

Women's Brain Health

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Center for Healthy Aging

Women's Brain Health Program



Objectives:

- Identify 3 contributions of sex and gender to women's Alzheimer's disease risk
- Describe common neurocognitive symptoms of the menopause transition
- Summarize 3 ways sex and gender factors can guide building of resilience and prevention practices

Mental Health Conditions are Common

- > 1 billion people worldwide living with a mental or addiction disorder
 - Often underdiagnosed due to stigma
 - Not all research & clinical care take into account gender/social determinants
- 2021
 - > 50 million (57.8 million) in U.S. **w/Any Mental Illness**
 - 1 in 5 adults aged >18 in U.S. or 22.8% of U.S. adults
 - ***Prevalence of AMI was higher among females (27.2%) than males (18.1%)***
 - Young adults aged 18-25 years had the highest prevalence of AMI (33.7%) compared to adults aged 26-49 years (28.1%) & aged >50 (15.0%)
 - Prevalence of AMI was highest among adults reporting two or more races (34.9%) then American Indian / Alaskan Native (AI/AN) adults (26.6%) & lowest among Asian adults (16.4%)

Approx 12 million report serious suicidal ideation, yet 57% do not receive mental health treatment

NIMH »Mental illness.

<https://www.nimh.nih.gov/health/statistics/mental-illness>

Women's Mental Health Conditions

- **Women**

- Are 2-3 X more likely to be diagnosed with a mental health condition
 - Depression, anxiety, eating disorders and trauma & stress related conditions
- Have no difference in incidence of bipolar or schizophrenia but different presentation
- More often victims of intimate partner violence & sexual trauma
- Have higher risk of dementia and age-related cognitive decline
- Dramatic increase in alcohol use

- The reasons why women are more at risk are multifactorial

- Sex differences, gender differences, socioeconomic differences
- Certain psychiatric disorders only found in women
 - PMDD, Perinatal depression, infertility & peri-menopausal related depression, anxiety, brain fog.



Estrogen, Stress, and Depression: Biological Interactions

Brain systems that are affected in depression and cognition are also sensitive to estrogen.

Research supports that estrogen affects stress response, emotional processes, and cognitive function.

In healthy women, estrogen may support brain functioning that optimizes the stress response, emotional processing, and cognitive function—preventing cycles of hypothalamic–pituitary–adrenal system dysregulation & emotional dysregulation from leading to depression, and cognitive decline.

In women with other vulnerability factors for depression, periods of estrogen fluctuation or reduction may present windows of increased risk for the effects of psychosocial stressors or other triggering events on memory and mood occurrence.

COVID-19 pandemic and women's mental health

- *Clinical Implications*
- Women who are pregnant, postpartum, miscarrying, or experiencing intimate partner violence are at especially high risk for developing mental health problems.
- Social support is a key protective factor. Syndemic of isolation, rising SU, financial and socio-emotional stress
- Parenting has been substantially more stressful during a pandemic. Offering specific parenting tips could improve mental health for parents/children and reduce the risk of domestic violence.
- For women at risk of intimate partner violence, maintaining up-to-date information about available hotlines, shelters and family courts could be lifesaving.
- Gender disparities may be accentuated, particularly for employed women or single parents, as women are disproportionately responsible for the bulk of domestic tasks, including childcare and eldercare.

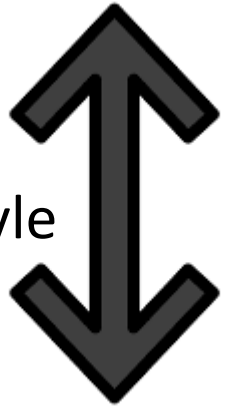
Racial/Ethnic Disparities and Women's Mental Health: Considerations for Providing Care with Cultural humility



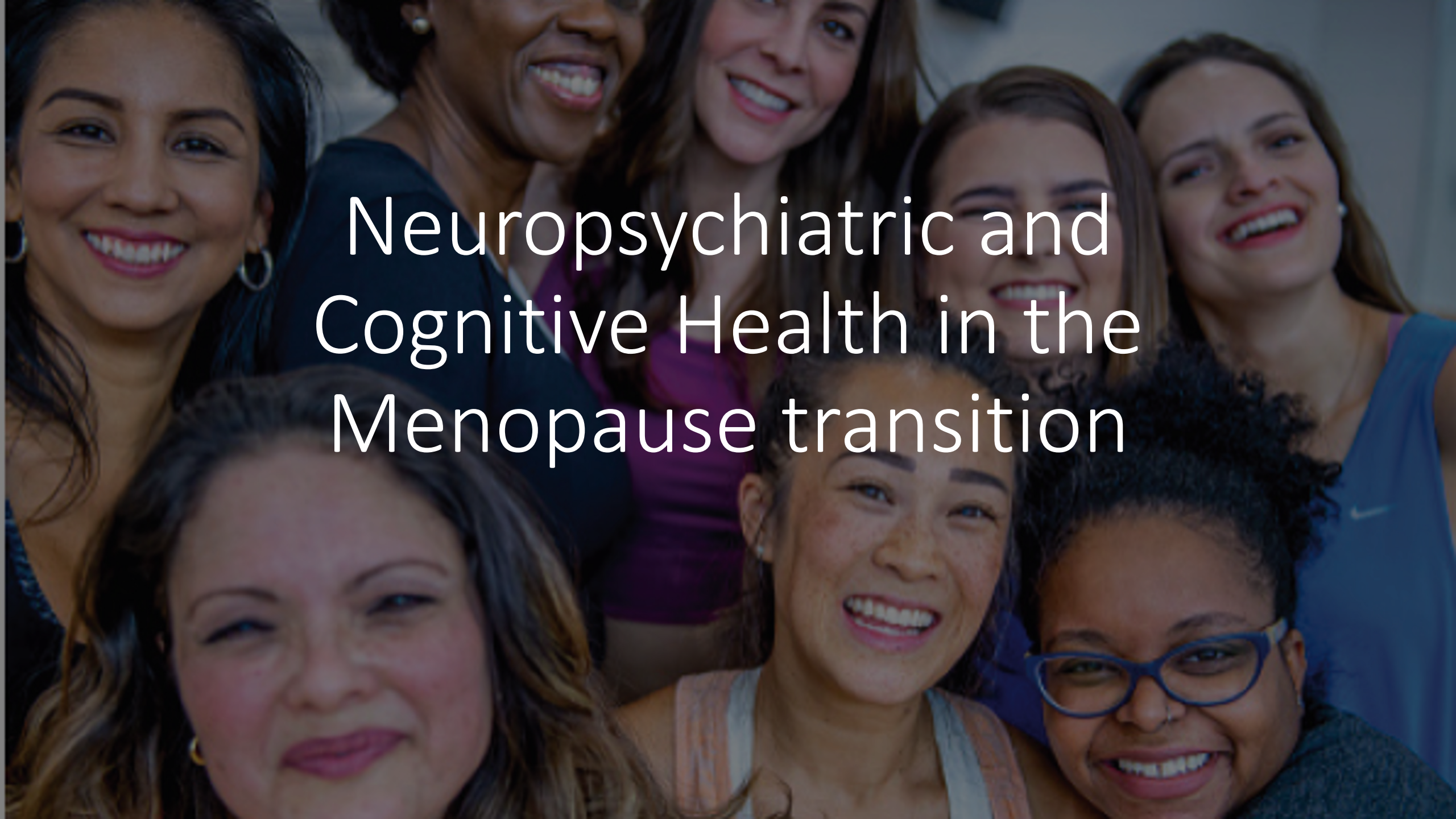
Ballone, N., & Richards, E. (2023). *Psychiatric Clinics*.

[Home](#) / [Current Opinion in Psychiatry](#), Volume 35, Number 3

Modifiable Lifestyle Factors and Mental Health



- Strong bidirectional interaction between mental health, cognitive health & lifestyle behaviors
- Negative thinking and negative emotions which are common manifestations
 - May lead individuals to do things that are not health promoting
- **Untreated symptoms of a mental health condition may lead women to:**
 - Skip meals or choose foods that are unhealthy for them which leads to higher body mass index & obesity, DM2, HLD
 - Use risky substances in an attempt to soothe themselves or alter energy levels
 - Interfere with or lower motivation for physical activity
 - Disturb sleep
 - Cause women to withdraw from family & friends
 - Interfere with coping with stress & influence adherence to treatment impacting outcome & mortality.



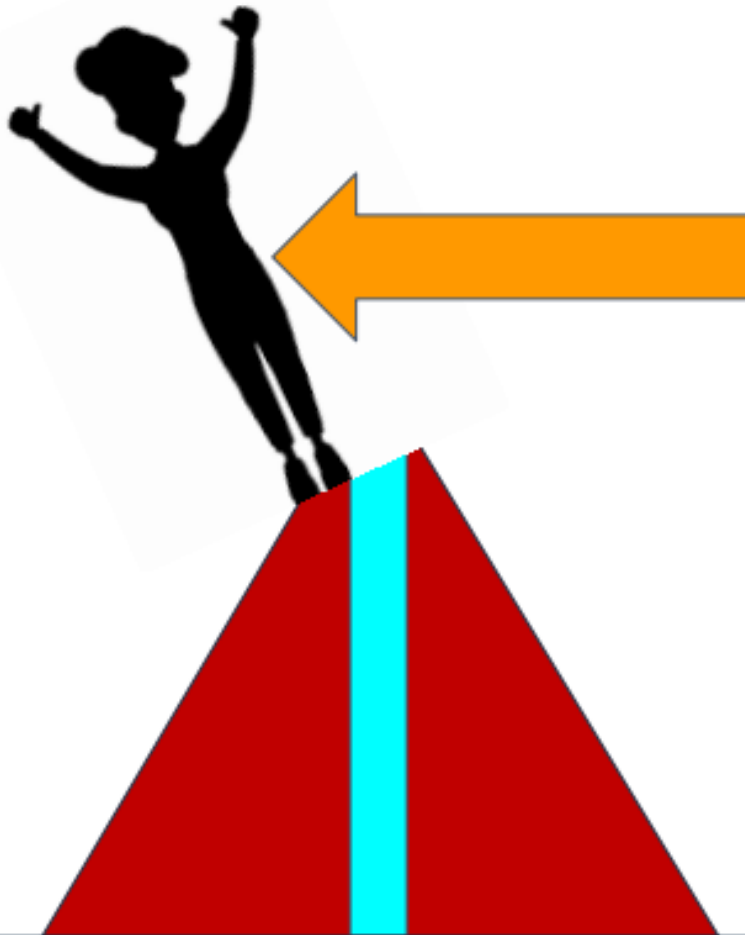
Neuropsychiatric and
Cognitive Health in the
Menopause transition

Menopause Basics

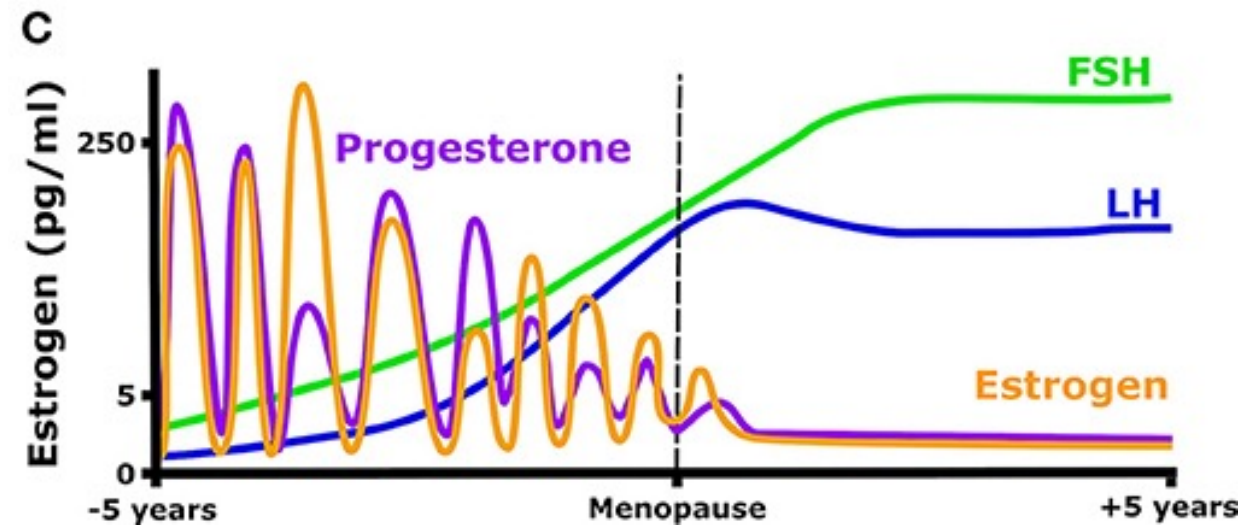
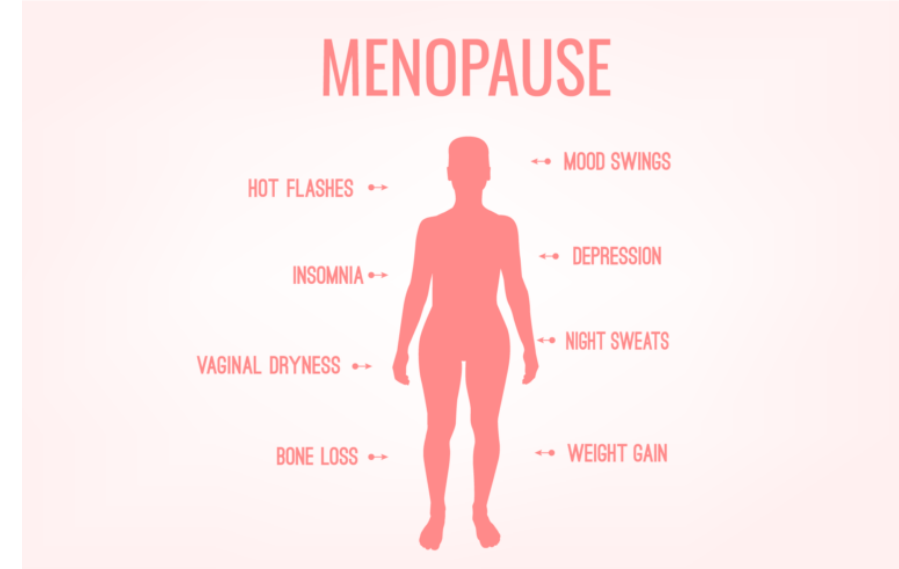
- Menopause is an **inevitable phase** in every woman's life as her reproductive years come to an end.
- It is defined as the time when a woman has gone without a period for **12 months in a row**.
- It occurs due to a **gradual decline** in reproductive hormones, estrogen and progesterone, because of natural aging.
- Menopause can also be induced through surgery, ovary removal, or certain medications.
- The average age of menopause is **51**.
- Perimenopause, which can last from 2 to 10 years, is when the **most intense menopause symptoms** occur, including irregular periods, hot flashes, and night sweats.
- A year after the last period, a woman is referred to as **postmenopausal**.
- Postmenopausal women have increased risk of dementia, heart disease and osteoporosis.

Risk Factors for Unwanted Stress Reaction

- Poor nutrition
- Unhealthy body composition
- Lack of physical fitness
- Inadequate sleep
- Lack of social support



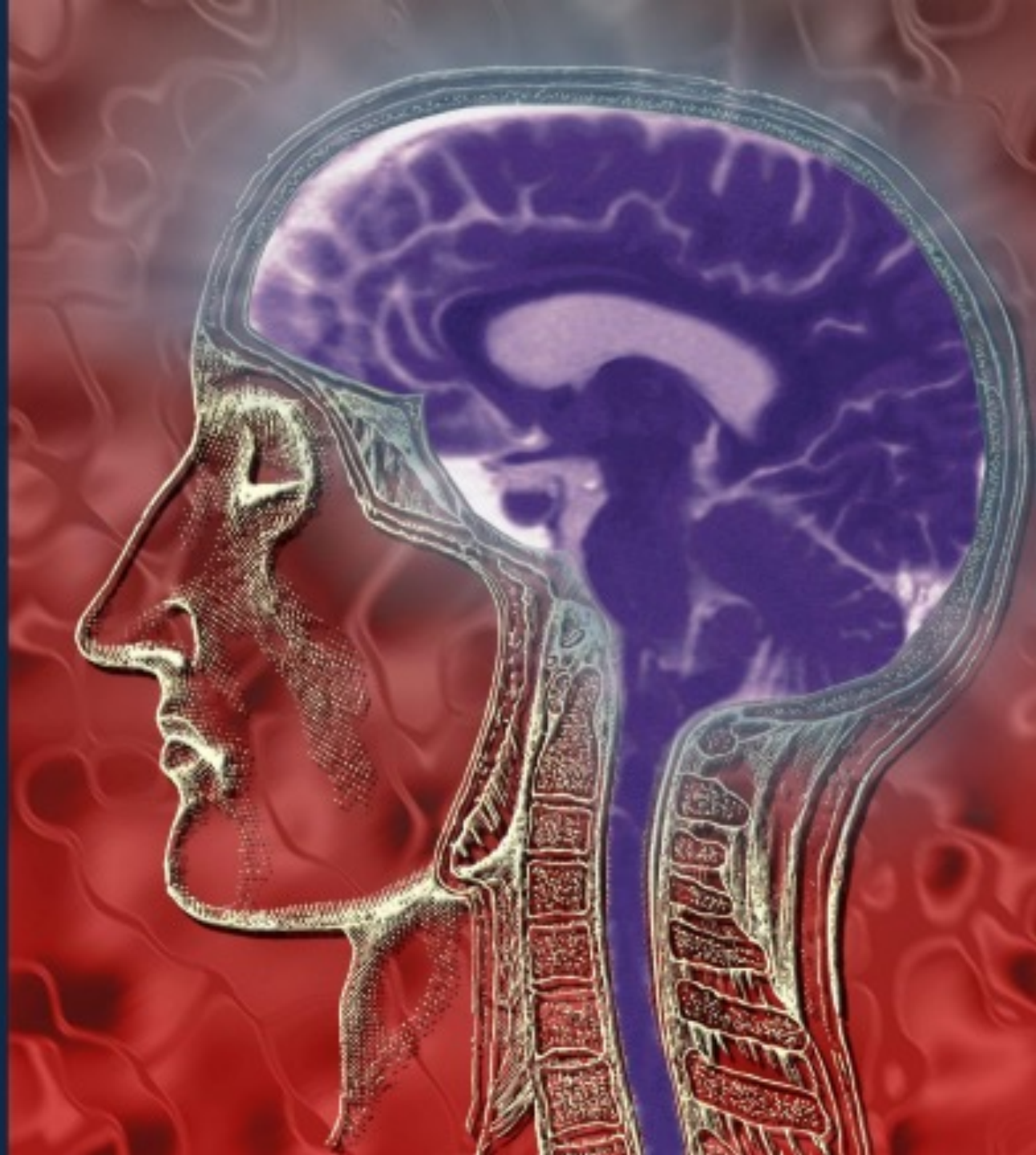
- Average age = 51
- Amyloid accumulation = 1-2 decades before symptoms
- Typical symptom onset of AD = mid-70s

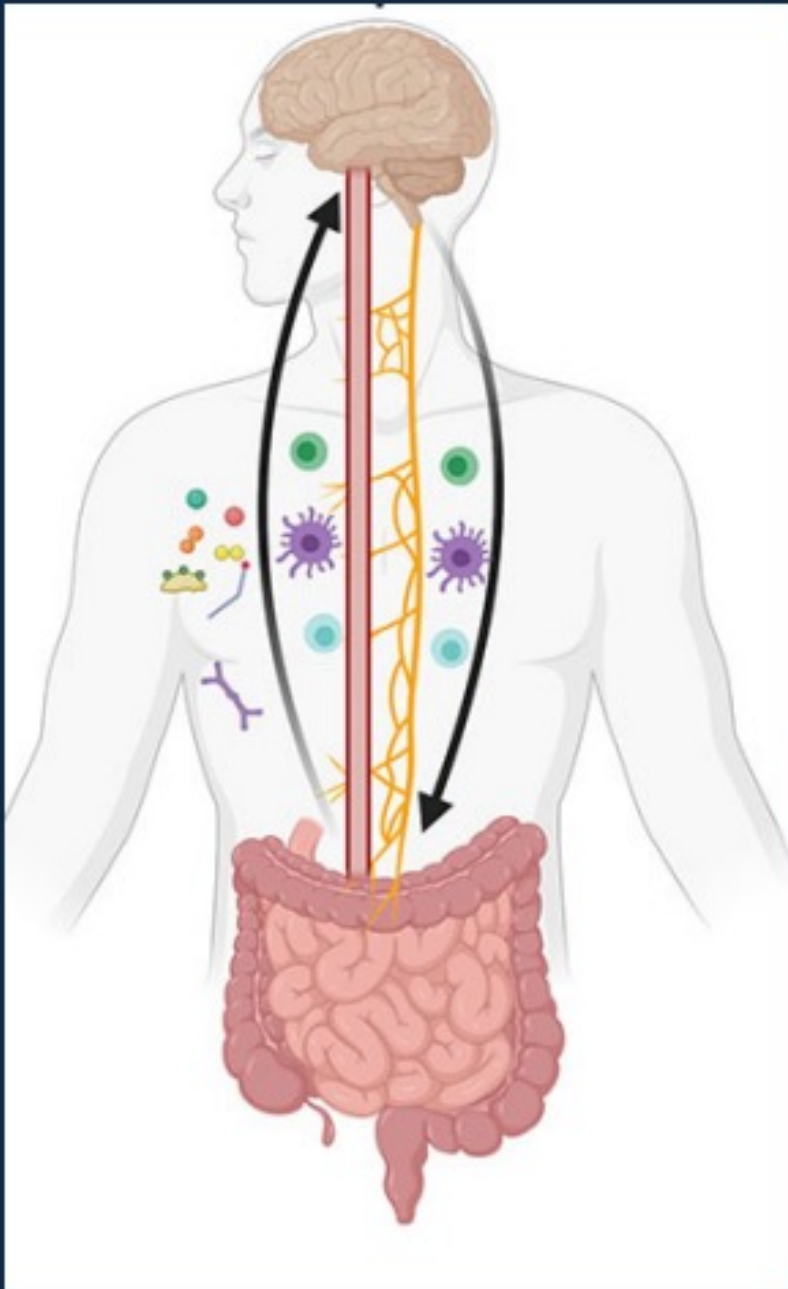


Decreased Estrogen = Increased Risk of

- Systemic inflammation
- Dysfunction of blood-brain barrier
- Brain vulnerability

Dion-Albert, L., et al. *Frontiers in Neuroendocrinology*, 2022.





Healthy Gut-Brain Axis

- Synapse formation
- Improved cognition
- Improved memory
- Improved mood

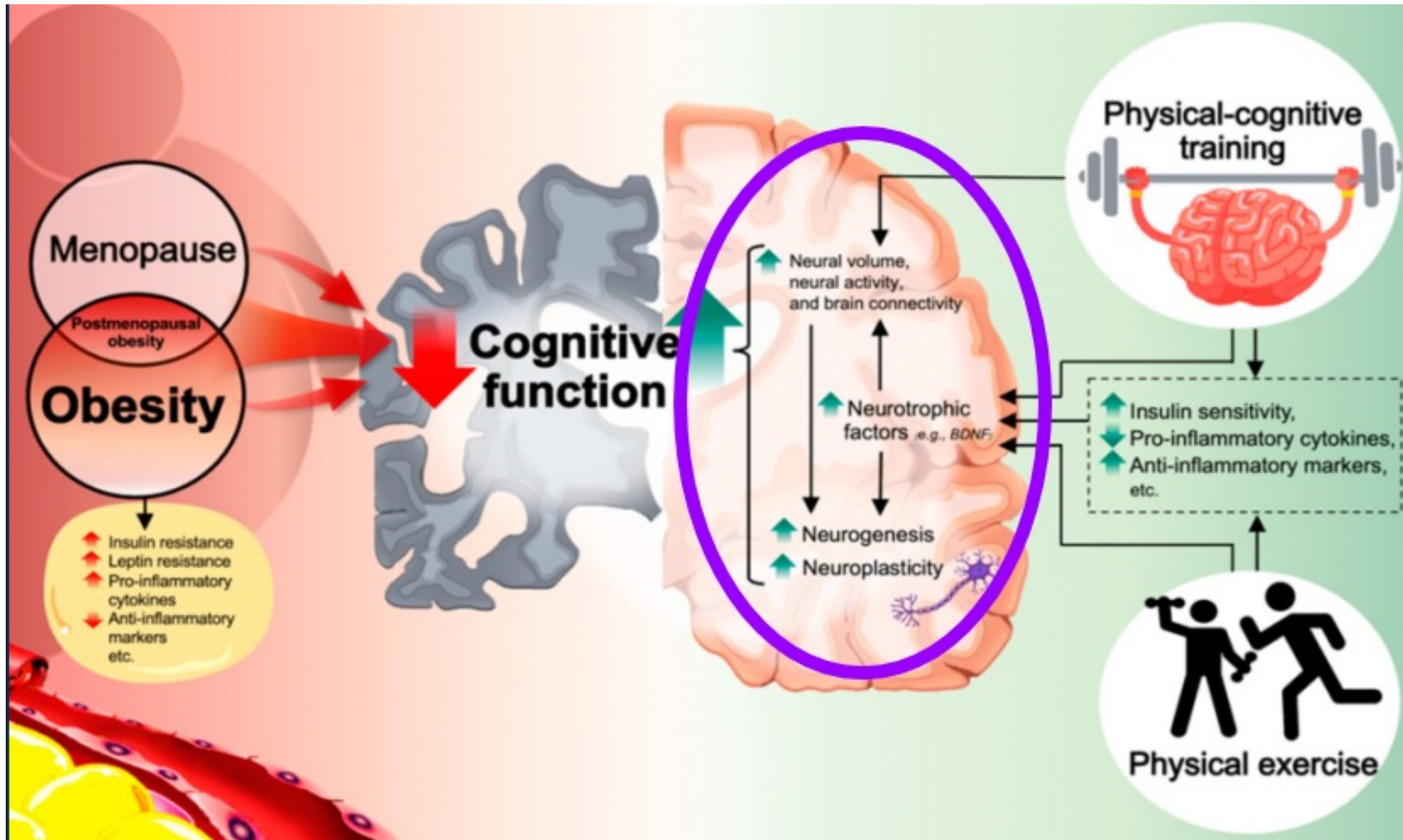
Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort Study

Huiping Li ¹, Shu Li ¹, Hongxi Yang ¹, Yuan Zhang ¹, Shunming Zhang ¹, Yue Ma ¹, Yabing Hou ¹, Xinyu Zhang ¹, Kaijun Niu ¹, Yan Borné ¹, Yaogang Wang ²

Affiliations + expand

PMID: 36219796 DOI: 10.1212/WNL.0000000000200871

Rutsch, A., et al. *Frontiers in Immunology*, 2020.



Keawtep, P., et al
 Intl
 Journal of Environm
 Research
 and
 Public
 Health.
 2022

A List of Menopause Symptoms

Physical symptoms

- Hair loss
- Weight gain
- Brittle nails
- Vaginal dryness
- Sleep disorders
- Dizziness
- Incontinence
- Allergies
- Breast pain
- Headaches
- Joint pain
- Itchy skin
- Irregular periods
- Irregular heartbeat
- Osteoporosis

Psychological symptoms

- Mood swings
- Fatigue
- Depression
- Anxiety
- Irritability
- Difficulty concentrating
- Memory lapses
- Loss of libido

Digestive symptoms

- Bloating
- Digestive problems

Vasomotor symptoms

- Changes in body odor
- Hot flashes
- Night sweats

Oral symptoms

- Burning tongue
- Gum problems

Nervous system symptoms

- Electric shock sensations
- Tingling extremities

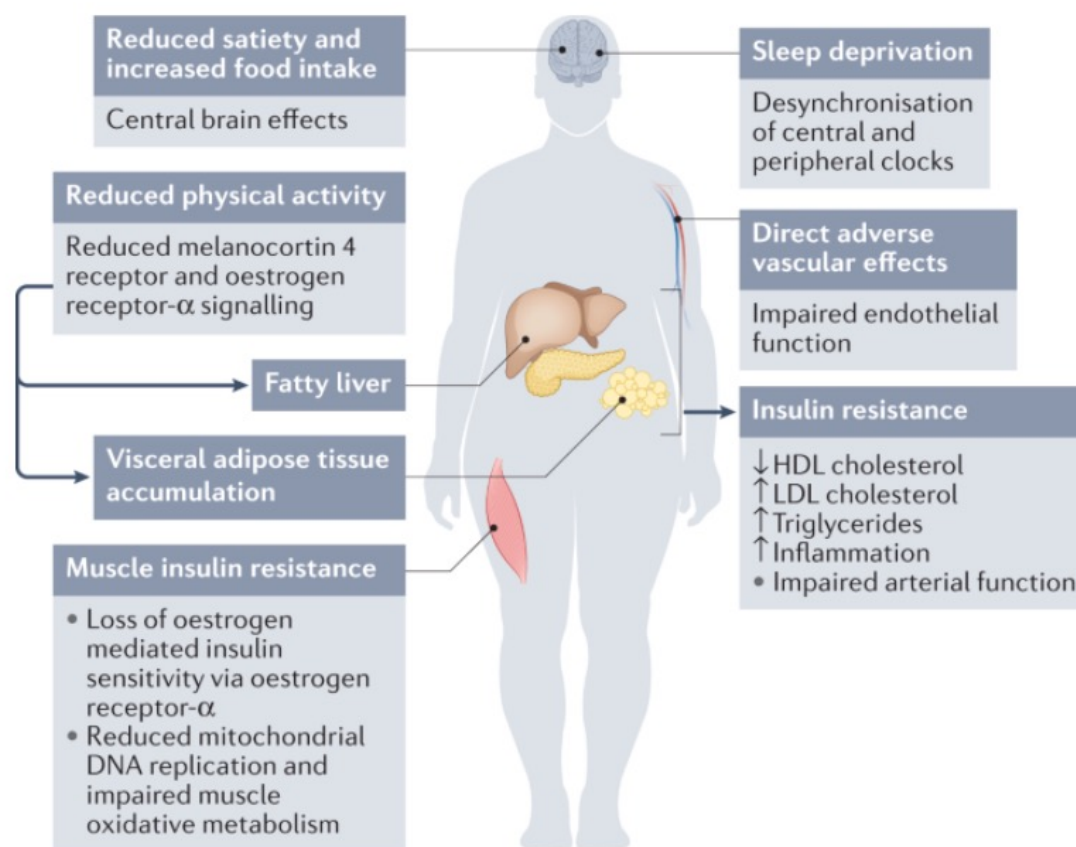


Treating menopause – MHT and beyond

[Susan R. Davis](#)  & [Rodney J. Baber](#)

[Nature Reviews Endocrinology](#) **18**, 490–502 (2022) | [Cite this article](#)

Fig. 2: Pathways by which oestrogen depletion at menopause adversely affects cardiometabolic health.





Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia

Matilde Nerattini^{1,2†}, Steven Jett^{1†}, Caroline Andy³, Caroline Carlton¹, Camila Zarate¹, Camila Boneu¹, Michael Battista¹, Silky Pahlajani^{1,4}, Susan Loeb-Zeitlin⁵, Yelena Havryulik⁵, Schantel Williams¹, Paul Christos³, Matthew Fink¹, Roberta Diaz Brinton⁶ and Lisa Mosconi^{1,2,4*}

OPEN ACCESS

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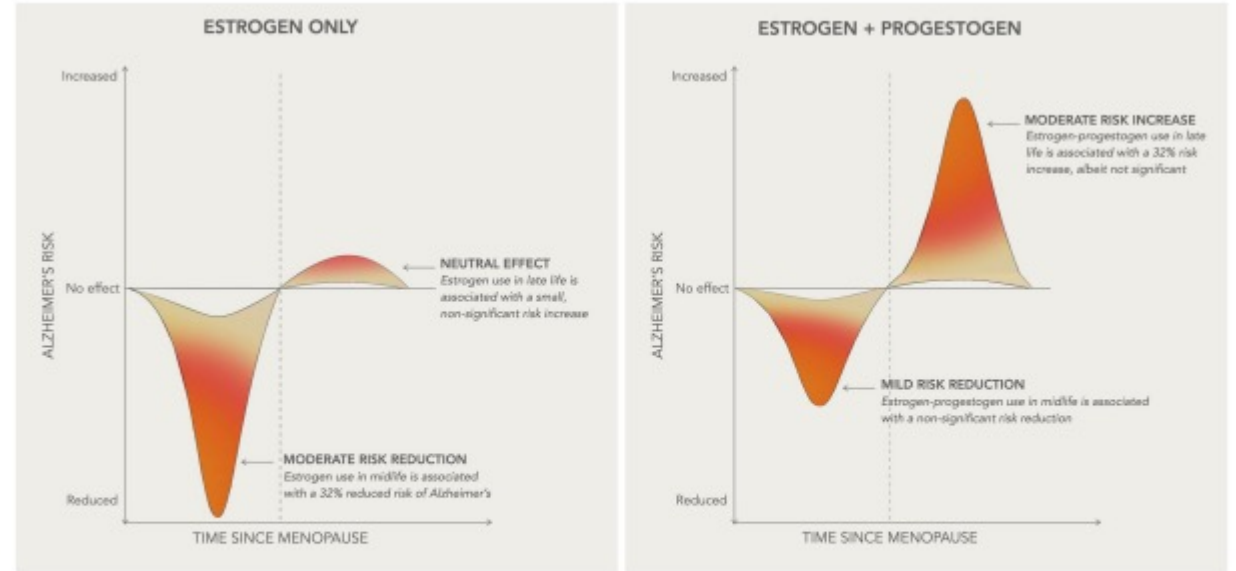


FIGURE 8

Summary of HT effects on AD risk Schematic overview of the main results of the study, illustrating how HT efficacy on AD risk varies based on initiation timing relative to menopause onset and HT formulation. In midlife, or more generally within 10 years of the final menstrual period, estrogen-only therapy is associated with a moderate decrease in AD risk, while estrogen-progestogen therapy is associated with a milder, non-significant risk reduction. In late-life, or more than 10 years after menopause, estrogen-only therapy presents neutral effects on AD risk, whereas estrogen-progestogen therapy is associated with a moderate risk increase, albeit non-significant.

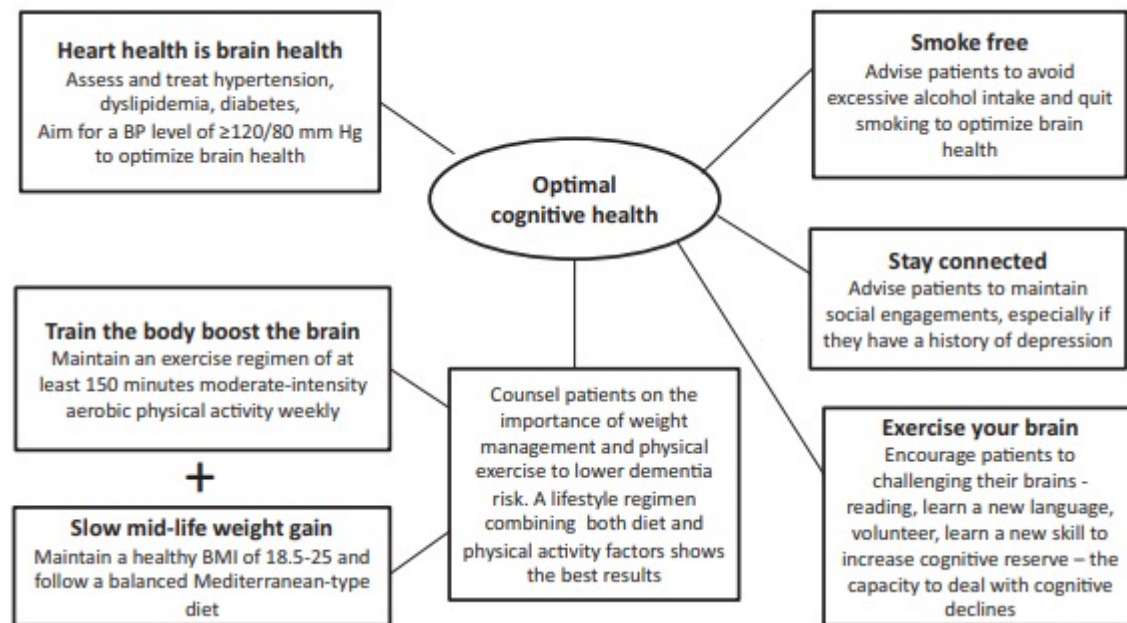
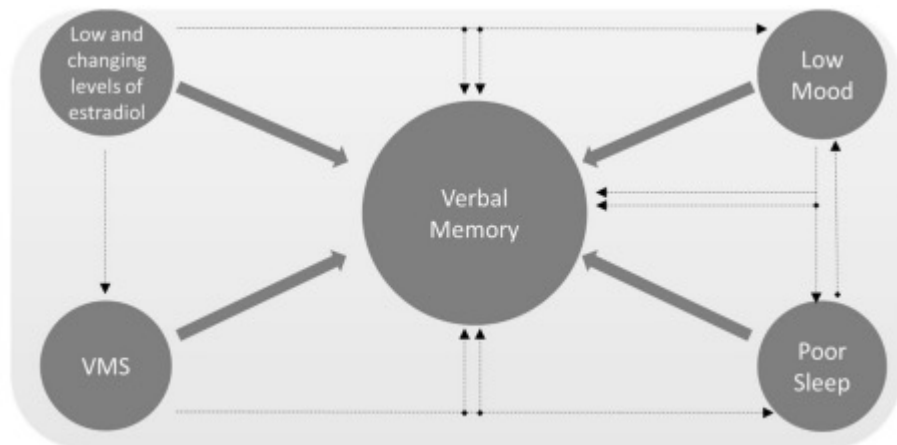


REVIEW

Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition


P. M. Maki^a and N. G. Jaff^b 

^aDepartment of Psychiatry, Psychology and OB/GYN, University of Illinois College of Medicine, Chicago, IL, USA; ^bDepartment of Chemi Pathology, National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa



Definition of menopause brain fog: the constellation of cognitive symptoms experienced by women around the menopause, which most frequently manifest in memory and attention difficulties and involve such symptoms as difficulty encoding and recalling words, names, stories or numbers, difficulty maintaining a train of thought, distractibility, forgetting intentions (reason for coming into a specific room), and difficulty switching between tasks.

RESEARCH ARTICLE


THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Microglial immunometabolism endophenotypes contribute to sex difference in Alzheimer's disease

Yuan Hou¹ | Jessica Z. K. Caldwell^{2,3} | Justin D. Lathia^{2,4} | James B. Leverenz⁵ | Andrew A. Pieper^{6,7,8,9,10,11} | Jeffrey Cummings¹² | Feixiong Cheng^{1,2}



Original article

“I can't be dealing with this brain fog”: A workplace focus group study investigating factors underpinning the menopausal experience for NHS staff

[Gemma Hobson](#)^a, [Nicola Dennis](#)^b  

Cognitive decline and dementia in women after menopause: Prevention strategies

[Bogdan Stefanowski](#)^{a 1}, [Marek Kucharski](#)^{b 1}, [Anna Szeliga](#)^c, [Milena Snopek](#)^a, [Anna Kostrzak](#)^c, [Roman Smolarczyk](#)^b, [Marzena Maciejewska-Jeske](#)^c, [Anna Duszewska](#)^d, [Olga Niwczyk](#)^c, [Sławomir Drozd](#)^e, [Monika Englert-Golon](#)^g, [Katarzyna Smolarczyk](#)^{f 2}  , [Blazej Meczekalski](#)^{c 2}  

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<https://doi.org/10.1016/j.maturitas.2022.10.012> 

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Table 2. Modifiable risk factors for dementia.

Modifiable risk factors for dementia

Low education
Hypertension
Hearing impairment
Smoking
Obesity
Depression
Physical inactivity
Diabetes
Low social contact
Excessive alcohol consumption
Traumatic brain injury
Air pollution

Source: Dementia prevention, intervention, and care 2020 report of the *Lancet* Commission [28].

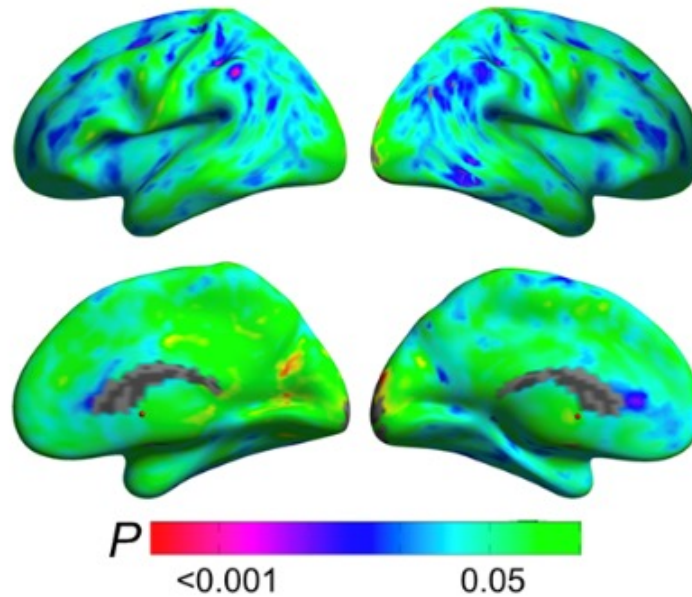
Menopause and Brain Function

Brain adjusts to a **New Normal**

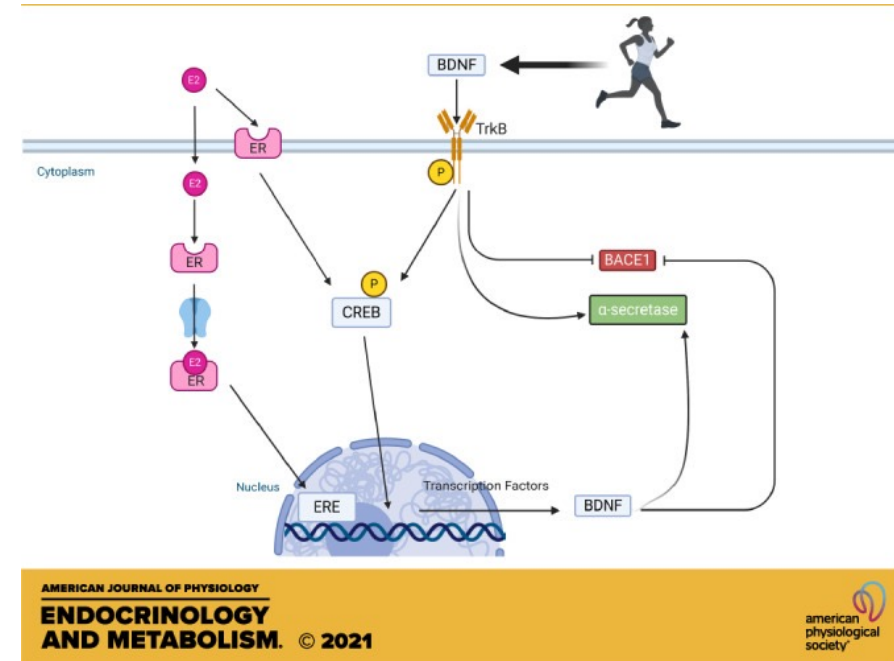
Adaptation in Areas subserving Higher-order Cognitive processes

Age, sex, ApoE4 all exert impact on cerebral metabolic and bioenergetic processes

Brain fog, multifactorial & **transient** in most cases



Brain regions showing metabolic adaptation during the transition to menopause. Courtesy of Dr. Lisa Mosconi.



AMERICAN JOURNAL OF PHYSIOLOGY
ENDOCRINOLOGY AND METABOLISM. © 2021



Mosconi, et al., *Scientific Reports* 2021

Bagit, et al., *Am J Physiol Endocrinol Metab* 2021

Maki, et al., *Climacteric* 2022 (shared decision making/counseling)

Curr Psychiatry Rep
2023 Oct;25(10):501-511.

doi: 10.1007/s11920-023-01447-3. Epub 2023 Sep 27.

Cognitive Problems in Perimenopause: A Review of Recent Evidence

[Christina A Metcalf](#)¹, [Korrina A Duffy](#)², [Chloe E Page](#)², [Andrew M Novick](#)²

MENO-BLUES

- Women are especially vulnerable to mood swings and depression in perimenopause, and following years. Women ages 45 - 55 are **four times more likely** to have depression than women who have not yet reached that stage in life.
- **Hormonal fluctuations** combined with stress, insomnia/VMS, or aging any one or a combination of these causes emotional distress that may result in mood swings, heightened anxiety and depression.
- **Signs of Major Depression**
- Nearly daily >2weeks
- Persistent sad, anxious, or “empty” mood
- Feelings of hopelessness or pessimism
- Irritability
- Feelings of guilt, worthlessness, or helplessness
- Loss of interest or pleasure in hobbies and activities
- Decreased energy or fatigue
- Moving or talking more slowly
- Feeling restless or having trouble sitting still
- Difficulty concentrating, remembering, or making decisions
- Difficulty sleeping, early morning awakening, or oversleeping
- Appetite and/or weight changes
- Thoughts of death or suicide or suicide attempts
- Aches or pains, headaches, cramps, or digestive problems without a clear physical cause and/or that do not ease even with treatment

GENDER

Socially-constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender diverse people.



SEX

Biological attributes of humans and animals, including physical features, chromosomes, gene expression, hormones and anatomy.



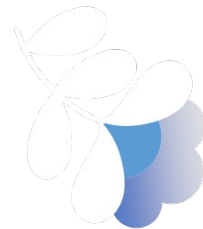
Canadian Institutes of Health Research.
Accessed August 11, 2021. <https://cihr-irsc.gc.ca>

Sex, Gender, and AD Risks



Disparities

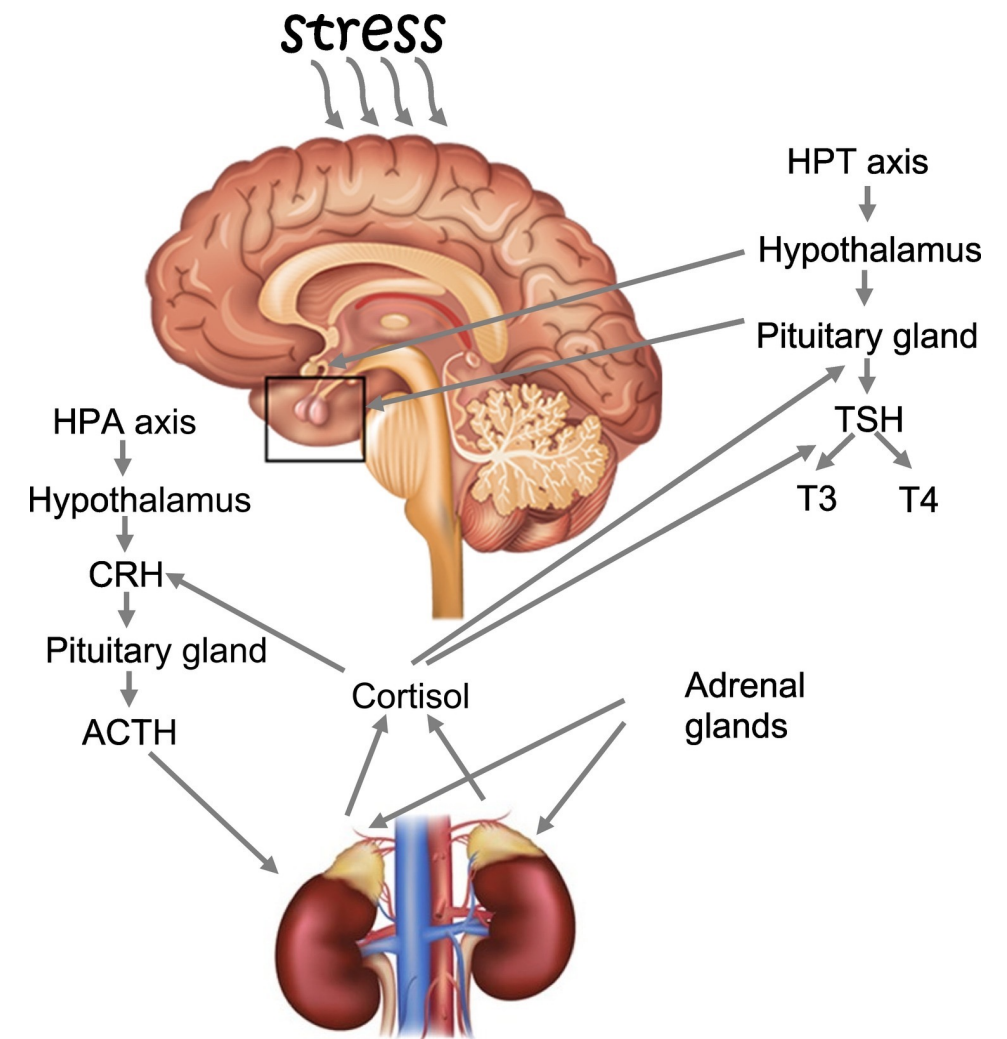
- 2/3 of Americans with AD are women ¹⁵
- 2/3 of dementia caregivers are also women¹⁵



Cortisol & Brain health

Cortisol

- Immediate and prolonged response differs by sex
- Poor memory
- Reduced plasticity
- Increased cell death in the hippocampus
- Risk for dementia and Alzheimer's disease



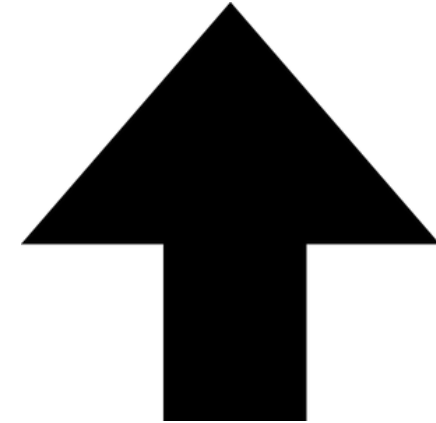
Trends in Endocrinology & Metabolism

Stress Response

Sympathetic Nervous System

“Fight, Flight or Freeze”

- Adrenalin
- Heart rate
- Blood pressure
- Breathing rate
- Muscle tension
- Memory/concentration difficulties

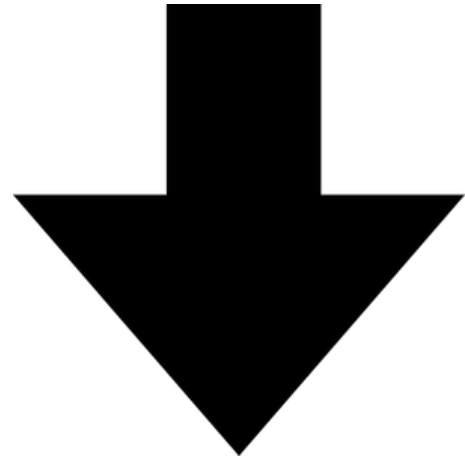


Relaxation Response

Parasympathetic

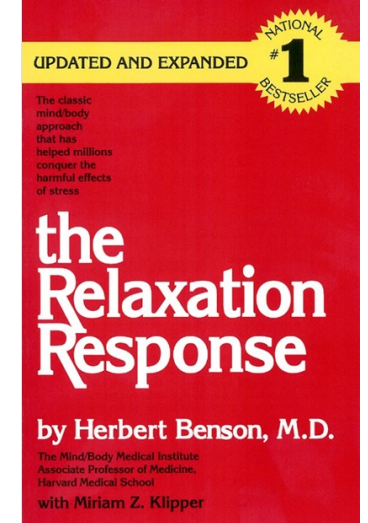
“Rest and Digest”

- Adrenalin
- Heart rate
- Blood pressure
- Breathing rate
- Muscle tension
- Memory/concentration difficulties



“The Relaxation Response is an inborn, anti-stress capacity”

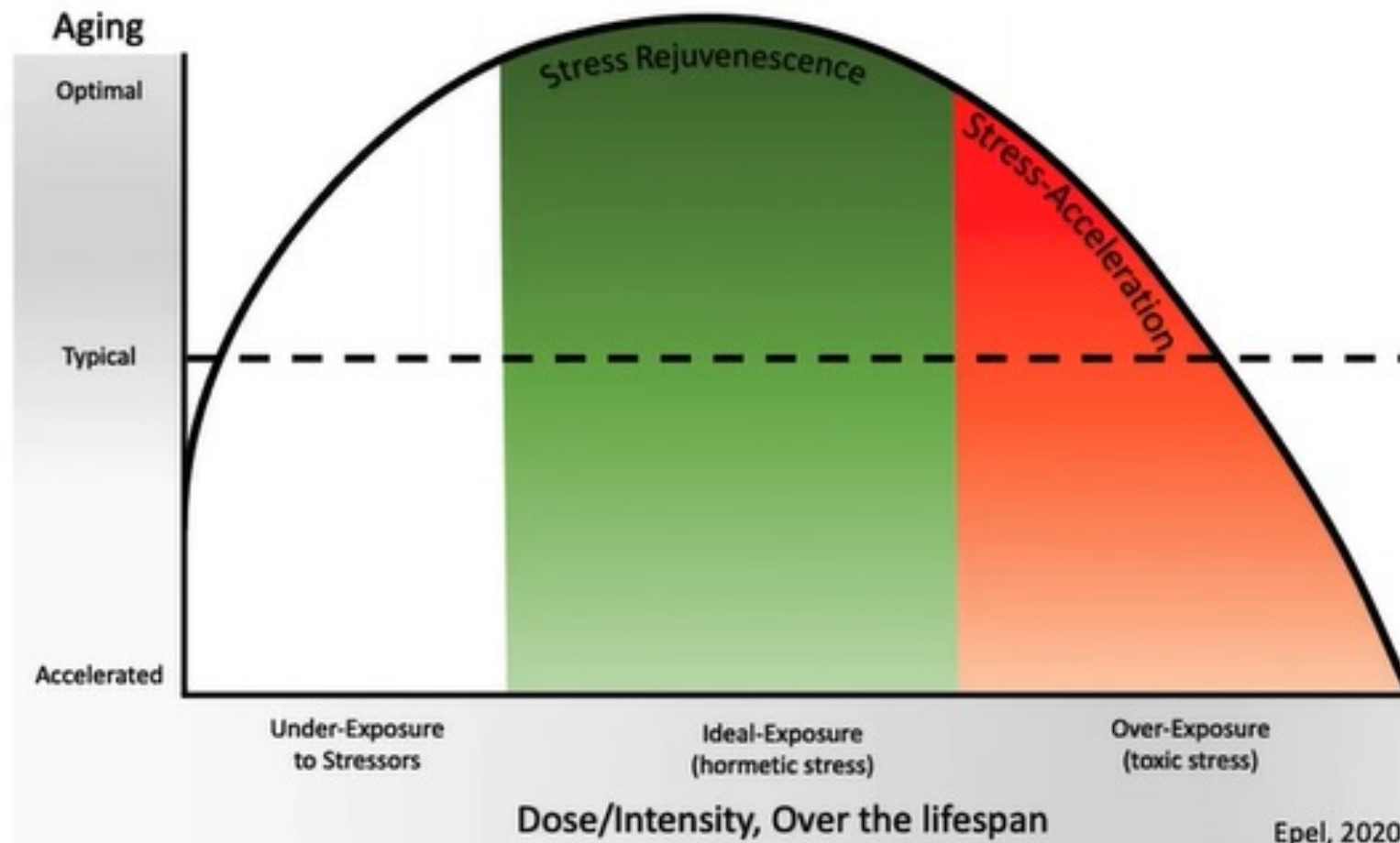
Herbert Benson, MD



Movement Break



Toxic vs Hormetic Stress & Aging



Benefits of Strength Training

- Lowers insulin more than any other type of exercise.
- Increases lean muscle mass.
- Decreases lymphedema in breast cancer patients.
- Increases strength and mobility after treatment.
- Improves quality of life.
- Lowers the risk of fractures.
- Lower risk of being placed in a nursing home.

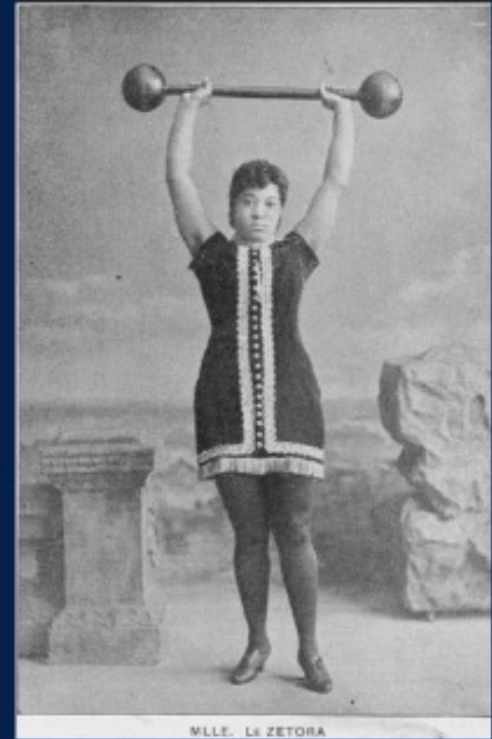
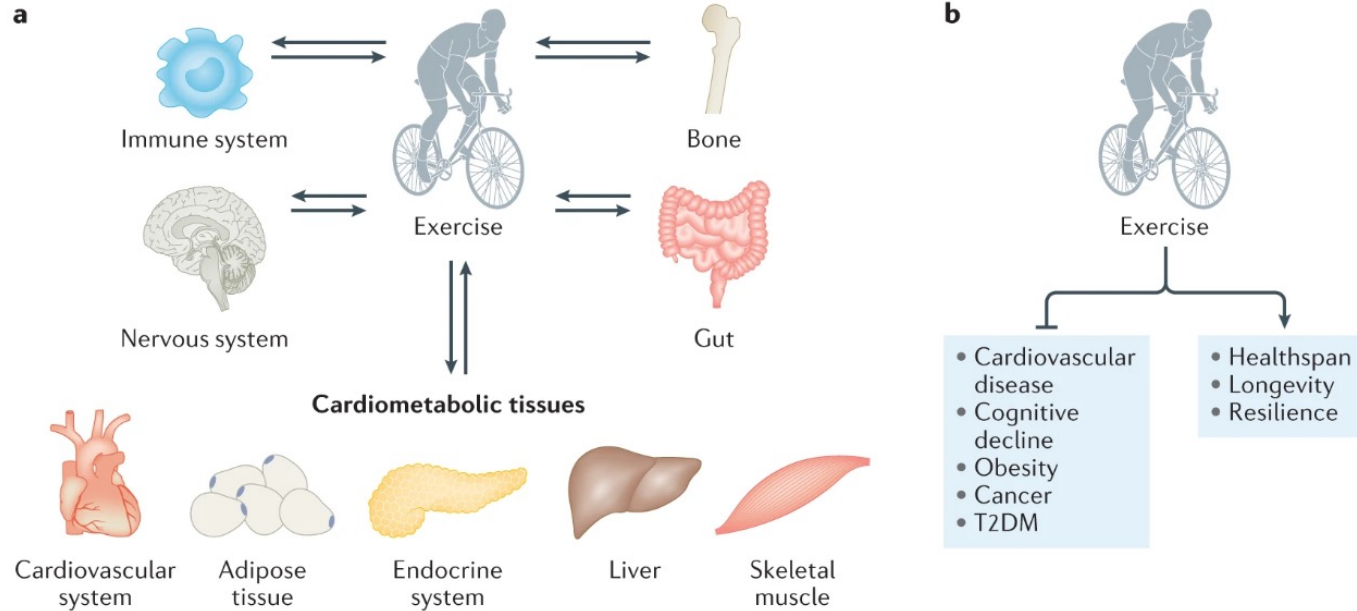
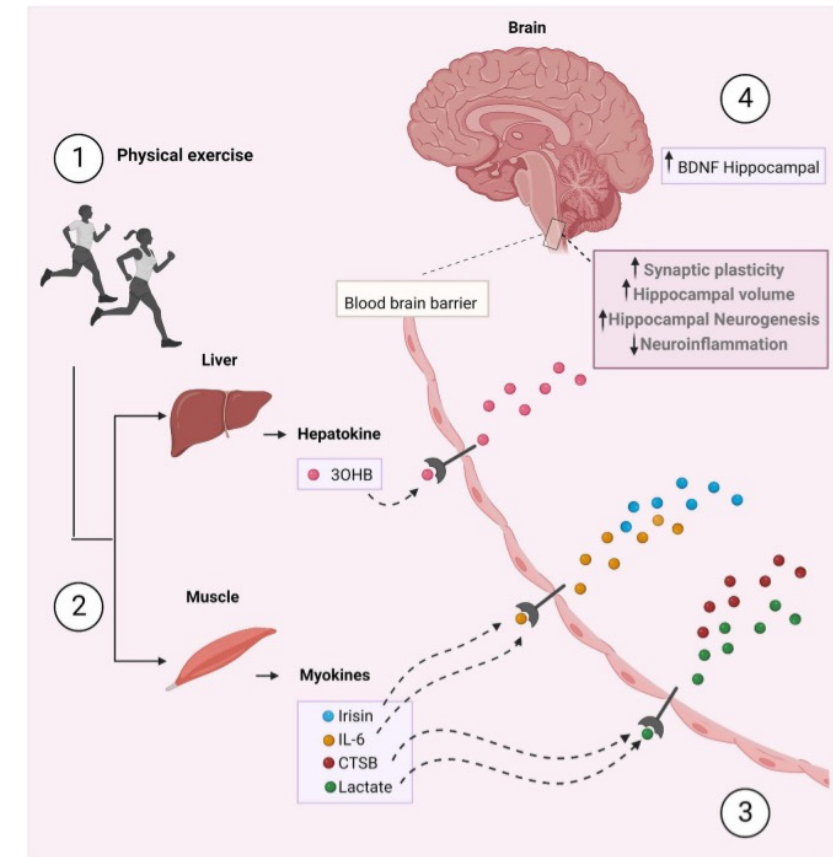


Fig. 1: The systemic effects of exercise.

From: [Exerkines in health, resilience and disease](#)



a | Organs and tissues that can serve as source of exerkines and that are directly affected by exercise. **b** | Exercise results in profound health benefits, including reductions in the presence or severity of certain diseases, as well as increases in healthspan, longevity and resilience. T2DM, type 2 diabetes mellitus.



Chow et al, *Nature Reviews Endocrinology* 2022

Review > [Front Aging Neurosci.](#) 2022 Aug 31;14:965190. doi: 10.3389/fnagi.2022.965190. eCollection 2022.

The emerging neuroprotective roles of exerkines in Alzheimer's disease

Tayna Rody¹, Julia A De Amorim¹, Fernanda G De Felice^{1 2 3 4}

Dementia Risk and Cardiovascular Fitness

- Midlife cardiovascular fitness associated with decreased dementia in women
- High compared to medium fitness: 88% difference in dementia risk (44 year f/u)
- Dose response relationship between fitness and dementia risk seen in several studies

Exercise Snacks

- Small strength training or aerobic exercises throughout the day:
- wall push ups, chair squats, a 5 minute walk
- Small amounts of strength training helps patients build confidence to do more.
- Exercise improves energy, motivation, and mood helping to get the person into a victorious cycle.



Let's Try Some Exercise Snacks!

- Chair March
- Overhead Hand Pumps
- Chest Punches
- Ankle Circles

Guidelines to work towards

Okay to start small and have these guidelines as the goal.

- **ACSM**

- **Cardiorespiratory Exercise:** 150+ min of moderate-intensity exercise per week.
- **Resistance Exercise:** 2-3 days/week, 2-4 sets of each exercise with 8-20 reps
- **Flexibility Exercise:** 2-3 days/week, hold stretches 10-30sec, repeat each stretch 2-4x accumulating 60sec/stretch
- **Neuromotor Exercise:** 20-30min/day, 2-3 days/week
 - -Balance, proprioception, agility

Treatments

Management of Menopausal Symptoms: A Review

Carolyn J Crandall ¹, Jaya M Mehta ^{2 3}, JoAnn E Manson ^{4 5}

Affiliations + expand

PMID: 36749328 DOI: [10.1001/jama.2022.24140](https://doi.org/10.1001/jama.2022.24140)

- MHT for those w/ VMS
- or GSM
- (in those **w/o** Estrogen dependent CA or CVD)
- CBT for depression, anxiety.
- Fezolinetant is a neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause. (approved in US in May 2023)
- Gabapentin, SSRI, venlafaxine- avoid paroxetine, as may worsen brain fog.

Stress

- Meditation
 - Lower blood cortisol and inflammation markers
 - Reduced self-reported stress
 - Lower BP
 - Improved concentration
 - More positive self-regard



eat plants
keep moving
sleep well
be present
stay calm
love people

- A 4 week app-based stress intervention showed improvement in wellbeing, self-compassion, loneliness & psychological distress with ~5 min/day in teachers, majority women, during early Covid-19 pandemic

<https://hminnovations.org/meditation-app>

- Health Coaching improves QoL and depression sx in post and peri-menopausal women



7
Days to
More Joy
and Ease

The
STRESS
Prescription

Promoting Resilience

- Ask about stress
- Have community resources ready
- Exercise
- Meditation
- Destigmatize
- Support resources

<https://www.nhs.uk/conditions/menopause/>

<https://www.nia.nih.gov/health/menopause/what-menopause>

Shared Medical Appointments

Shared Medical Appointment Benefits

Patients

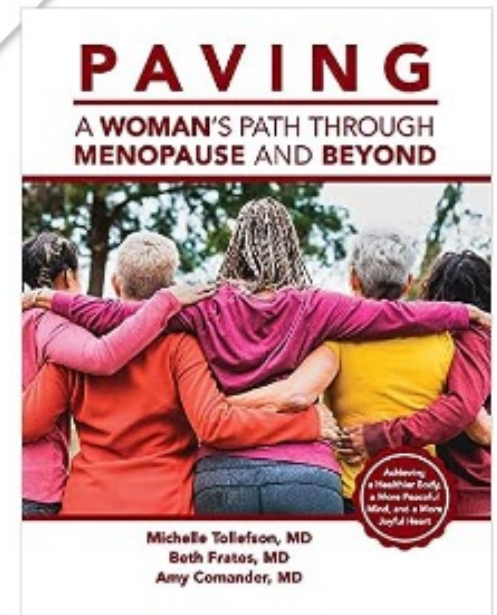
- Access, quality
- Additional resources
- Education
- Health management skills
- Patient satisfaction

Providers

- Provider/team satisfaction
- Improve access
- Leverage resources
- High quality of care

Enterprise

- Cost-effective, high quality
- Decrease cost/episode
- Decrease hospital readmissions
- Resource integration



Cognitive Checklist/Plan

Labs: B12 + TSH, routine studies

Screen questions: EtOH, SUD + depression

Meds: Benzos, Ambien, oxybutynin, benadryl

Other: Sleep apnea + hearing loss/cataracts/sensory challenges/hormones

Imaging: MRI with hippocampal volumes as appropriate



Brain Health Rx

Medications: deprescribe/avoid sedating and anticholinergic.

Contributing Conditions: Sleep apnea, hearing loss, poor vision, depression, frailty.

Exercise: >150 min/week aerobic & strength training twice/week.

Stress Resilience/Mindfulness-try HealthyMinds
<https://hminnovations.org/meditation-app>

Cognitive & Social engagement

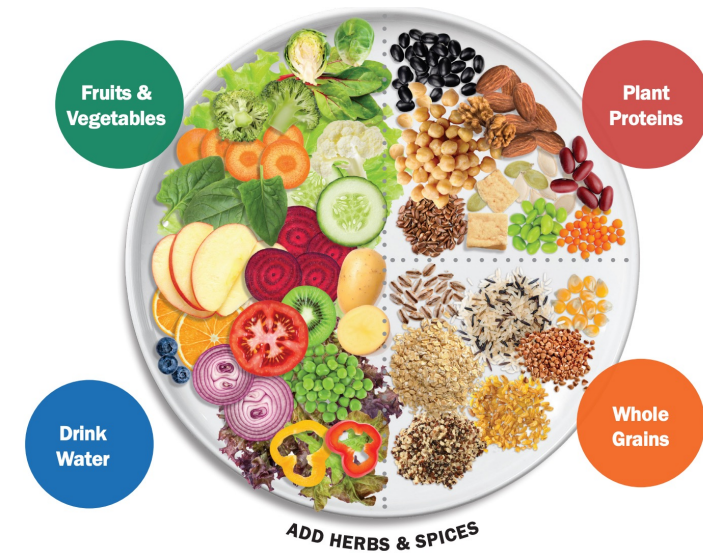
Nutrition Mediterranean/ MIND/ WFPF

Alcohol: Limiting 0-1 drinks, no smoking/drugs

Blood pressure SBP <120

Lipids LDL <70 if prior TIA or stroke

Blood Sugar A1c < 5.6 w/o DM, <7 w/ DM2



Menopause, MHT and Brain Health

KEY POINTS

- Women's risks for poor brain aging include those similar to men's as well as unique risks.
- Interventions to support healthy brain aging in women must consider risks for disease as well as the broader context of women's health.
- Women may need more stringent memory and medical screening, lifestyle medicine support, and education about menopause as a risk factor for dementia.
- Social determinants of health contribute to medical and lifestyle risks formerly conceptualized as based on race and ethnicity.
- Data on some interventions, such as menopausal hormone therapy, remains incomplete, though important advances have been made.

- ApoE is the most common genetic risk for LOAD.
- Having ApoE4 increases risk 4-10 times (1 v 2copies) higher in white women compared to men age 65-75. Also shifts risk curve 5-10 years earlier
- Association differs based on ancestry w/decreasing effect: East Asian, non-Hispanic White, non-Hispanic Black, and Hispanic individuals doi:10.1001/jamaneurol.2023.3599
- ?Window of opportunity:
- MHT shows clear cognitive benefit in women with early (<44) menopause
- WHI (initiated after menopause >65) demonstrated negative outcomes for CVD, AD, all cause mort.
- MHT is not currently recommended for AD prevention or cognition preservation in women of menopausal age
- Personalized approach/window of opportunity including: age, menopausal stage, comorbidities & symptoms
- Little known about Gender-affirming Hormone Therapy and long-term cognitive health (area of needed research)

Benefit



Risk

Women's Brain Health Program

The Women's Brain Health Program serves to help women experiencing mid-life cognitive changes or family history of AD.

- Launched August 2022
- Co-located with Center for Healthy Aging at Cherry Hill



Community Education & Impact

- Teaching Kitchen Collaborative, Innovator Member <https://teachingkitchens.org/>
- AARTH <https://www.aarth.org/>
- National conference presentations
- HKHL <https://www.gaplesinstitute.org/>