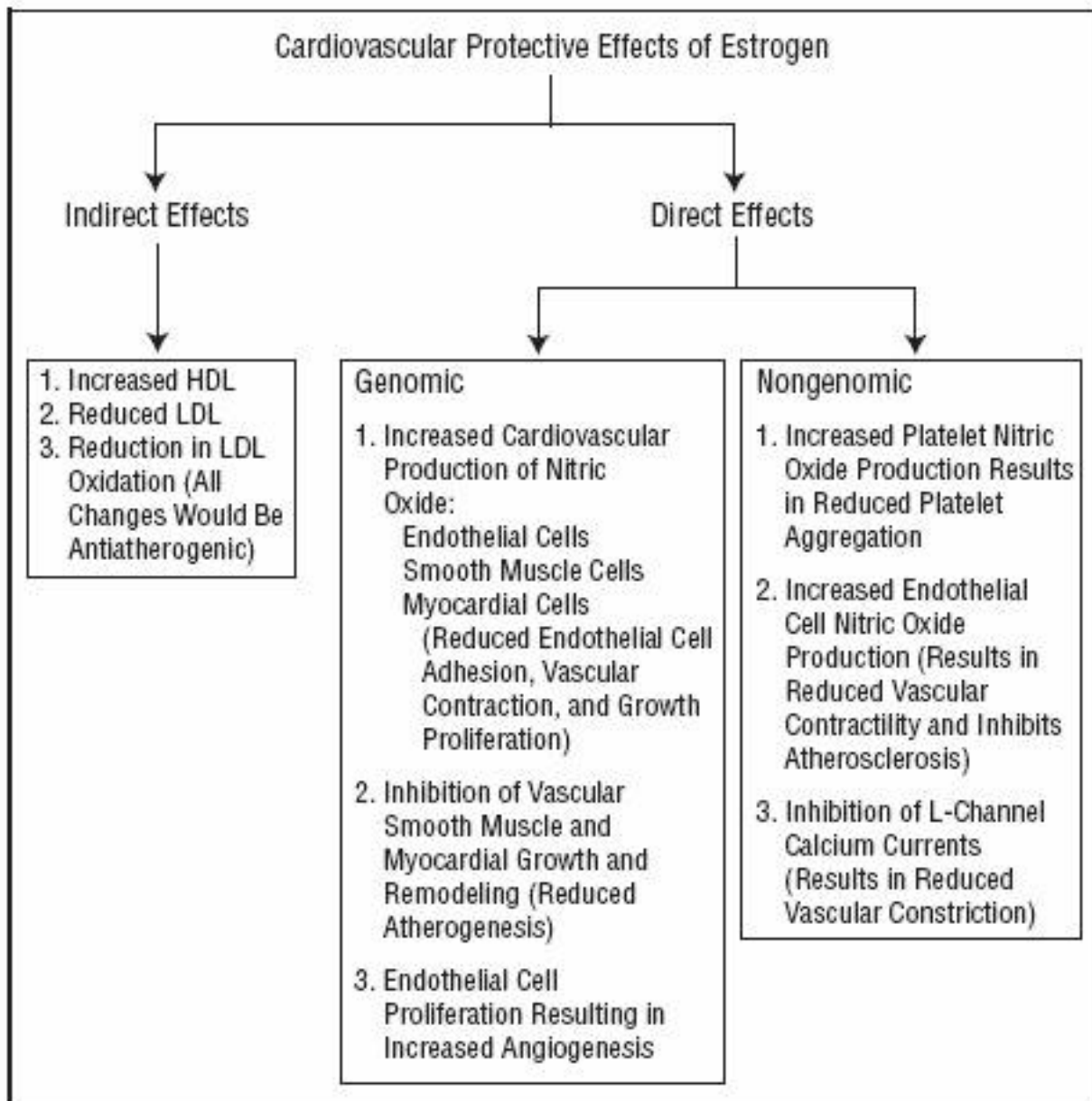
only 4% of women fell into this ideal state and a further 13% had no risk factors but failed to follow a healthy lifestyle. There was a 18% difference in major CVD events in favour of the ideal life-style vs. the no-risk factor groups: 2.2% and 2.6% per 10 years, respectively.

Vassalle C *et al.* Cardiovascular disease in women

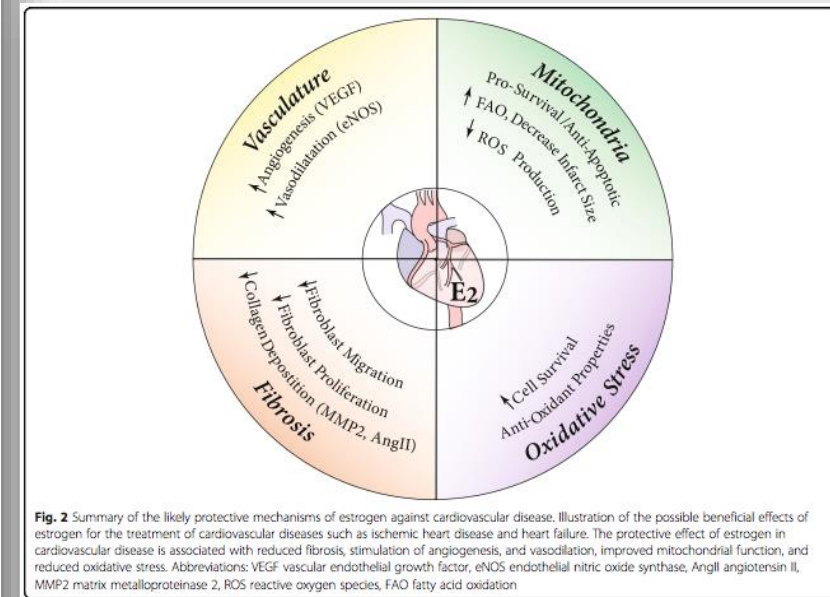


Le cellule endoteliali e le cellule muscolari lisce esprimono i recettori per gli estrogeni ERs-alpha and ERs-beta.

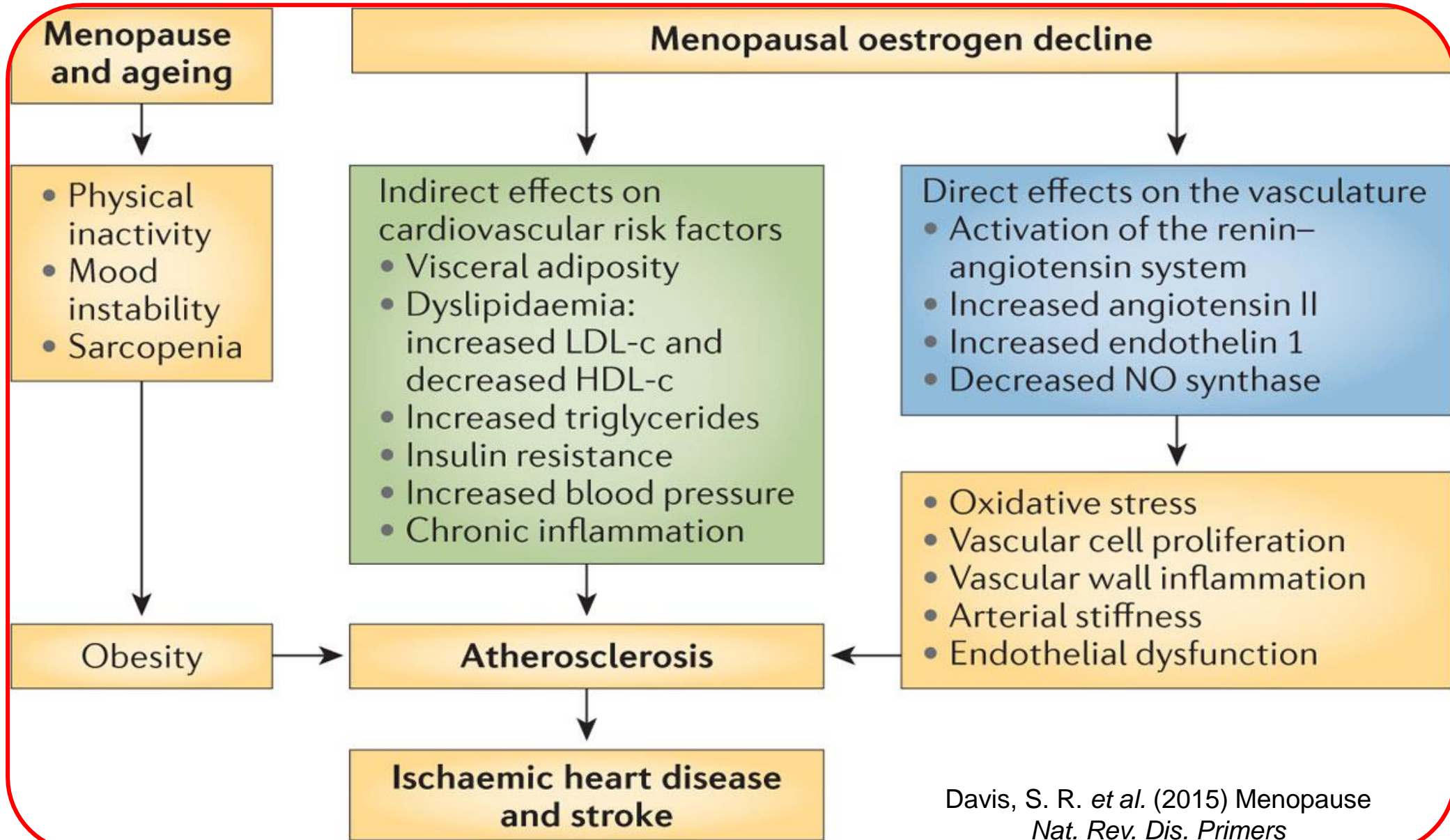
Gli estrogeni hanno a breve termine un effetto vasodilatante e a lungo termine una azione di inibizione verso il danno vascolare e di prevenzione dell'aterosclerosi



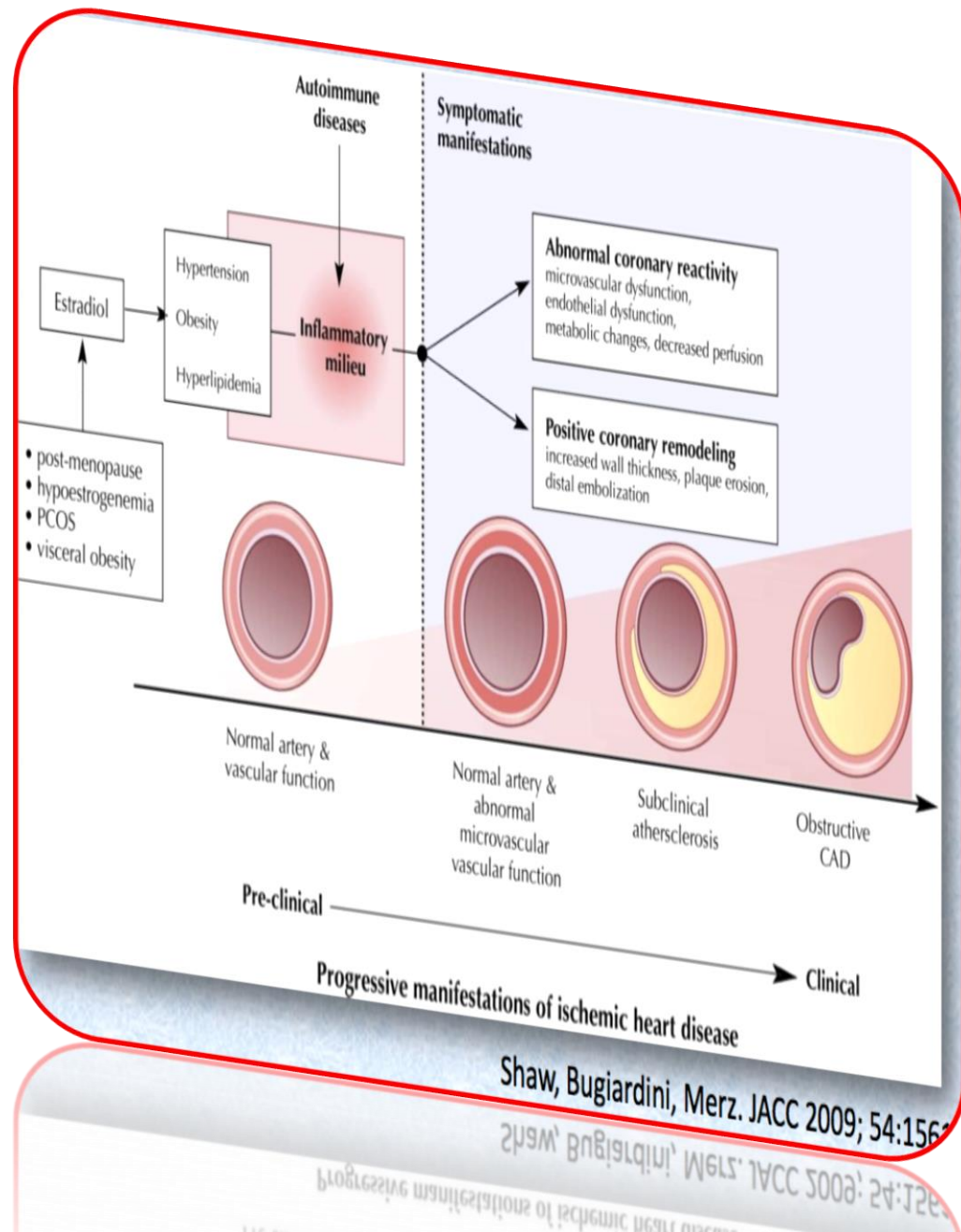
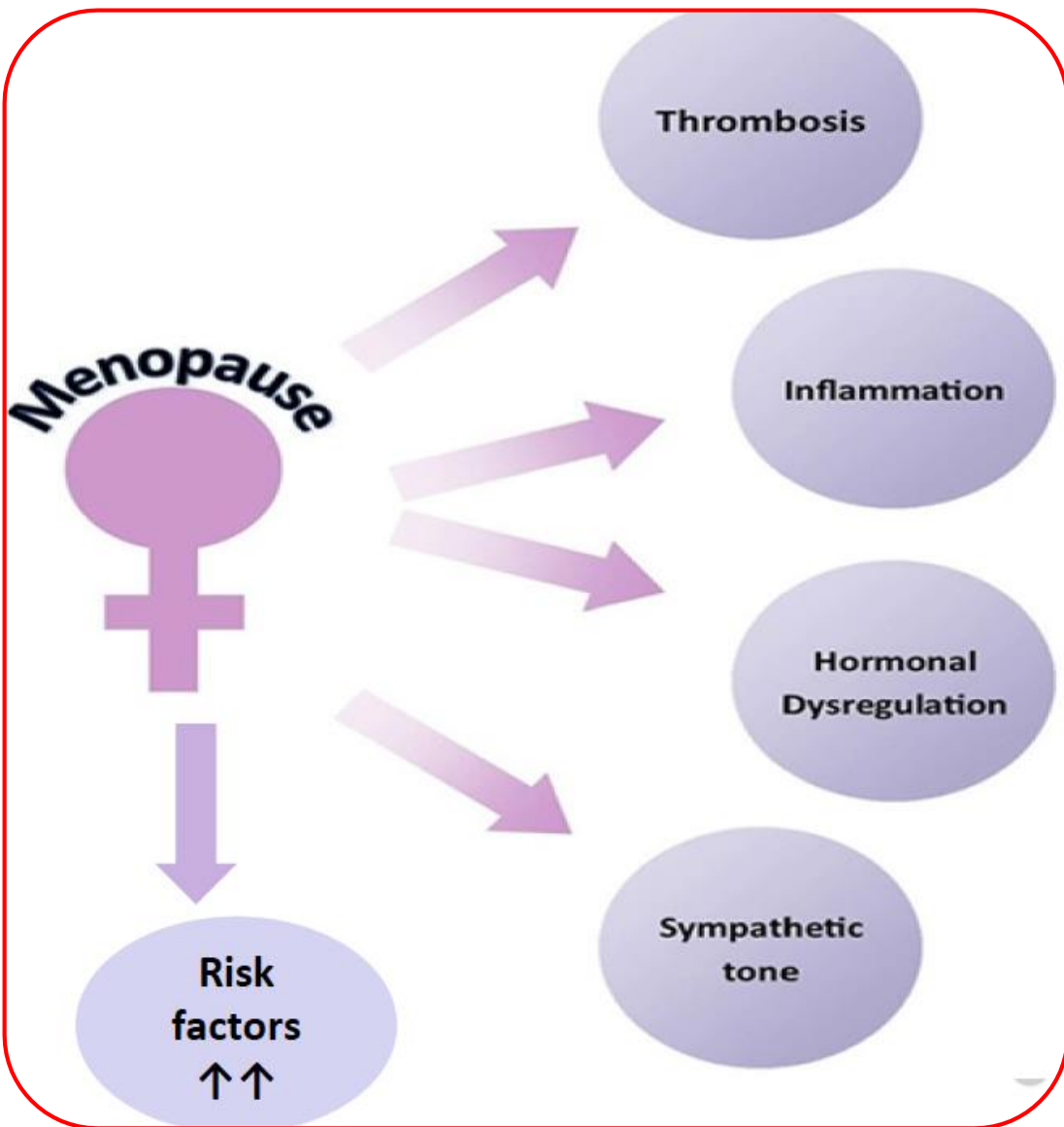
Cardiovascular protective effects of estrogen. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.



Consequences of menopause on the cardiovascular system



Davis, S. R. *et al.* (2015) Menopause
Nat. Rev. Dis. Primers



Stage 1:
Infiltration of LDL
Into healthy vessels

Stage 2:
Inflammatory process to clear LDL
starts by monocyte infiltration

Stage 3:
Atherosclerotic plaque containing large
macrophage foam cells starts to form

Stage 4:
Inflammatory process
continues until
the plaque ruptures
and a thrombus is
formed.

Vascular occlusion
by thrombus

~~CARDIOVASCULAR CHEMICAL~~



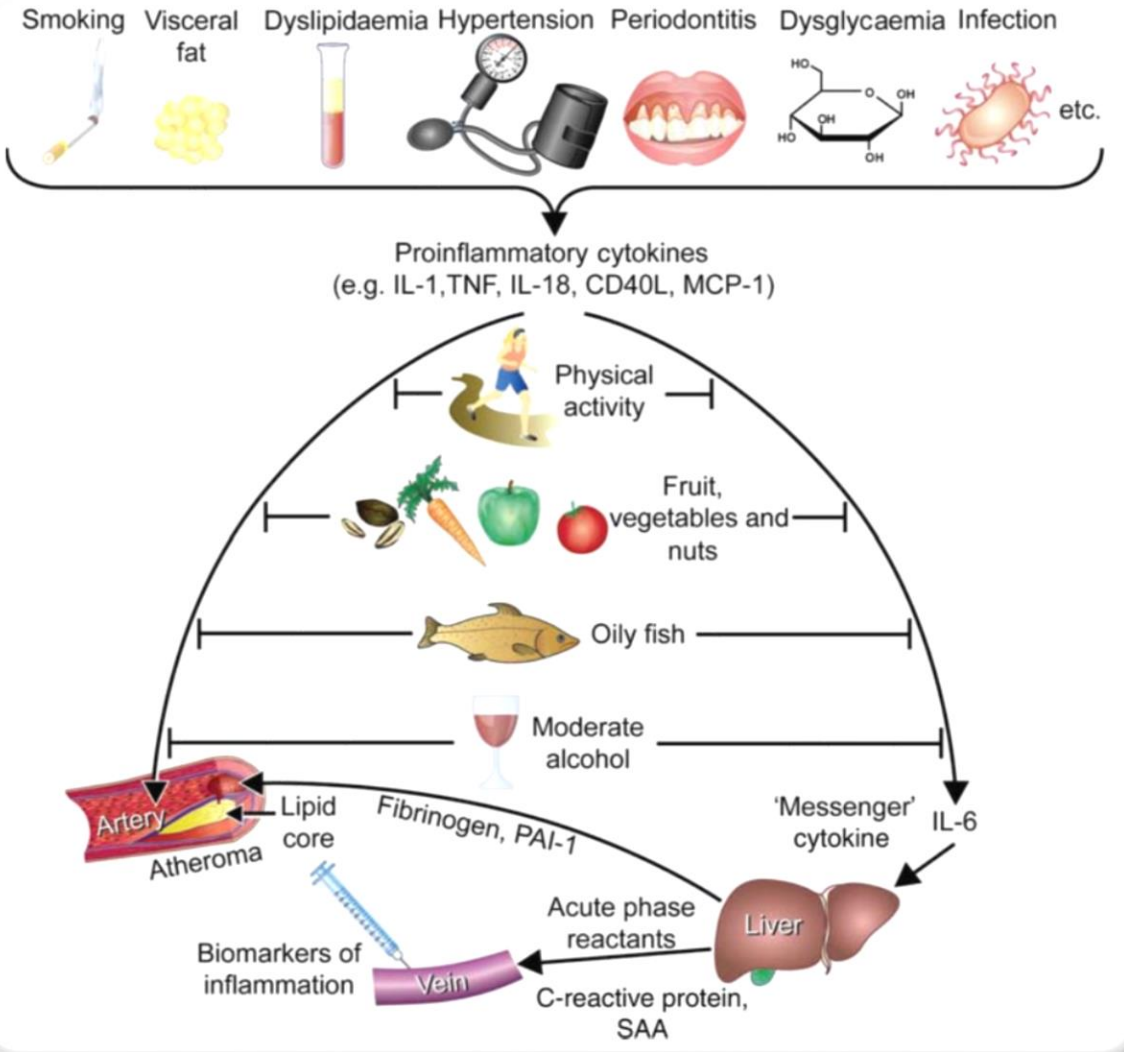
European Heart Journal (2010) 31, 777–783
doi:10.1093/eurheartj/ehp222

Controversies in cardiovascular medicine

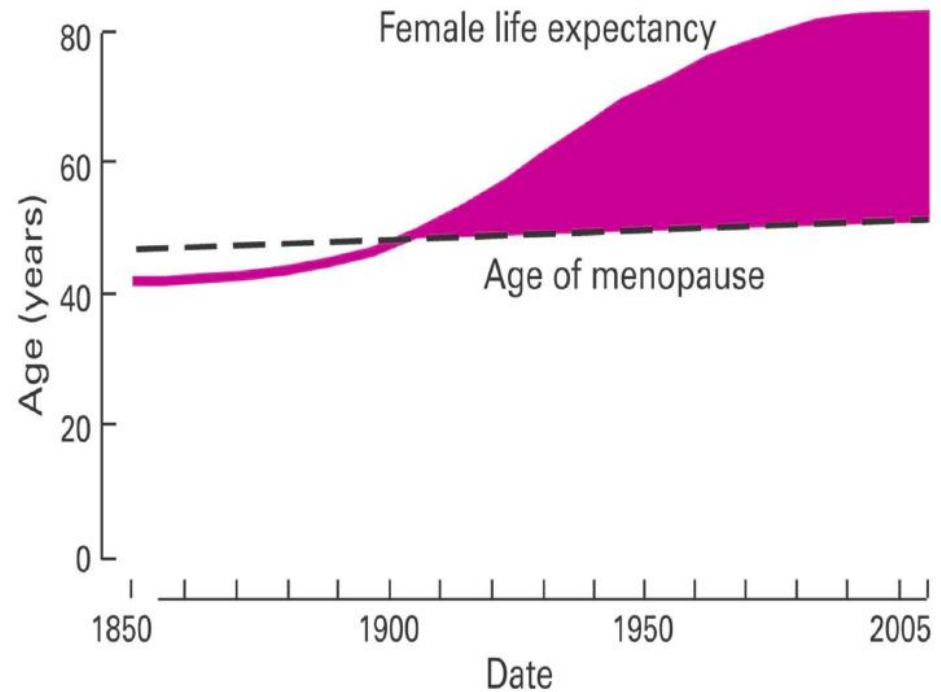
Clinical implications of inflammation for cardiovascular primary prevention

Peter Libby^{1*} and Filippo Crea²

CLINICAL REVIEW

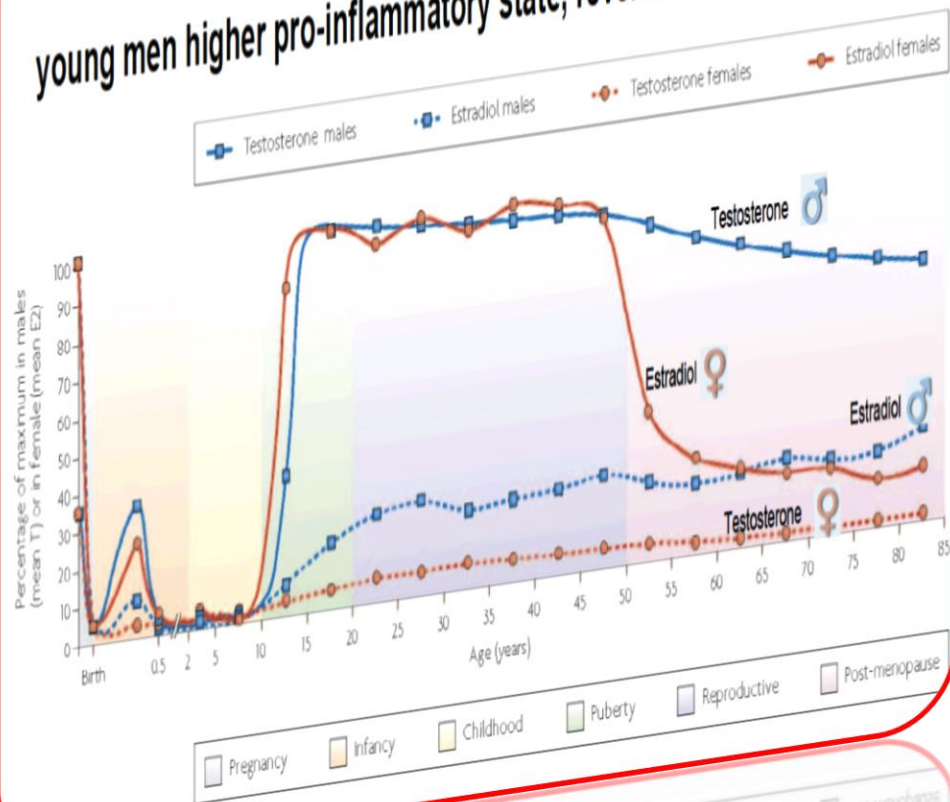


Age at Menopause Has Remained Constant While Life Expectancy Has Increased



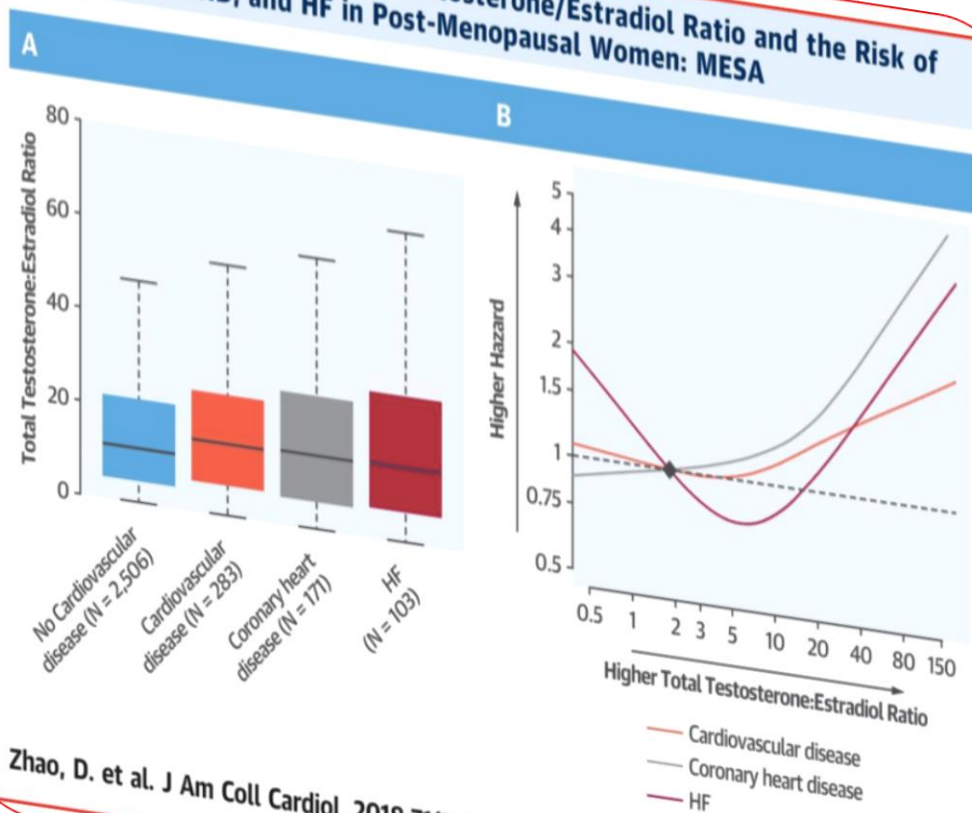
Campbell S, ed. *The Management of the Menopause and Postmenopausal Years*. Baltimore, Md: University Park Press; 1976.

Sex hormones (m/f) over life-time: young men higher pro-inflammatory state, reverses after menopause



Ober C et al. Nat Rev Genetics 2008

CENTRAL ILLUSTRATION: Testosterone/Estradiol Ratio and the Risk of Incident CVD, CHD, and HF in Post-Menopausal Women: MESA



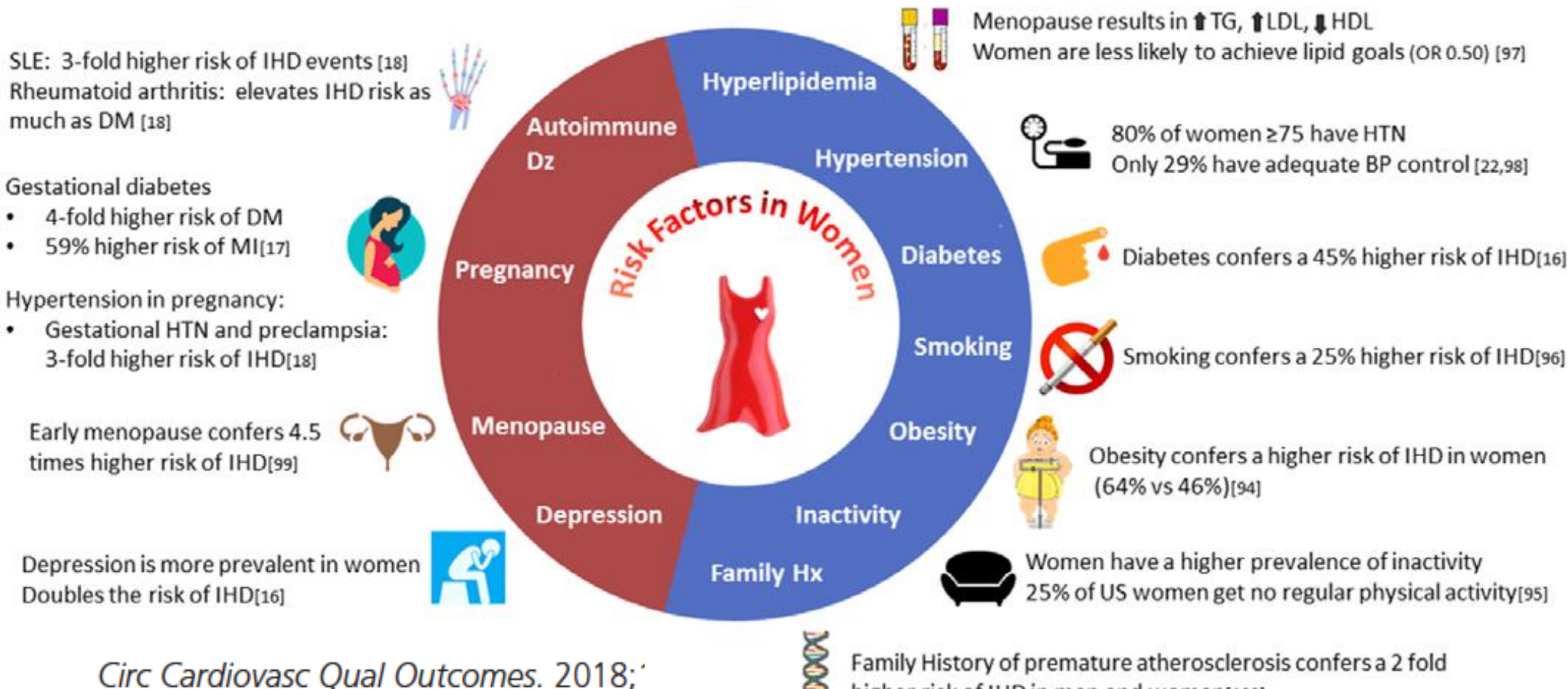
Zhao, D. et al. J Am Coll Cardiol. 2018;71(22):2555-66.

Sex Differences in Ischemic Heart Disease

Advances, Obstacles, and Next Steps

Emerging Risk Factors

Traditional Risk Factors



Menopause accelerates biological aging

Morgan E. Levine^{a,b}, Ake T. Lu^a, Brian H. Chen^c, Dena G. Hernandez^d, Andrew B. Singleton^d, Luigi Ferrucci^e, Stefania Bandinelli^f, Elias Salfati^f, JoAnn E. Manson^g, Austin Quach^a, Cynthia D. J. Kusters^h, Diana Kuhⁱ, Andrew Wong^j, Andrew E. Teschendorff^{j,k,l,m}, Martin Widschwendter^j, Beate R. Ritz^h, Devin Absherⁿ, Themistocles L. Assimes^f, and Steve Horvath^{a,o,1}

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Edited by Peter T. Ellison, Harvard University, Cambridge, MA, and approved June 17, 2016 (received for review March 18, 2016)

Key Points

Question Are age at onset of menopause and years since onset of menopause associated with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality?

Findings In this meta-analysis of 32 observational studies, premature or early-onset menopause in women younger than 45 years were associated with an increased risk of coronary heart disease and all-cause mortality. Time since onset of menopause in relation to vascular outcomes was reported in 4 studies and showed inconsistent results.

Meaning Our findings underscore a potential increased risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause.

Duration of Reproductive Life Span, Age at Menarche, and Age at Menopause Are Associated With Risk of Cardiovascular Disease in Women

Sylvia H. Ley, PhD, RD; Yanping Li, PhD; Deirdre K. Tobias, ScD; JoAnn E. Manson, MD, DrPH; Bernard Rosner, PhD; Frank B. Hu, MD, PhD; Kathryn M. Rexrode, MD, MPH

Conclusions—A shorter duration of reproductive life span is associated with a higher risk of CVD, which is likely driven by the timing of menopause induced either naturally or surgically. Extremely early age at menarche is also associated with a higher risk of CVD. (*J Am Heart Assoc.* 2017;6:e006713. DOI: 10.1161/JAHA.117.006713.)

Clinical Perspective

What Is New?

- In this prospective cohort study, a shorter duration of reproductive life span, extremely early age at menarche, and early age at menopause were associated with a higher risk of cardiovascular disease.
- The association remained significant in a sensitivity analysis among nonusers of hormone therapy, indicating that the observed association was not driven by the use of exogenous hormones.

What Are the Clinical Implications?

- The associations of timing of menarche and menopause with cardiovascular disease suggest an underlying role of sex hormones in cardiovascular disease.



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Menopause. 2012 October ; 19(10): 1081–1087. doi:10.1097/gme.0b013e3182517bd0.

Early Menopause Predicts Future Coronary Heart Disease and Stroke: The Multi-Ethnic Study of Atherosclerosis (MESA)

Melissa Wellons, MD, MHS, NCMP¹, Pamela Ouyang, MBBS², Pamela J Schreiner, PhD³, David M Herrington, MD⁴, and Dhananjay Vaidya, MBBS, PhD²

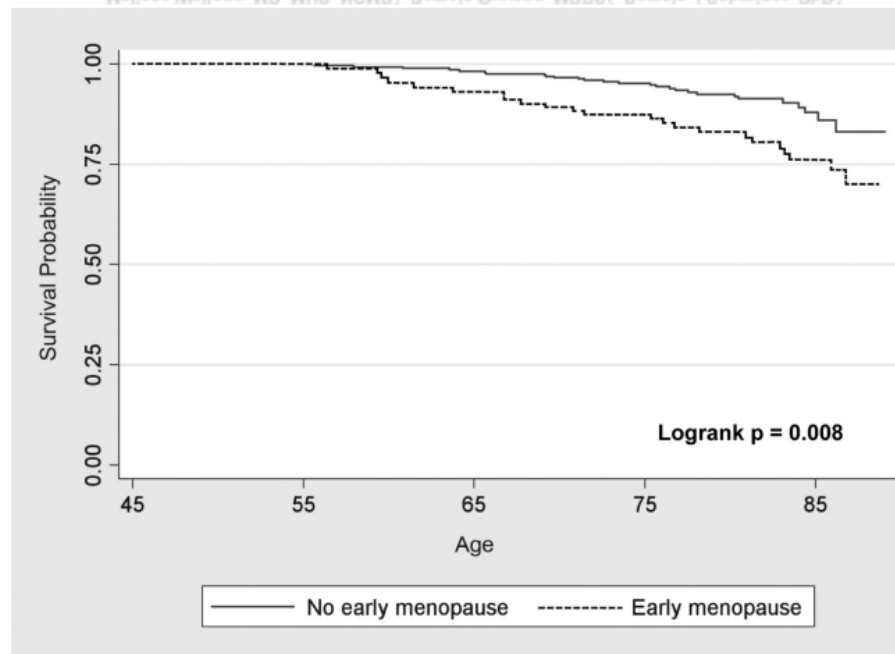
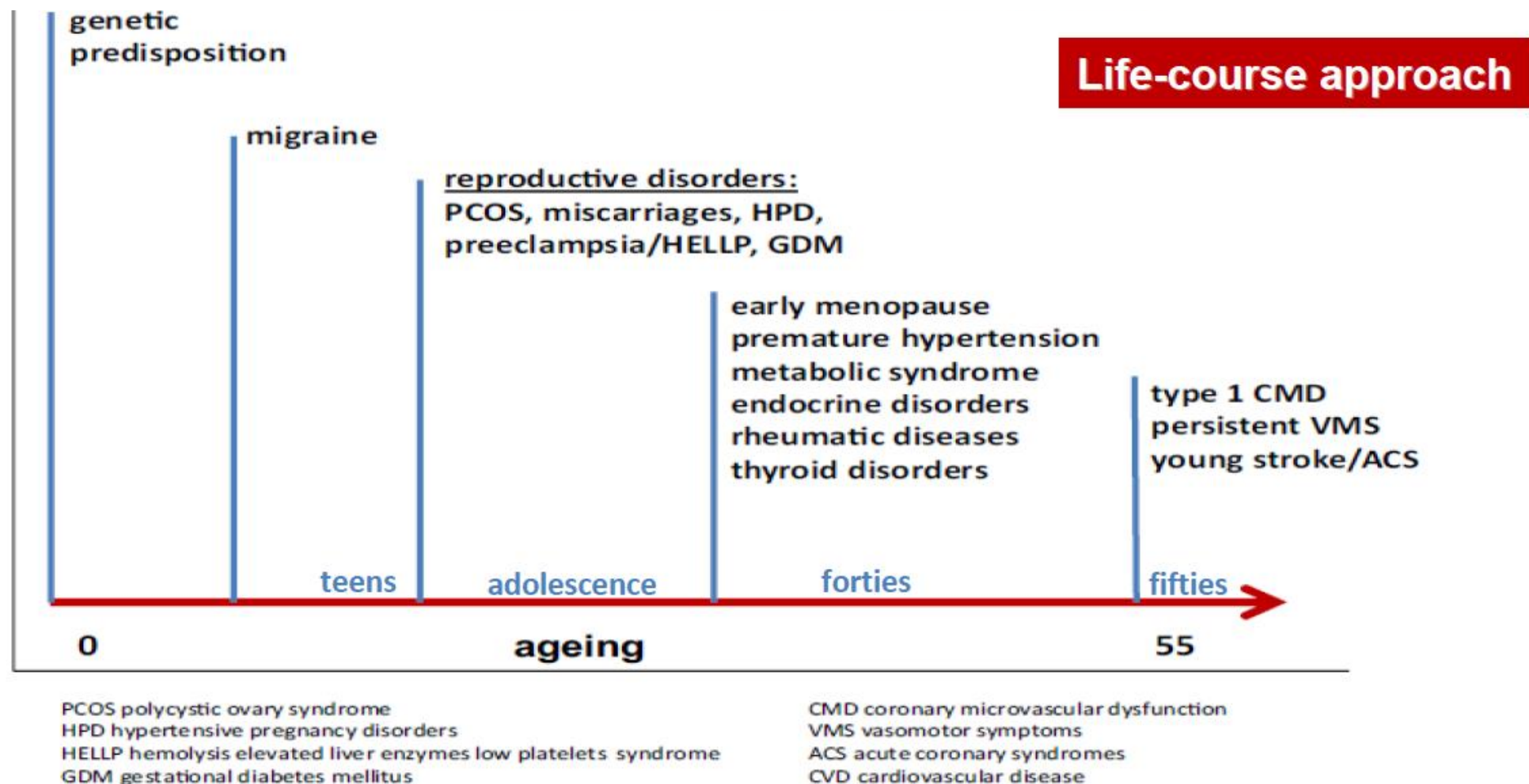
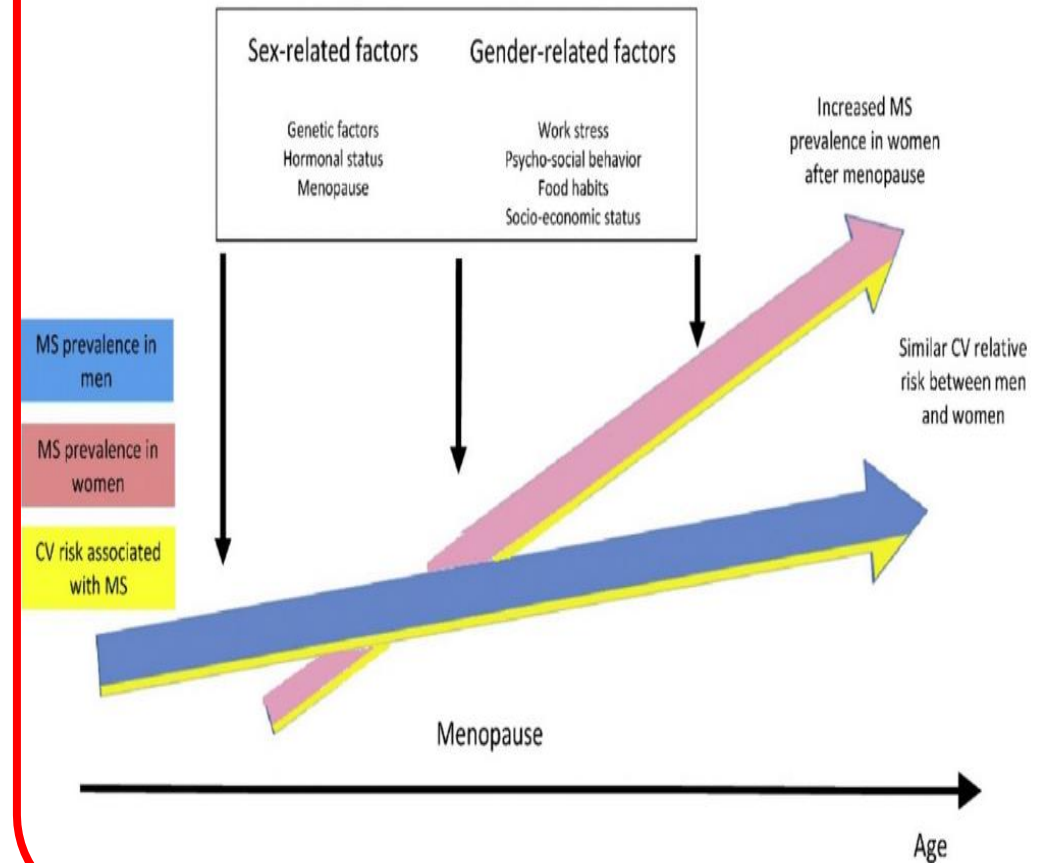
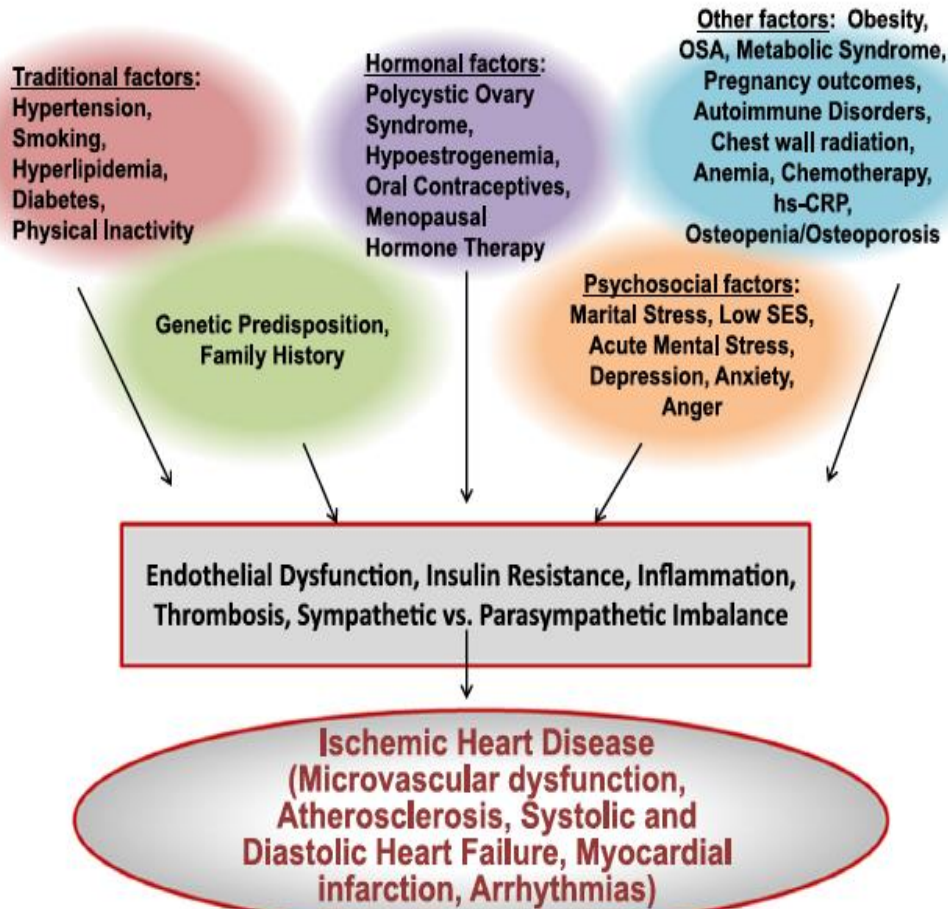


Figure 2. Kaplan Meier Survival Curves for Coronary Heart Disease in Women with and without Early Menopause.

Gynecardiology: Distinct patterns of ischemic heart disease in middle-aged women

Suzette E. Elias-Smale, Arzu Günal, Angela H.E.M. Maas*





Menopause, atherosclerosis and cardiovascular risk: a puzzle with too few pieces

Ilaria Jane Romano¹, Laura Lenatti¹, Nicoletta Franco², Leonardo Misuraca³, Nuccia Morici⁴, Chiara Leuzzi⁵, Elena Corrada⁶, Delia Colombo⁷, Stefano Savonitto¹

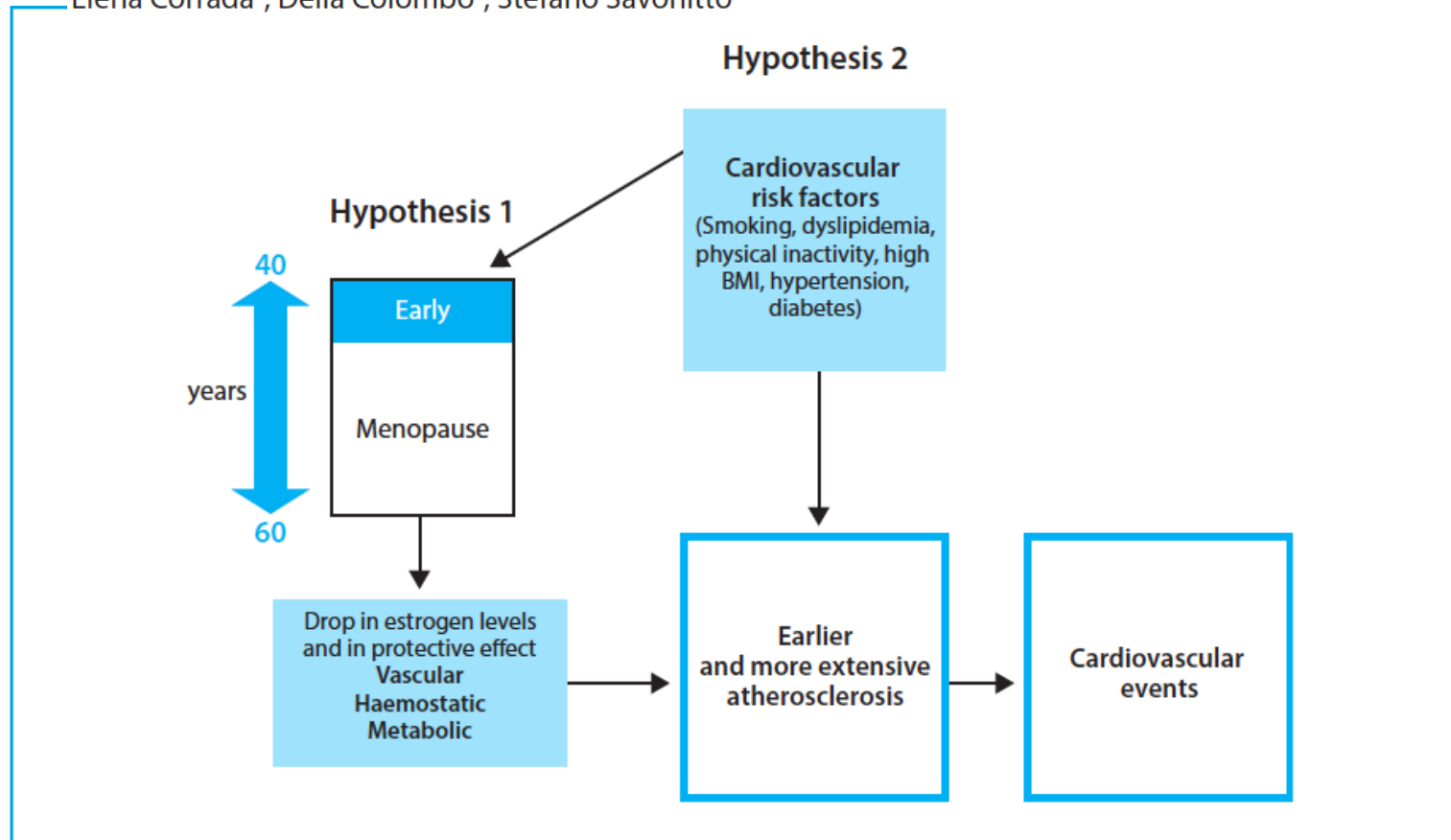


Figure 3. Two hypotheses on the relations between menopause (and “early” menopause), atherosclerosis and risk of cardiovascular events. “Hypothesis 1” indicates that estrogen has a protective effect on the progression of atherosclerosis, and that the earlier drop in estrogen levels reduces estrogen exposure time, accelerating atherosclerosis and increasing the risk of cardiovascular events in women with “early” menopause¹². “Hypothesis 2” argues that the same risk factors of cardiovascular disease, in addition to causing *per se* accelerated atherosclerosis, are themselves involved in causing early menopause, with the adverse consequences mentioned above²¹. The two hypotheses do not exclude one another. BMI, body mass index.

REVIEW

Open Access



Strategies and methods to study female-specific cardiovascular health and disease: a guide for clinical scientists

Pamela Ouyang^{1,9*}, Nanette K. Wenger², Doris Taylor³, Janet W. Rich-Edwards⁴, Meir Steiner⁵, Leslee J. Shaw², Sarah L. Berga⁶, Virginia M. Miller⁷ and Noel Bairey Merz⁸

Table 1 Variables affecting women across their lifespan

I. Reproductive health

Hypogonadotropic conditions

Polycystic ovarian syndrome is associated with vascular changes [20, 229, 230]

Stress reduces pituitary LH and FSH secretion leading to anovulation and secondary hypogonadism [31, 32].

Pregnancy hypertension

A women's recall of pregnancy hypertensive disorders is specific but sensitivity varies and the positive predictive value is low [65]. Investigators have suggested standardization of study design for research involving women with preeclampsia [231]

Maternal/fetal exposure to other pregnancy disorders

Women with histories of preeclampsia, gestational diabetes, small-for-gestational-age deliveries, or preterm deliveries (whether spontaneous or medically indicated) are at about twofold the increased risk of coronary heart disease and stroke compared with women who have had pregnancies uncomplicated by these factors [12]

Microchimerism

Fetal cells passage transplacentally into the maternal circulation during pregnancy and persist for decades (this is termed fetal microchimerism or FMC). FMC is potentially associated with detrimental effects, e.g., preeclampsia and autoimmune disease, and with beneficial effects, e.g., female longevity due to regeneration and repair due to FMC. FMC has been identified in explanted idiopathic cardiomyopathy hearts [77] and the frequency and concentration are higher in women with preeclampsia [78, 232]

Early menopause

Associated with greater coronary artery disease and stroke risk [58]

II. Sex hormones

Endogenous sex hormones

Sex hormone levels are associated with body composition, incident diabetes, and other risk factors [233].

Hormone therapy and age of therapy

Sub-analyses from Women's Health Initiative indicate age of hormone therapy (HT) may impact risk/benefit. The KEEPS trial showed no difference in progression of carotid intima-media thickness in women treated early post-menopause with oral or transdermal estrogen [46]

III. Psychosocial issues

Depression

More common in women and associated with incident CVD and worse prognosis [234, 235]. The AHA has recognized depression as a risk factor for poor prognosis among patients with acute coronary syndrome [236]

Stress

Reduces pituitary LH and FSH secretion leading to anovulation and secondary hypogonadism [31, 32]

Elderly age

Women are the majority of the elderly with high burden of CVD [161]

IV. Other variables

Impact of diabetes

DM confers greater risk in women than men [171]

Non-atherosclerotic coronary disease

Vasomotor dysfunction and coronary microvascular disease are often not considered despite women having lower prevalence of obstructive CAD [34]

Inflammatory autoimmune disease

Rheumatologic disorders, particularly systemic lupus erythematosus and rheumatoid arthritis, are more prevalent in women and are associated with more prevalent CVD [176, 237, 238]



26x

26x zebrafish gene expression

26x proteins

Sex Differences in Ischemic Heart Disease

Advances, Obstacles, and Next Steps

Circ Cardiovasc Qual Outcomes. 2018;

Take-Home Points for the Clinician

- Sex-specific risk of traditional and novel risk factors for ischemic heart disease should be considered for improved risk stratification of at-risk women.
- Diagnostic imaging should evaluate the full spectrum of ischemic heart disease and include assessment with stress testing and coronary computed tomography for epicardial stenosis and with positron emission tomography and magnetic resonance imaging for microvascular disease.
- Psychosocial variables, including perceived social support, depressive symptoms, and caretaking responsibilities, play an important role in influencing health-seeking behaviors and clinical outcomes in women.
- Increased awareness of ischemic heart disease in women, attention to social determinants of health, health and cultural literacy, improved adherence to sex-specific guidelines, and adequate inclusion of women in trials are needed to address the existing disparities in research and clinical care.