



CARDI·OH

Ohio Cardiovascular and Diabetes Health Collaborative



CASE WESTERN RESERVE
UNIVERSITY
School of Medicine

In partnership with:



THE OHIO STATE
UNIVERSITY
COLLEGE OF MEDICINE



COLLEGE OF MEDICINE
AND LIFE SCIENCES
THE UNIVERSITY OF TOLEDO



OHIO
UNIVERSITY
Heritage
College of
Osteopathic
Medicine



Northeast Ohio
MEDICAL UNIVERSITY



University of
CINCINNATI
COLLEGE OF MEDICINE



Sourashtra
School of Medicine
SOURASTRA UNIVERSITY



OHIO COLLEGES OF MEDICINE
GOVERNMENT
RESOURCE CENTER



medtapp



Ohio
Department of
Medicaid



Cardi-OH ECHO

Health Equity and Cardiovascular Risk

March 14, 2024

About Cardi-OH

Founded in 2017, the mission of Cardi-OH is to improve cardiovascular and diabetes health outcomes and eliminate disparities in Ohio's Medicaid population.

WHO WE ARE: An initiative of health care professionals across Ohio's seven medical schools.

WHAT WE DO: Identify, produce, and disseminate evidence-based cardiovascular and diabetes best practices to primary care teams.

HOW WE DO IT: Best practices resources are available via an online library at Cardi-OH.org, including monthly newsletters, podcasts, webinars, and virtual clinics using the Project ECHO® virtual training model.

[Learn more at Cardi-OH.org](http://Cardi-OH.org)



CARDI•OH

Ohio Cardiovascular and Diabetes Health Collaborative



Cardi-OH ECHO Team

FACILITATOR

Goutham Rao, MD

Case Western Reserve University

CONTENT EXPERTS

Karen Bailey, MS, RDN, LD, CDCES

Ohio University

Kristen Berg, PhD

Case Western Reserve University

Elizabeth Beverly, PhD

Ohio University

Danette Conklin, PhD

Case Western Reserve University

Kathleen Dungan, MD, MPH

The Ohio State University

Adam Perzynski, PhD

Case Western Reserve University

Marilee Clemons, PharmD

University of Toledo

Chris Taylor, PhD

The Ohio State University

Kelsey Ufholz, PhD

Case Western Reserve University

James Werner, PhD, MSSA

Case Western Reserve University

Jackson Wright, MD, PhD

Case Western Reserve University

Disclosure Statements



- The following speakers and subject matter experts have a relevant financial interest or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of their presentation*:
 - Danette Conklin, PhD; Kathleen Dungan, MD, MPH; Adam T. Perzynski, PhD; Christopher A. Taylor, PhD, RDN, LD, FAND; Jackson Wright, MD, PhD
- The remaining speakers and subject matter experts have no financial relationships with any commercial interest related to the content of this activity:
 - Karen Bailey, MS, RDN, LD, CDCES; Kristen Berg, PhD; Elizabeth Beverly, PhD; Merilee Clemons, PharmD; Revital Gordodeski Baskin, MD; Allyson Hughes, PhD; George Matar, MD; Kelsey Ufholz, PhD; Goutham Rao, MD; James Werner, PhD, MSSA
- The following members of the planning committee DO NOT have any disclosures/financial relationships from any ineligible companies:
 - Shari Bolen, MD; Anderson Christopher; Richard Cornachione; Carolyn Henceroth; Gillian Irwin; Michael Konstan, MD; Elizabeth Littman; Devin O'Neill; Steven Ostrolencki; Ann Nevar; Claire Rollins; Catherine Sullivan

* These financial relationships are outside the presented work.

** For more information about exemptions or details, see www.acme.org/standards



Cardiovascular Risk and Menopause

Danette Conklin, PhD

Assistant Professor of Psychiatry and
Reproductive Biology
Case Western Reserve University
Director, Behavioral Health Services, Bariatric
Surgery and Weight Management Center
Department of Psychiatry
University Hospitals Cleveland Medical Center

Revital Gorodeski Baskin, MD

Assistant Professor
Obesity Program Director
Division of Endocrinology
University Hospitals of Cleveland

Learning Objectives

- 1) Describe changes in cardiovascular risk among women experiencing menopause.
- 2) List and describe key elements of a clinical evaluation of menopausal women, including assessment of cardiovascular risk
- 3) Describe a strategy for counseling peri-menopausal women about cardiovascular risk.



WHO Facts



- 1975 → 2016 OBESITY PREVALANCE TRIPLED
- Most of the world's population live in countries where overweight and obesity kills MORE people than underweight.
- No longer just a high-income country problem.



World-Wide:

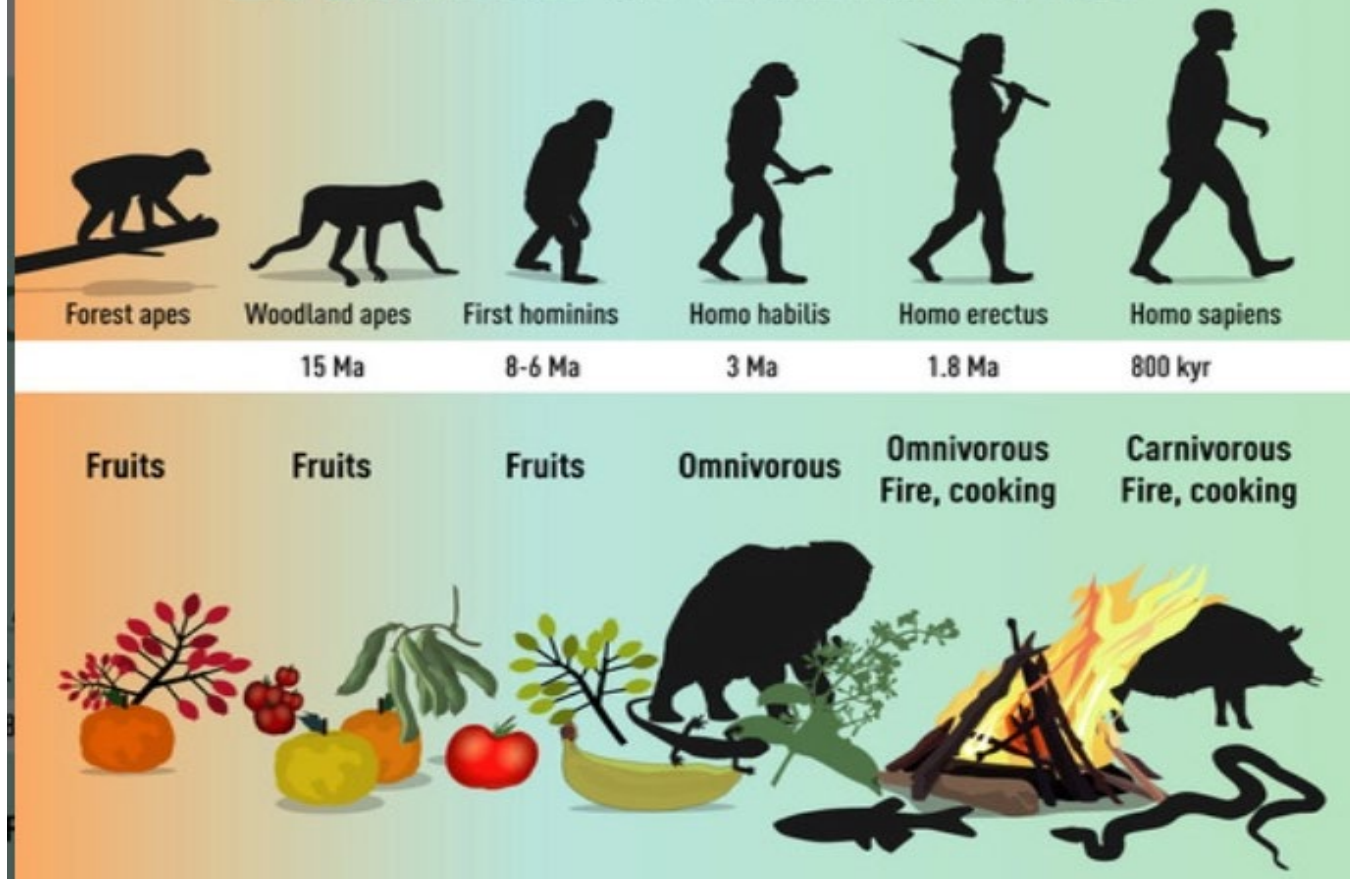


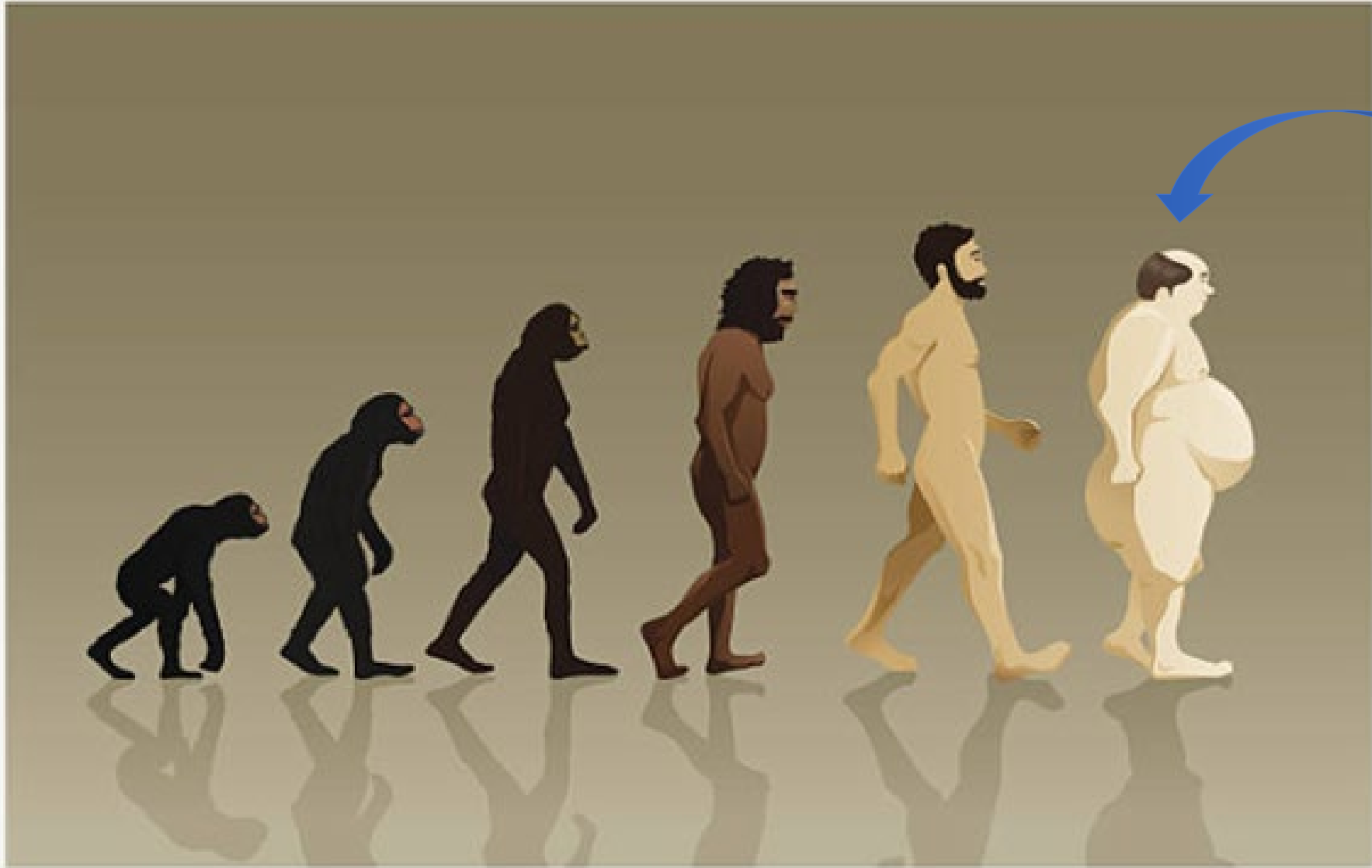
Obesity:
671 Million

Cardiovascular
Disease:
523 Million

Type 2 Diabetes:
439 Million

Evolution of human diet

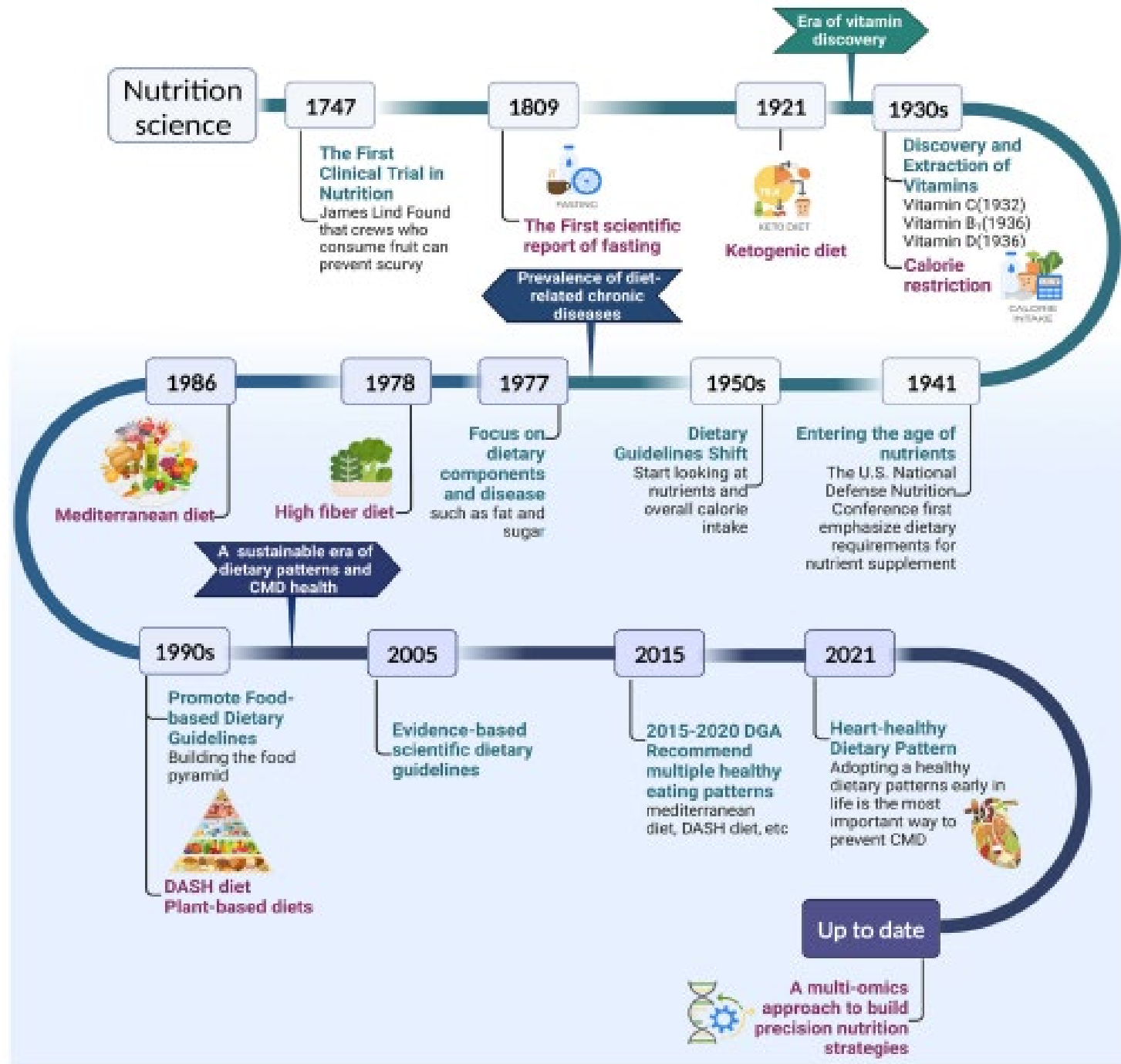




CARDI•OH
Ohio Cardiovascular and Diabetes Health Collaborative

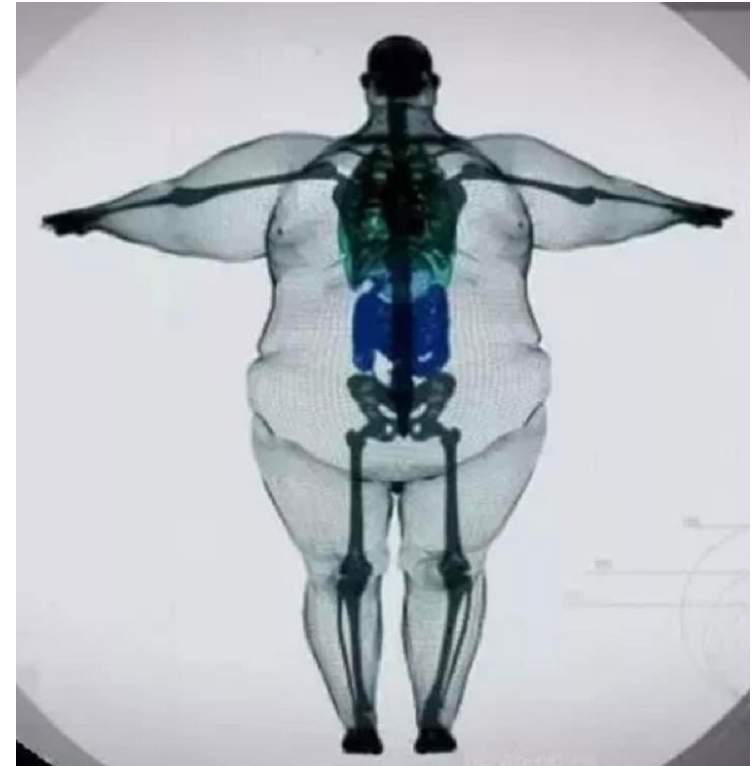


2023



Heart Disease Risk Factors

- ~2,200 adults die daily in the US due to Cardiovascular Disease (CVD)
- Obesity increases the risk of CVD by ~two-fold.
- Heart Disease and Stroke risk factors:
 - Unhealthy diet
 - Visceral adiposity
 - Physical inactivity & sedentary lifestyle
 - Tobacco use
 - Harmful use of alcohol



Visceral Adiposity



The Metabolic Syndrome

Hypertension

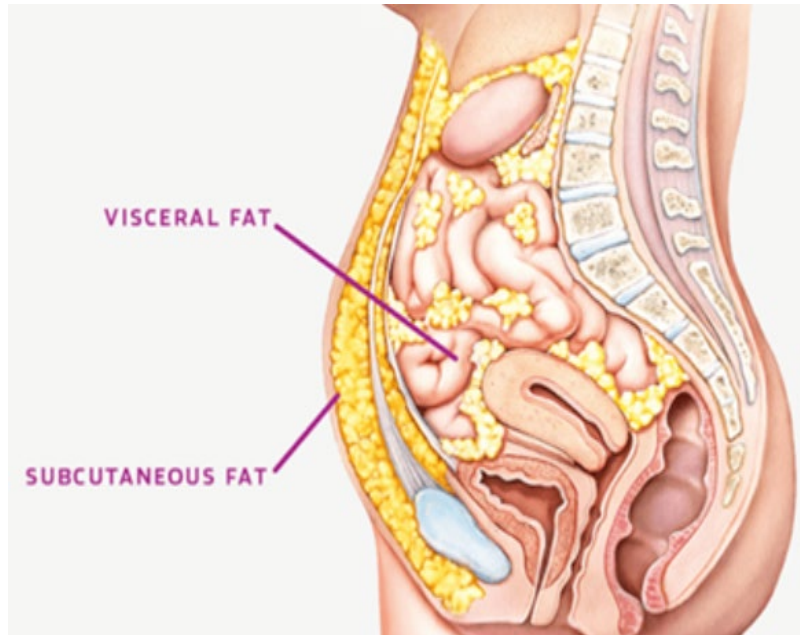
Dyslipidemia

Cardiovascular Disease

Type 2 Diabetes

Non-alcoholic fatty liver disease

Several cancers



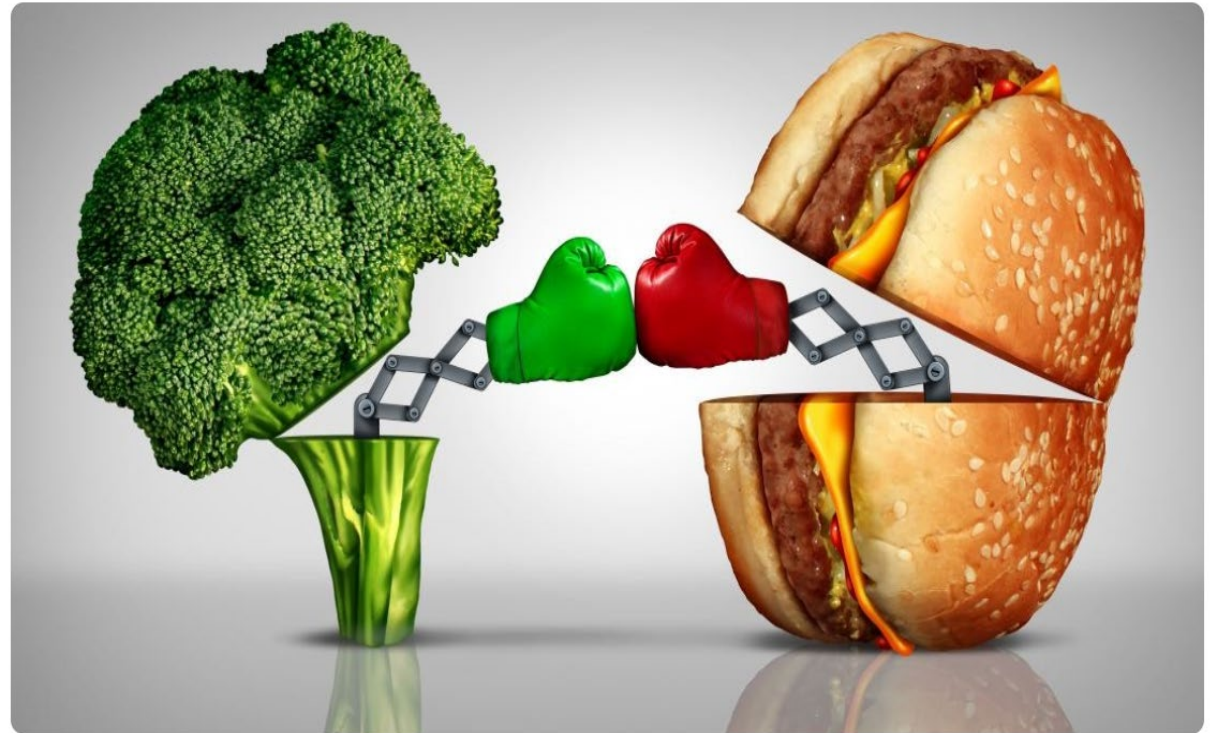
Unhealthy Nutrition Habits

- Added sugars
- Excessive salt
- Refined foods
- Unhealthy fats
- Low intake of: vegetables, fruits, whole grains, fibers, fish and nuts



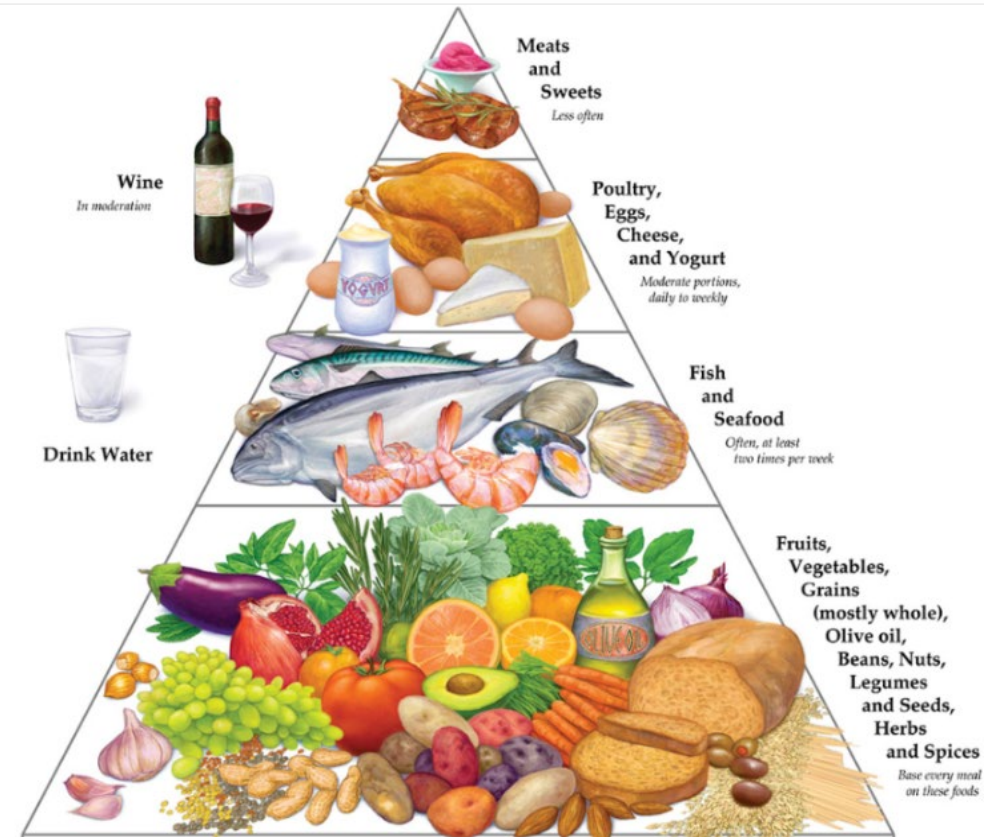
Dietary Interventions that Impact CVD

- Calorie Restriction
- Fat Restriction
- The Mediterranean Diet
- The DASH Diet
- The Ketogenic Diet
- Plant Based Diet
- Intermittent Fasting



The Mediterranean Diet

- **High intake:**
 - Vegetables and whole-grain cereals
 - Extra virgin olive oil, fruit, tree-nuts,
- **Moderate intake:**
 - Fish and poultry, wine
- **Low intake:**
 - Dairy, red meat (twice/month), processed meats, and sweets

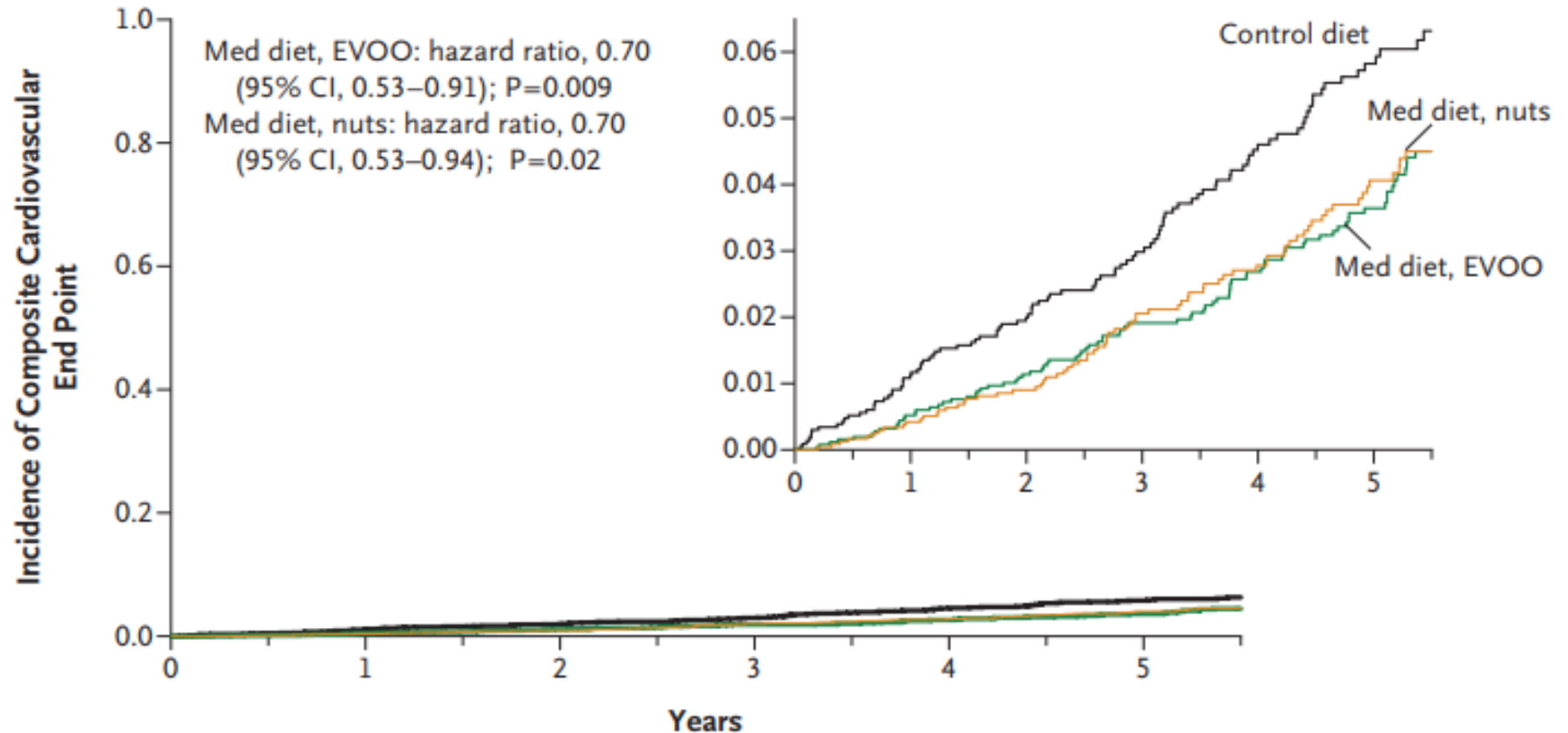


PREDIMED Study: The Mediterranean Diet



CARDI•OH
Ohio Cardiovascular and Diabetes Health Collaborative

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



NEJM

Menopausal Transition

Depletion of ovarian follicles



Decreased ovarian follicle responsiveness to the pituitary gonadotropins (FSH & LH)



Lower serum levels of ovarian hormones Estrogen and Progesterone



Vasomotor symptoms, hot flashes, vaginal dryness

Osteoporosis, CV disease, and breast cancer

The Mediterranean Diet and Menopause

- Severity of menopausal symptoms have been shown to have an inverse association with adherence to the MD.
- The intake of legumes and EVOO was associated with lower severity of menopausal and psychological symptoms.
- Soy intake (known as a legume) has been shown to help.
 - Soy → isoflavones → chemical structure resembling estrogens.
- Dietary phytoestrogens are bioactive compounds with estrogenic activity

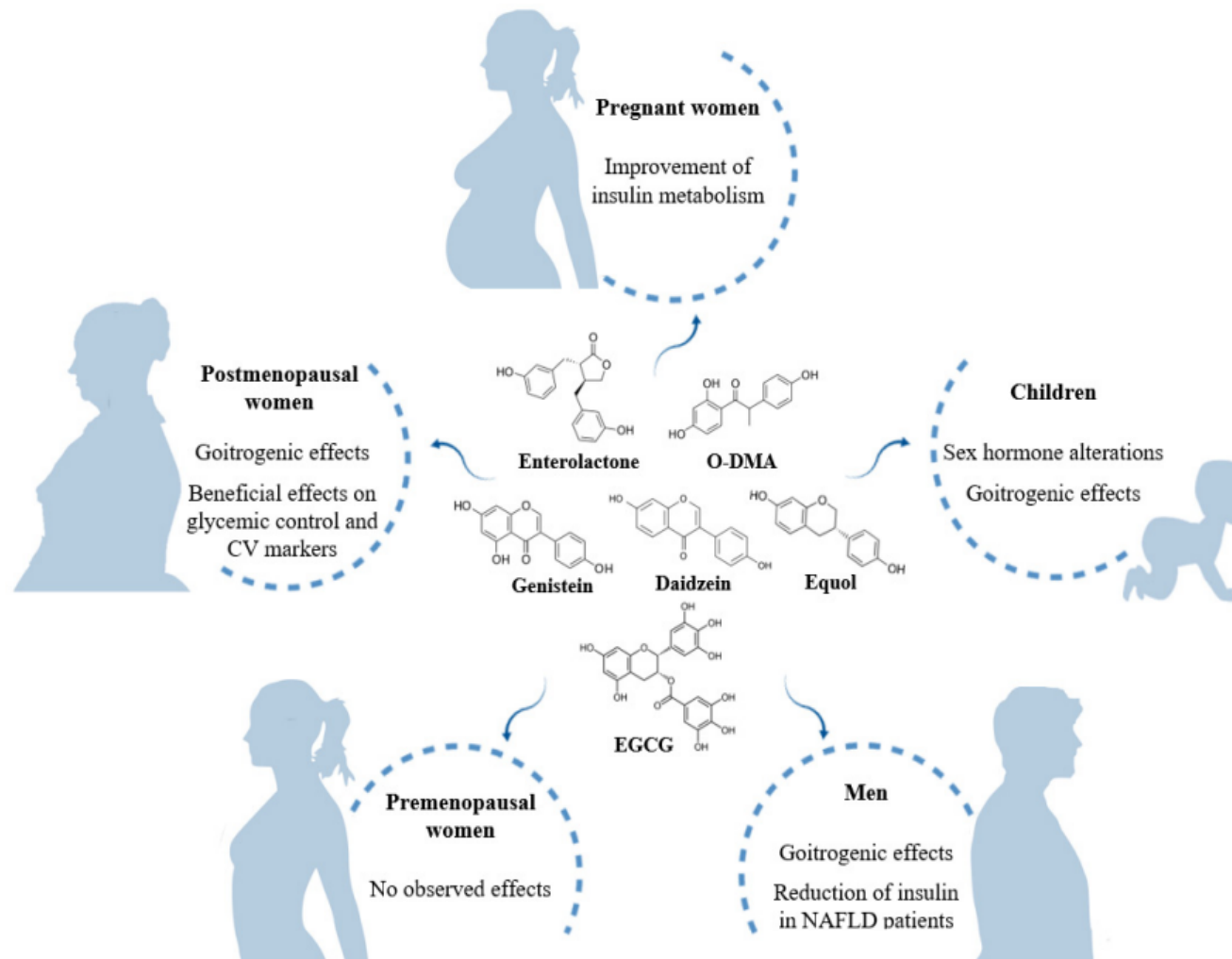


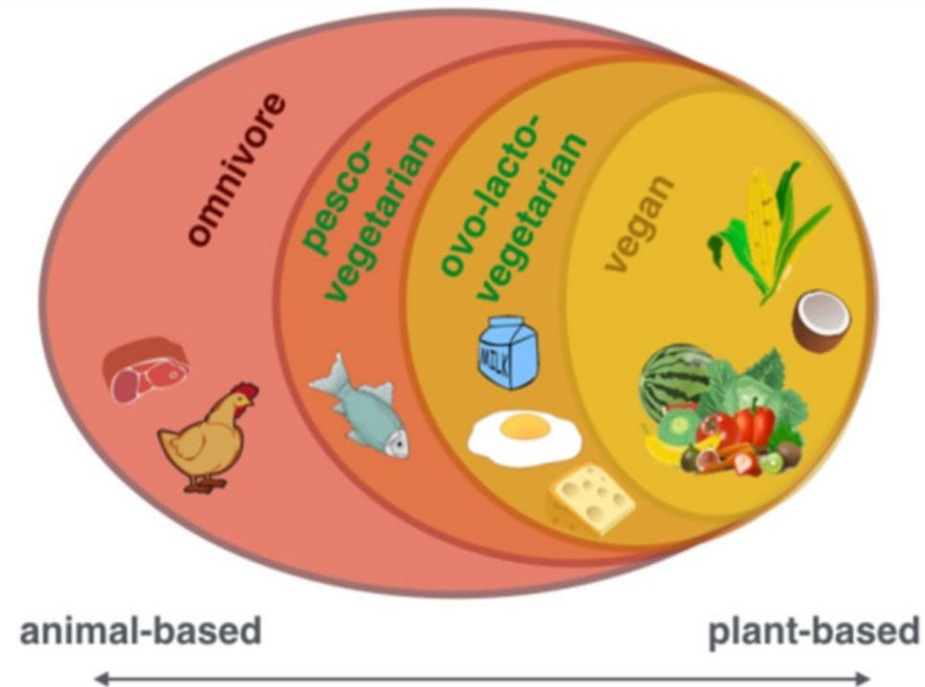
Figure 3. Summary of the effects of dietary phytoestrogens at different life stages. NAFLD: non-alcoholic fatty liver disease.

BUT – Evidence of the effect of Phytoestrogens on the Endocrine biomarkers is inconclusive

Plant-Based Diets

- Characterized by the intake of plant products and reduction or elimination of animal-based food.

- Subcategories:



Plant-Based Diets

- Large prospective cohort studies: vegetarians exhibit:
 1. Lower all-cause mortality
 2. CV-related mortality
 3. Less cardiometabolic risk than meat eaters
- May reduce risk of :
 - Coronary heart disease events by ~40%,
 - Risk of Cerebral vascular disease by ~29%



Adventist Health Study-2

- Vegan patients had a 77% risk reduction in developing diabetes

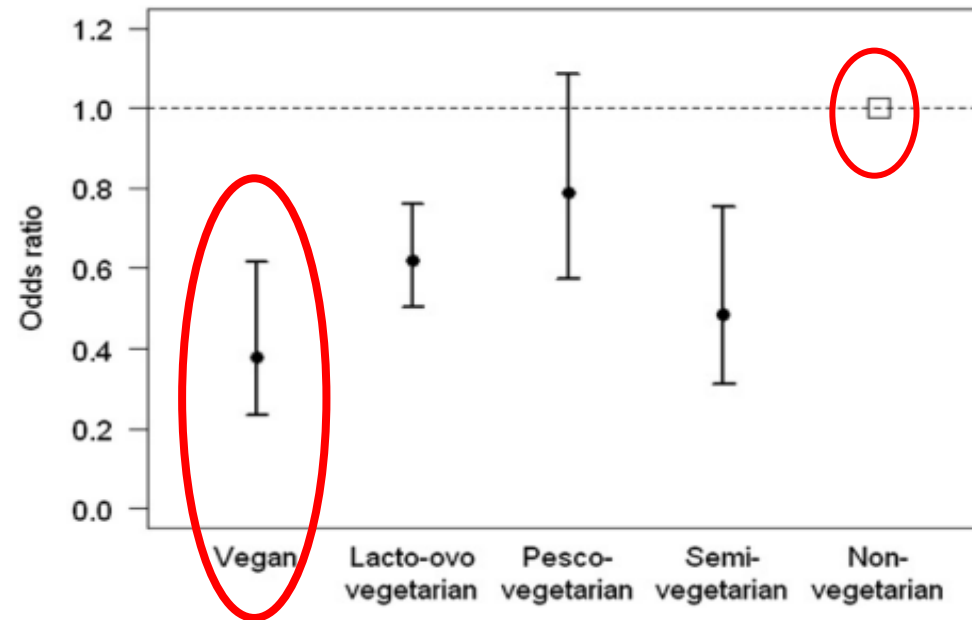
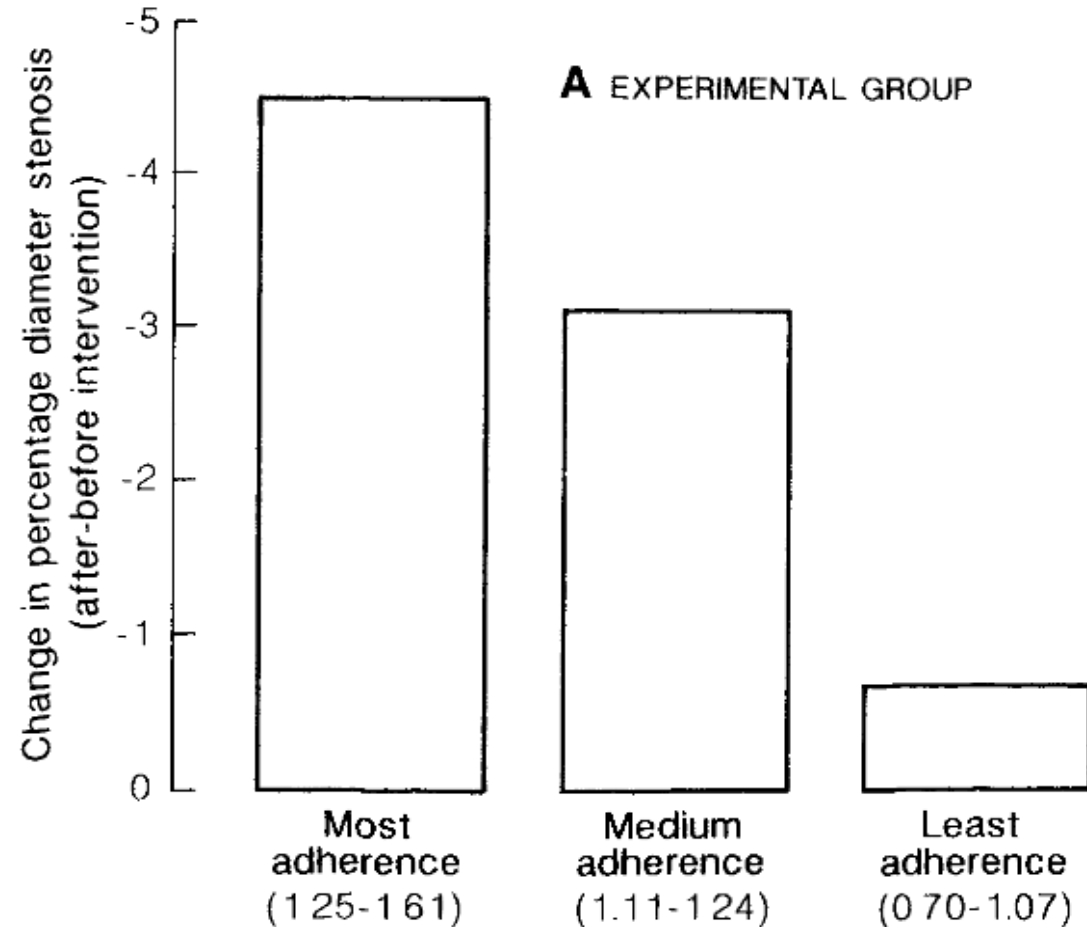


Figure 1 Odds ratios with 95% confidence intervals for incident diabetes by dietary group adjusted for age, BMI, ethnicity, gender, educational level, income, TV watching, sleep, alcohol, physical activity and cigarette smoking.

The Lifestyle Heart Trial



**Atherosclerosis
stenosis regression**

The Lifestyle Heart Trial: 4 Year Extension

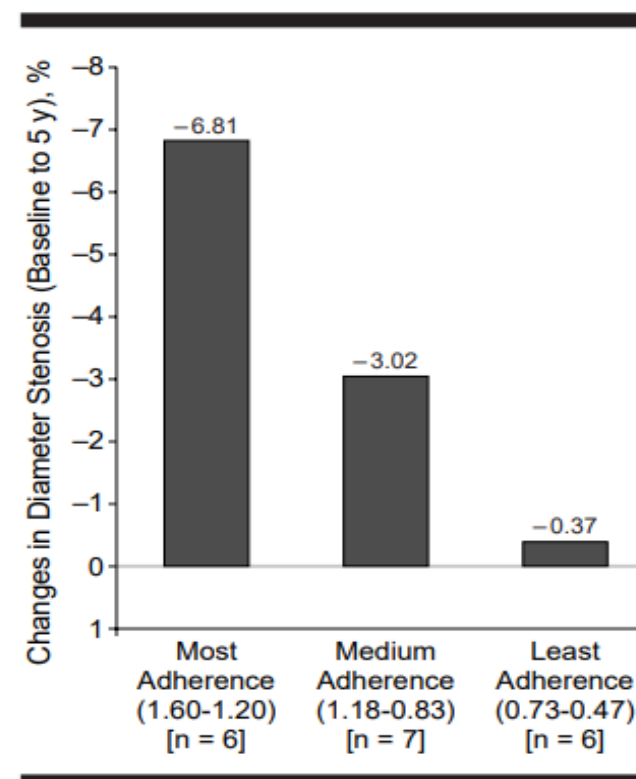
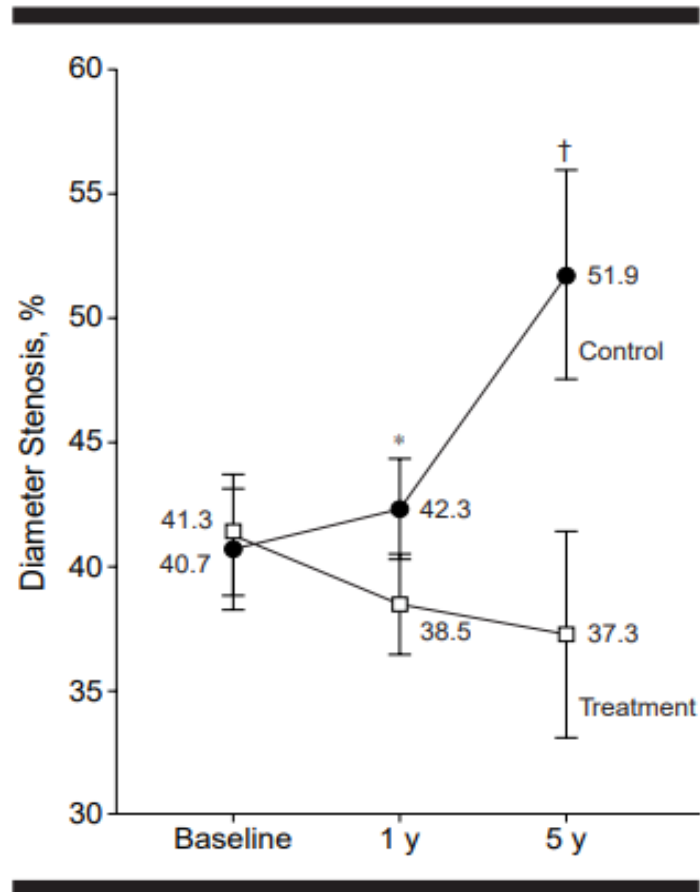


Figure 2.—Changes in percentage diameter stenosis by 5-year adherence tertiles for the experimental group.

Acknowledgements



- Sally MacPhedran, OBGYN, MSCP
- Corinne Bazella, OBGYN, MSCP
- Jean Marino, APRN, MSCP
- Goutham Rao, MD Family Medicine

Cardiovascular Disease

- Cardiovascular disease (CVD) is the leading cause of death for women worldwide.
- Most CVD in women occur after 55, which is during post-menopause for most women.
- However, premature, early, or surgical menopause are also established risk factors for CVD.



Traditional vs Emerging: Nontraditional Risk Factors for Atherosclerotic CVD in Women

Traditional

- Diabetes
- Smoking
- Obesity or excess weight
- Physical inactivity
- Hypertension
- Dyslipidemia



Traditional vs Emerging: Nontraditional Risk Factors for Atherosclerotic CVD in Women



Non-traditional

- Preterm labor
- Intrauterine growth restriction (IUGR)
- Hypertensive disorders of pregnancy (preeclampsia, gestational diabetes, pregnancy induced-HTN)
- Breast cancer treatment
- Autoimmune disease
- Depression

North American Menopause Society, Menopause practice: a clinician's guide, Mayfield Heights, OH: The North American Menopause Society, 6th ed, 2019.

Garcia J, et al. Cardiovascular disease in women: Clinical perspectives. Circ Res. 2016; 118(8): 1273-1293.

Menopause Transition and Cardiovascular Disease Risk

Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association

<https://www.ahajournals.org/doi/10.1161/CIR.0000000000000912>



Circulation

Volume 142, Issue 25, 22 December 2020; Pages e506–e532
<https://doi.org/10.1161/CIR.0000000000000912>



AHA SCIENTIFIC STATEMENT

Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association

Samar R. El Khoudary, PhD, MPH, FAHA, Chair, Brooke Aggarwal, EdD, MS, FAHA, Theresa M. Beckie, PhD, FAHA, Howard N. Hodis, MD, FAHA, Amber E. Johnson, MD, MS, MBA, Robert D. Langer, MD, MPH, FAHA, Marian C. Limacher, MD, FAHA, JoAnn E. Manson, MD, DrPH, FAHA, Marcia L. Stefanick, PhD, FAHA, Matthew A. Allison, MD, MPH, FAHA, Vice Chair, and On behalf of the American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing

Abstract: Cardiovascular disease (CVD) is the leading cause of death in women, who have a notable increase in the risk for this disease after menopause and typically develop coronary heart disease several years later than men. This observation led to the hypothesis that the menopause transition (MT) contributes to the increase in coronary heart disease risk. Over the past 20 years, longitudinal studies of women traversing menopause have contributed significantly to our understanding of the relationship between the MT and CVD risk. By following women over this period, researchers have been able to disentangle chronological and ovarian aging with respect to CVD risk. These studies have documented distinct patterns of sex hormone changes, as well as adverse alterations in body composition, lipids and lipoproteins, and measures of vascular health over the MT, which can increase a woman's risk of developing CVD postmenopausally. The reported findings underline the significance of the MT as a time of accelerating CVD risk, thereby emphasizing the importance of monitoring women's health during midlife, a critical window for implementing early intervention strategies to reduce CVD risk. Notably, the 2011 American Heart Association guidelines for CVD prevention in women (the latest sex-specific guidelines to date) did not include information now available about the contribution of the MT to increased CVD in women. Therefore, there is a crucial need to discuss the contemporary literature on menopause and CVD risk with the intent of increasing awareness of the significant adverse cardiometabolic health-related changes accompanying midlife and the MT. This scientific statement provides an up-to-date synthesis of the existing data on the MT and how it relates to CVD.

Menopause Characteristics and CVD Risks

- Increased incidence of CVD morbidity and mortality for women with early onset of natural menopause (before 45 years old) or premature menopause (before 40 years old).
- Early-onset menopause < 45 is a significantly risk for CVD, heart failure, and fatal Congenital Heart Defects (CHD) compared to natural menopause ≥ 45 , after adjusting for traditional CVD risk factors.
- 2-3-fold increased risk of myocardial infarction (MI) if menopause occurs before 35 years old.



Menopause Practice, A Clinician's Guide. 6th edition. NAMS. The North American Menopause Society; Simoncini T, Cecchi E, Genazzani AR. (2015). In N. Panay, P. Briggs, G. Kovacs (Eds), Managing the Menopause, 21st Century Solutions. (pp. 36-44). Cambridge.

Menopause Characteristics and CVD Risks



Age and natural menopause

- Natural menopause between 50-54 compared to < 50 lower relative risk for CVD.
- Estrogen: common belief that estrogen is a protective factor in premenopausal women



Surgical Menopause

Bilateral Oophorectomy (BSO)

- Surgical-induced menopause caused by BSO puts women at a higher risk for CHD with no estrogen hormone therapy compared to natural menopause.
- Other studies showed a small to no association between BSO and CHD risk, if performed close to the age of expected menopause. CHD risk is higher if BSO is performed < 40-45 years old.



Other CVD Risk Factors Related to the Menopause Transition



- Hot flashes/night sweats (i.e., vasomotor symptoms)
- Problems related to sleep disturbance
- Depression
- Weight gain

Menopause Practice, A Clinician's Guide. 6th edition. NAMS. The North American Menopause Society.

Differences of Opinion and Menopausal Hormone Therapy



The Menopause Society (MS), formerly North American Menopause Society, and the U.S. Preventive Services Task Force (USPSTF)



The
**Menopause
Society™**

Leading the Conversation



NAMS Position Statement. The 2022 hormone therapy position statement of The North American Menopause Society;
<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/menopausal-hormone-therapy-preventive-medication>

The Menopause Society (MS)

- Studies found that initiating Menopausal Hormone Therapy (MHT) < 60 years of age or within 10 years of a woman's final menstrual period is the safest time to be on hormone therapy (HT).
- Menopause Society (MS) concludes that observational data and meta-analyses have shown that if MHT is initiated as noted above, the risk of CHD is reduced.
- MS cites observational and preclinical studies show potential benefits for systemic HT, reducing the risk for CVD.
- MS also states that most Randomized Controlled Trials (RCTs) do not show that MHT can reduce the risk for CVD.



Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long? Leslie Cho, Andrew M. Kaunitz, Stephanie S. Faubion, Sharonne N. Hayes, Emily S. Lau, Nicole Pristera, Nandita Scott, Jan L. Shifren, Chrisandra L. Shufelt, Cynthia A. Stuenkel, Kathryn J. Lindley and for the ACC CVD in Women Committee. Originally published 13 Feb 2023 <https://doi.org/10.1161/CIRCULATIONAHA.122.061559> Circulation. 2023;147:597–610
NAMS Position Statement. The 2022 hormone therapy position statement of The North American Menopause Society; Menopause Practice, A Clinician's Guide. 6th edition. NAMS. The North American Menopause Society.

U.S. Preventive Services Task Force



- “The literature supporting a critical role for the time of initiation of MHT use relative to menopause strongly calls for further research assessing MHT use, including potential contrasts by form, route, and duration of administration, on cardiometabolic effects in women traversing menopause, a large proportion of whom experience menopausal symptoms before even reaching menopause.”
- “Adequate evidence that estrogen and progestin or estrogen alone has no benefit for coronary heart disease.”

Communication, Dr. Goutham Rao (12/8/2023).

<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/menopausal-hormone-therapy-preventive-medication>

Differences of Opinion and Menopausal Hormone Therapy



Huang and Grady (2022) opined that:

- U.S. Preventive Services Task Force guidelines did not use any update literature or evidence to make their guidelines
- NAMS/MS position statements were much more up-to-date using current literature to support their recommendations

Huang AJ, Grady D. Menopausal Hormone Therapy for Prevention of Chronic Conditions: When Is Enough, Enough? *JAMA*. 2022;328(17):1712–1713. doi:10.1001/jama.2022.19098

Differences in Opinion



Simoncini, Cecchi, & Genazzan opined that

- Hormone Replacement Therapy (HRT) most favorable in the first 10 years post-menopause. No CVD harm and benefits will ensue
- Hormone Therapy (HT) has to be individualized
- Risks if long term; more risk if oral but not if transdermal
- Reduced CVD risks for younger women but not older

Simoncini T, Cecchi E, Genazzani AR. (2015). In N. Panay, P. Briggs, G. Kovacs (Eds), *Managing the Menopause, 21st Century Solutions*. (pp. 36-44). Cambridge.

So What Can We Do?

Areas of Focus for Women in the Menopause Transition.



- USPSTF and MS agree, MHT can be used to treat menopause symptoms
- Vasomotor Symptoms (VMS) of menopause (hot flashes and night sweats)
- Genitourinary symptoms of menopause (GSM) (vaginal dryness and dyspareunia [pain with sexual activity])
- Prevent bone loss and fractures

Vasomotor Symptoms (Hot Flashes and Night Sweats)

Studies show that VMS during the midlife years are linked to

- Adverse lipid profile
- Insulin resistance
- Greater risk for incident hypertension
- VMS associated with palpitations have even higher risk of CVD than VMS without palpitations



Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Janssen I, Hollenberg SM, El Khoudary SR. Arterial Stiffness Accelerates Within 1 Year of the Final Menstrual Period: The SWAN Heart Study. *Arterioscler Thromb Vasc Biol.* 2020 Apr;40(4):1001-1008. doi: 10.1161/ATVBAHA.119.313622; *Menopause Practice, A Clinician's Guide.* 6th edition. NAMS. The North American Menopause Society

Vasomotor Symptoms (Hot Flashes and Night Sweats)

Studies that compare women with and without menopause symptoms show that VMS are associated with increased risk of CVD, CHD and stroke

- Higher carotid intima-media thickness (cIMT) for women with hot flashes, with higher risk for women who fall in the BMI ranges of overweight or obese
- VMS increases vasodilation and heart rate



Menopause Hormone Therapy



- Estrogen has been shown to have the best efficacy to reduce the number and intensity of VMS, thus overall improved quality of life
- Micronized progesterone metabolites are responsible for improved sleep (specifically falling asleep) but not for VMS
- There is an old study that shows Micronized progesterone, substituted for MPA (medroxyprogesterone acetate), had a more synergistic effect with estradiol for most VMS. But the progesterone itself does not help most with VMS
- Synthetic progesterones (MPA) are associated with increased BP

Sally MacPhedran, MD personal communication (03/07/2024)

Circulation, 2020. 142:e506 discusses prevention of CVD and early age of menopause

In addition ...

MHT is also used off label to treat:

- Sleep disturbance, particularly if sleep disturbance is due to night sweats
- Depression
- Some studies used MHT to treat abdominal adiposity



Problems Related to Sleep Disturbance

- Shorter sleep duration
- Poorer sleep quality
- Greater severity of insomnia
- Poor sleep impacts mood, weight/obesity, problems with memory, metabolic syndrome and greater risk for CVD



Depression Study Findings



Depression is related to incident CVD and VMS.

The occurrences of depression are more frequent during the perimenopausal and postmenopausal years.

SWAN Heart Study

Five-year follow-up in healthy 46–59 years old women showed that having ≥ 3 episodes of depression versus no episodes of depression was significantly associated with elevated coronary artery calcification scores.

Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Janssen I, Hollenberg SM, El Khoudary SR. Arterial Stiffness Accelerates Within 1 Year of the Final Menstrual Period: The SWAN Heart Study. *Arterioscler Thromb Vasc Biol.* 2020 Apr;40(4):1001-1008. doi: 10.1161/ATVBAHA.119.313622. Epub 2020 Jan 23. PMID: 31969013; PMCID: PMC7101253.

Depression Study Findings



Women's Health Initiative (WHI trials)

Depression was found as an independent predictor of CVD death and all-cause mortality for women with no history of CVD, after adjusting for established CVD risk factors and demographics. Follow up was an average of 4.1 years.

Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, Robbins J, Aragaki A, Dunbar-Jacob J. Depression and cardiovascular sequelae in postmenopausal women: the Women's Health Initiative (WHI). *Arch Intern Med.* 2004;164:289–298. doi: 10.1001/archinte.164.3.289

Menopause Hormone Therapy



- Estrogen therapy (ET) has been shown to have antidepressant effects similar to antidepressant agents when prescribed to treat perimenopausal depression, and more so for women with depression and VMS
- Estrogen therapy has been found to be ineffective to treat depression in postmenopausal women
- Evidence has been inconclusive regarding estrogen plus progestin and antidepressant effects
- NOTE: ET is not FDA approved to treat depression

Maki PM, Freeman EW, Greendale GA, et al. Summary of the National Institute on Aging-sponsored conference on depressive symptoms and cognitive complaints in the menopausal transition. **Menopause** 2010;17:815–822. [Crossref](#), [Medline](#)

Positive Physiological Changes and Estrogen



Positive changes that happen physiologically with Oral E2

- Decreased LDL
- Decreased Total cholesterol
- Increased HDL

Transdermal estrogen

- Lowers LDL
- Lowers total cholesterol
- Has a neutral effect on HDL

Weight Gain

Changes in Fat to Lean Mass in the Menopause Transition (MT)

- Central and visceral fat increases and lean muscle mass decreases
- The increase in central adiposity has been found to be associated with an increased risk of mortality, even for midlife women with a normal BMI
- Independent of age, after menopause, paracardial fat volumes are higher, which could be influenced by estradiol levels of MHT use

Weight Gain

Changes in Fat to Lean Mass in the MT

- After menopause, paracardial fat volumes are higher after menopause, independent of age, which could be influenced by estradiol levels of MHT use.
- Postmenopausal women with a BMI ≥ 40 kg/ m², a waist circumference of 45.35” to 48” and > 48 ”, compared to waist circumference ≤ 34.65 ”, were found to be associated with higher total mortality and incidence of heart failure and CHD.
- Postmenopausal women in the normal BMI range with a waist circumference ≥ 34.65 ” were at higher risk of mortality compared to midlife women with normal BMI and no central adiposity.

Interventions to Manage Weight and Better Manage Increase in Abdominal Adiposity



Limited Randomized Controlled Trial (RCT) studies examining lifestyle interventions

Studies show that for women undergoing the MT, lifestyle interventions can prevent weight gain while reducing

- Triglycerides
- SBP and DBP
- Blood glucose
- Insulin

Interventions



Reasonable lifestyle interventions based on current data: target ideal body weight, with low central adiposity, and maintenance of skeletal muscle mass.

- Diet most recommended has been the Mediterranean diet
- Lipid lowering interventions remains ambiguous.
- Exercise: 60-90 minutes, moderate intensity, most days

MHT is not FDA approved. Though some studies show a small effect that HT attenuates abdominal adiposity and weight gain, it is not generally accepted that HT helps.

Other Interventions



- Other interventions for VMS, depression, weight and sleep disturbance, includes Cognitive Behavioral Therapy (CBT) and other/or medication management.

Summary

Menopausal Hormone Therapy is controversial.

- It is accepted to treat menopause symptoms during perimenopause or the Menopausal Transition (MT).
- Other societies/study groups suggest it is an acceptable treatment within 10 years post menopause and that it is acceptable to treat early onset, surgical and premature menopause.
- Include non-traditional risk factors and risk factors related to menopausal women in your assessment and evaluation.

Summary

Menopausal Hormone Therapy is controversial.

To help menopausal women reduce CVD risks, educate patients about CVD and increased risks during the MT, educate women about the risks/benefits of MHT, and use gold standard interventions to treat:

- VMS
- Depression
- Sleep disturbance
- Weight and abdominal adiposity



Thank you!

Questions/Discussion