

Laboratory of BEHAVIOURAL Neuroendocrinology
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 mental health • health

Association between menopause age and estradiol-based hormone therapy with cognitive performance in cognitively normal women in the CLSA

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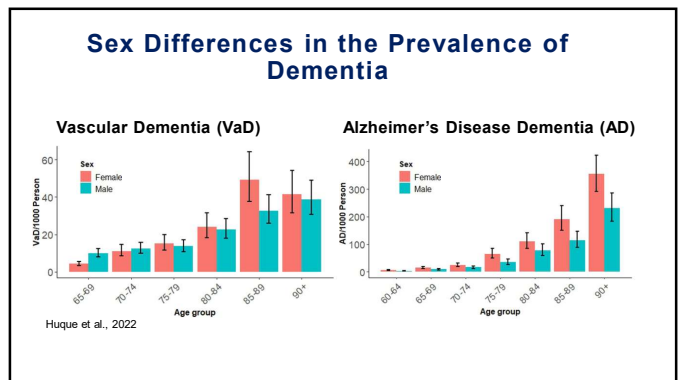
Laura Gravelins, Ph.D.
 Postdoctoral Researcher, CAMH

Women's health is more than comparing to men's health

....and it's not just bikini medicine....

Objectives

- Understand the menopause transition as a key inflection point for brain health, offering important opportunities for support and intervention
- Evaluate discrepancies in findings on menopausal hormone therapy and brain health, accounting for therapy type and individual factors (e.g., genotype, reproductive history) to inform precision medicine



Sex vs Gender, Stronger Together

SEX
 Nature

GENDER
 Nurture

Sex (biological factors): Genetics (e.g., chromosomes, autosomal genes, epigenetic modifications), Anatomy (e.g., reproductive organs), Physiology (e.g., sex hormones, immune response).

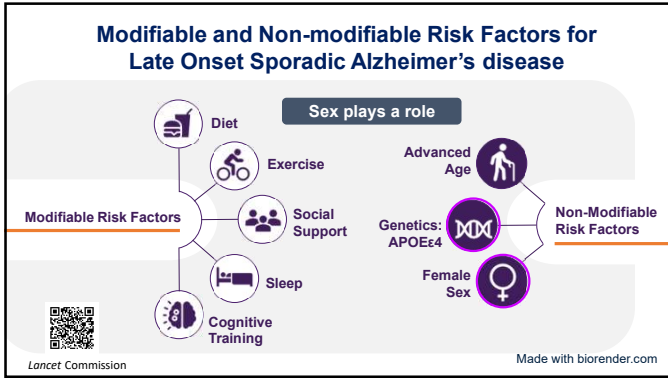
Gender (sociocultural factors): Sex role, gender expression, Gender identities, Gender dysphoria, Gendered networks and relationships (e.g., caregiver roles), Gendered social environments (e.g., institutionalized gender, health care system), Gendered identity (e.g., self-identity, activity).

Alzheimer's Disease

2/3 AD Patients

Brain atrophy

Maximum
 Minimum
 Time



Menopause is an inflection point of aging

Menopause accelerates biological aging

Menopausa E. Giamberini, Ana I. Lopez-Abrego, Oscar Chavar, Diana B. Hernandez, Andriana B. Sanguino, Leigh Thompson, Sofiane Benabdel, Elise Lattier, Julian F. Mawson, Amin Qureshi, Cynthia D. L. Kimm, Steven Kail, Andrew Wrony, Andrew T. Richardson, Wendy Richardson, Brian K. Ritz, Steven Kleiner, Theodoros S. Kouris, and Steve Harvey

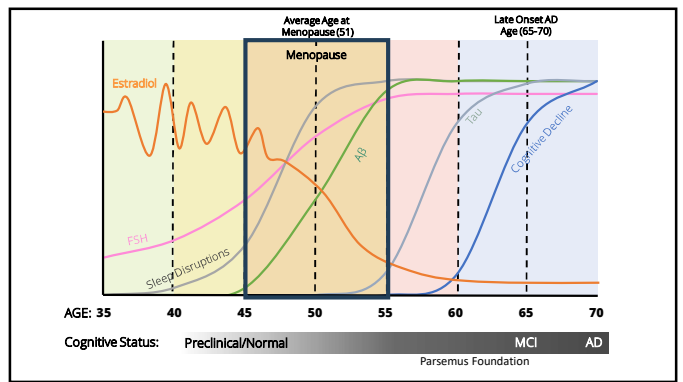
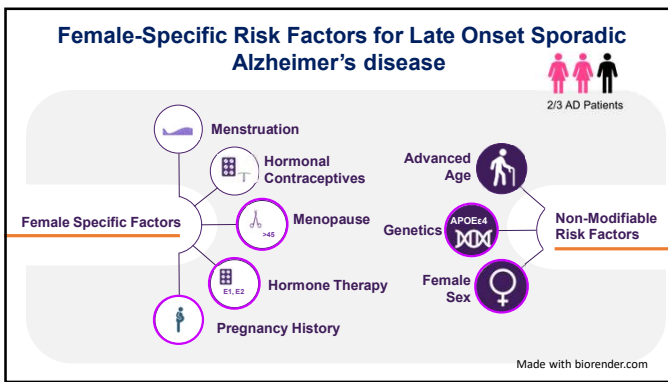
Journal of Reproductive Immunology | Volume 156, August 2022, 103466

Perimenopause as a neurological transition state

Rodrigo C. Britton, Jia Yao, Hai Yin, Wendy J. Mack and Enrique Galea

Menopause is an inflection point of age-related immune changes in women

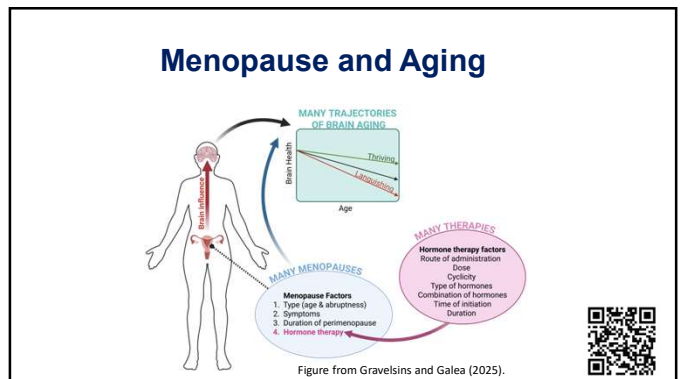
Amelina T. Jeehan-Khan, Jessica Koshkin, Spring H. Lee, J. A. B.

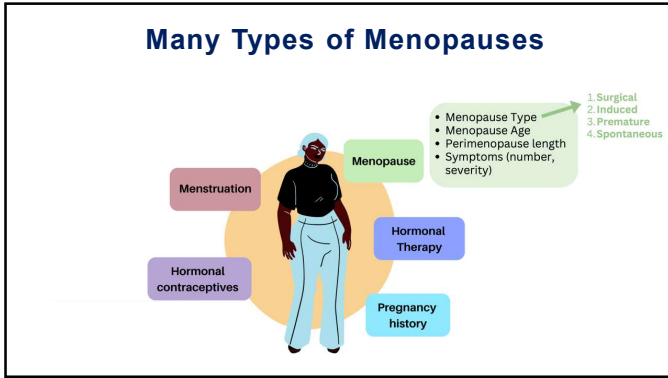


What is menopause?

- 12 months after your last period
- Perimenopause and Postmenopause
- Perimenopause can last 2-10 years

Symptoms of Menopausal Transition – average duration >7 years!





How does the age of menopause affect different cognition domains in females?

Cognitive Tests

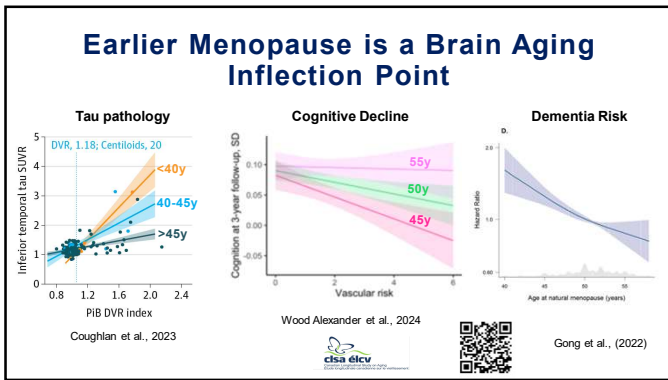
- Episodic Memory Composite
 - Event Based Prospective Memory Test
 - Time Based Prospective Memory Test
- Executive Functions Composite
 - Mental Alternation Test
 - Controlled Oral Word Association Test
 - Animal Fluency Test

Age at Menopause

csa elvc
Canadian Longitudinal Study on Aging
Cutsa longitudinal coordinates for its well-being

Puri, Gravelins, Wood Alexander, Rabin, Murphy, Galea. 2025. Neurology

Created in biorender



Canadian Longitudinal Study of Aging

csa elvc
Canadian Longitudinal Study on Aging
Cutsa longitudinal coordinates for its well-being

Comprehensive dataset contains 30,097 individuals

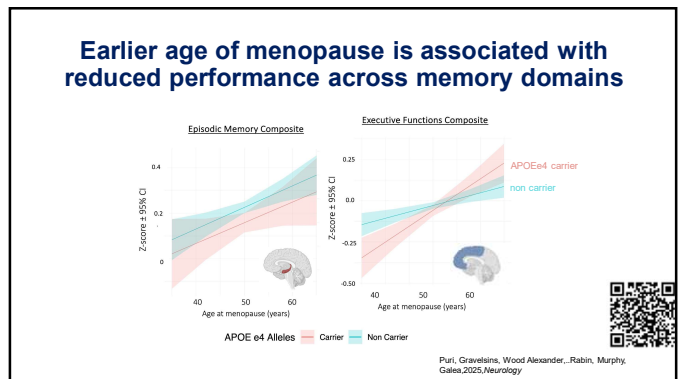
Performed a variety of cognitive tests, physical assessments, medical histories

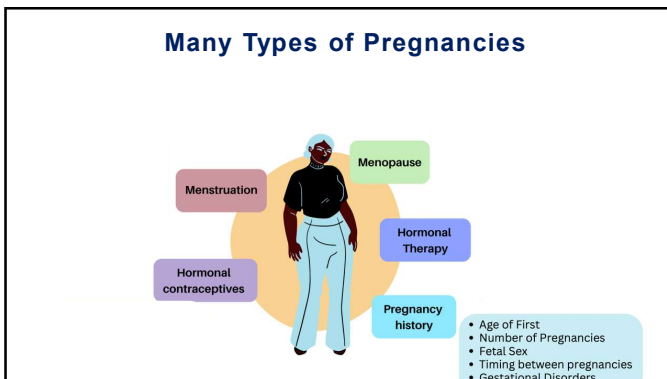
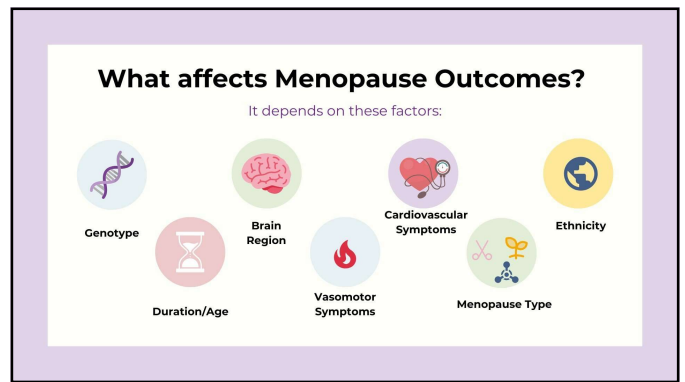
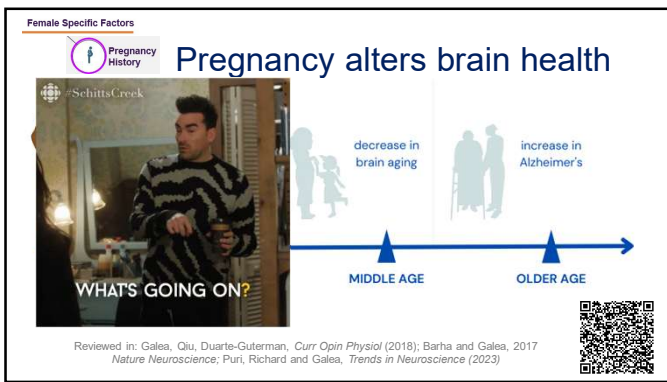
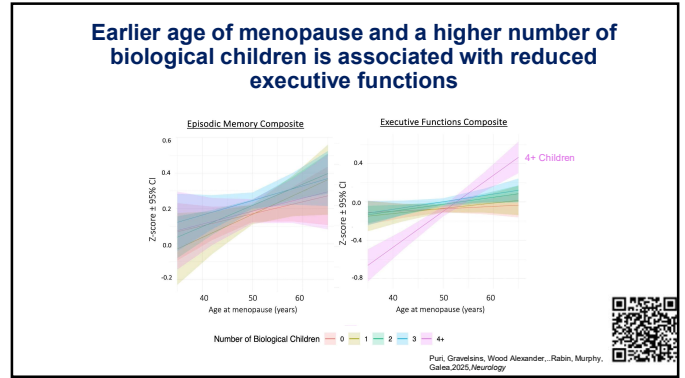
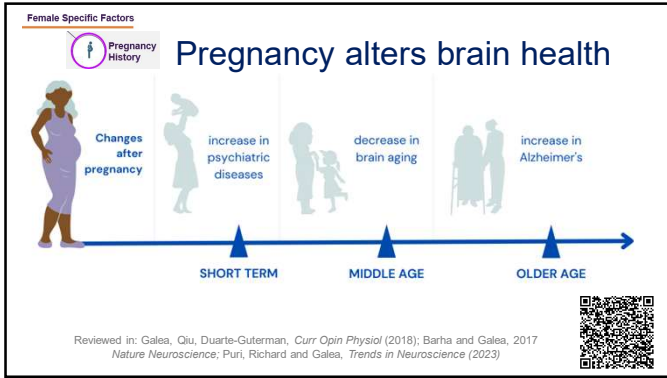
Variable	Mean (SD)
Age	60.50 (10.25)
Years of Education	14.95 (2.56)
Body Mass Index	27.55 (5.87)
Age of Menopause	50.50 (4.25)
APOEε4 Allele - Non Carrier(n)	4703
Carrier(n)	1587
Missing(n)	961

Flowchart showing participant selection: N = 35,097 CLSA Comprehensive Cohort participants, N = 14,777 female participants, N = 3 report impregnated, N = 15,139 participants that report no impregnated, N = 4 AAs for all cognitive tests, N = 15,313 participants with scores for all tests from cognitive tests, N = 3,220 diagnosed with depression, N = 12,123 participants without diagnosed depression, N = 12,063 participants without diagnosed AD, N = 3,185 didn't take cognitive tests in English, N = 30,096 participants that took the cognitive tests in English, N = 384 menopausal age < 39 or > 65, N = 30,582 participants that reported menopausal between age 39 and 65, N = 28,097 women in 30 years old or > 30 years post-menopausal, N = 30,295 female participants in the sample that were analyzed.

Is menopause linked to impaired cognition?

YES	NO	MAYBE?
<p>Menopause</p> <p>Cognition in perimenopause: the effect of transition stage</p> <p>Walker, Alkassab, F. (2021), Walker, F. (2021), Walker, F. (2021)</p>	<p>eLife</p> <p>Menopause, Brain Anatomy, Cognition and Alzheimer's Disease</p> <p>Wood Alexander et al. (2024)</p>	<p>Neurology</p> <p>Associations Between Age at Menopause, Vascular Risk, and 3-Year Cognitive Change in the Canadian Longitudinal Study on Aging</p> <p>Wood Alexander et al. (2024)</p>





Menopause Symptoms are Varied

- 20-60 symptoms
- Highly variable! (regular periods, irregular periods)
- Vaginal changes (dry, wet)
- Dry eyes!
- Tinnitus
- Painful Intercourse

scientific reports

OPEN Clustering of > 145,000 symptom logs reveals distinct pre, peri, and menopausal phenotypes

Table 1. Typical menopausal symptoms and their prevalence in middle women

Symptom	Prevalence (%)
Hot flashes and/or night sweats	36 - 67
Sleep problems	40 - 60
Mood symptoms	33 - 78
Weight gain	40 - 70
Muscle and/or joint pain	48 - 72
Palpitation	44 - 50
Headache	32 - 71
Memory impairment	41 - 64
Gastrointestinal symptoms	25 - 30
Sexual dysfunction	20 - 30

Data from references 1, 10, 11, 100, 105

Baker et al., (2018)

Loss of Estrogens: How could it cause so many symptoms? ERs everywhere

Figure from Gravelsins and Galea (2025). Modified from Rocca et al., (2018)

Does Menopausal Hormone Therapy Influence Cognition?

Reduced Risk	Increased Risk	No association
<p>Association between menopausal hormone neurodegenerative diseases: Implications for hormone therapy</p> <p><i>"HT was associated with reduced risk of all NDDs, including AD and dementia..."</i></p>	<p>Menopausal hormone therapy and dementia: nationwide, nested case-control study</p> <p><i>"Menopausal hormone therapy was positively associated with development of all cause dementia and Alzheimer's disease..."</i></p>	<p>Use of menopausal hormone therapy and risk of dementia: nested case-controlled studies using QResearch and CPRD databases</p> <p><i>"...no increased risks of developing dementia overall."</i></p>

Hot flashes and night sweats (vasomotor symptoms) reduce brain health

Maki et al., (2008) Crockford et al., (2025) Thurston et al., (2016, 2023)

Many Hormone Therapies

- Type
- Route of Administration
- Age of initiation related to Menopause
- Dose
- Duration
- Cyclic vs continuous

What reduces Vasomotor Symptoms?

Approved NK3-Receptor Antagonist for Vasomotor Symptoms

Ye et al., (2022)

Figure 2. Adjusted mean number of vasomotor symptoms per day, by study group.

Newton et al., (2006)

Menopausal hormone therapy is the most effective treatment for vasomotor symptoms

ACOG The Menopause Society

Menopausal Hormone Therapy: Why not as widely prescribed? Misinterpretations and bad study design

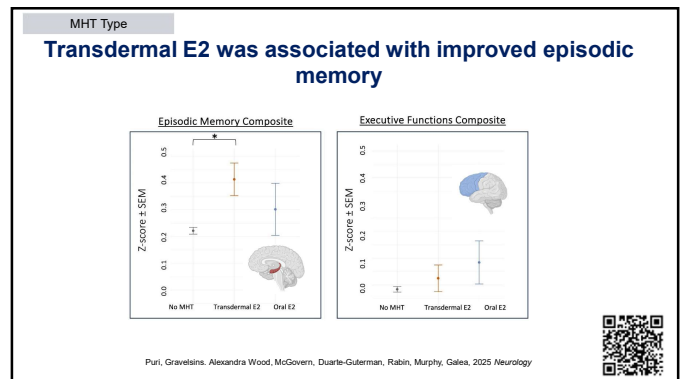
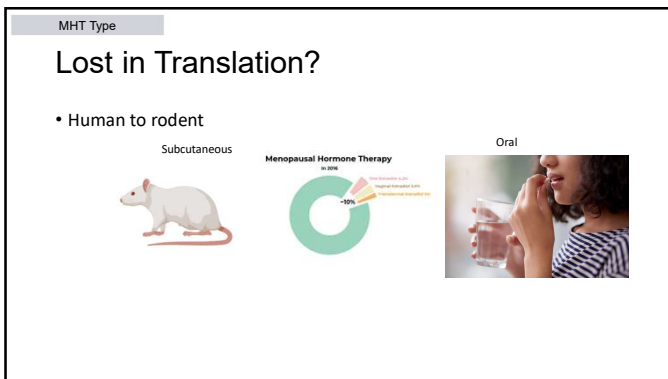
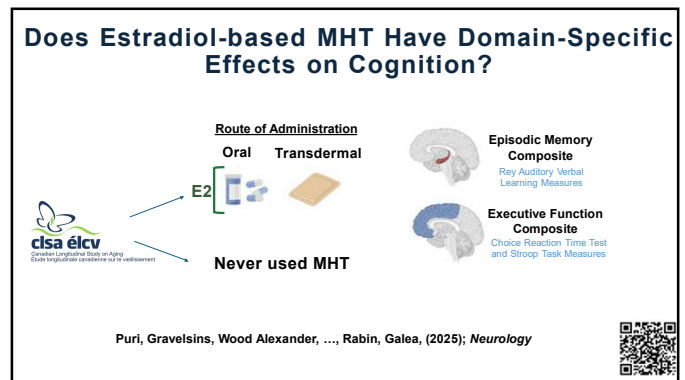
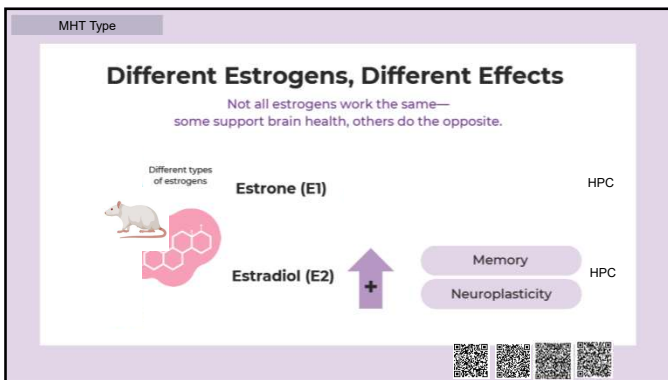
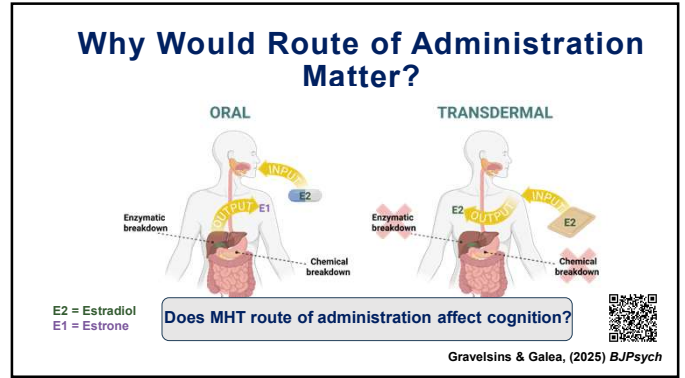
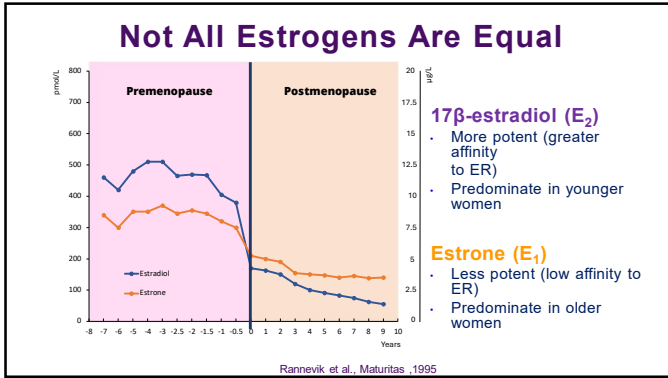
60% reduction in prescription of MHT

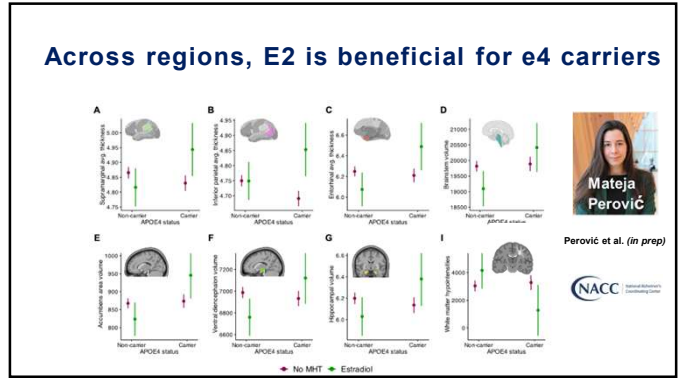
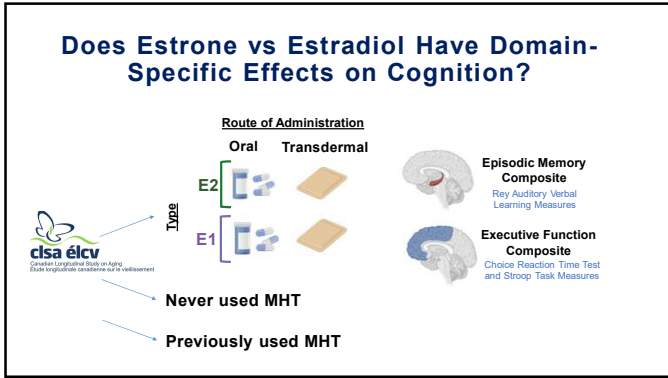
Women's Health Initiative Study

Criticisms

- Critical Window
- Healthy Cell Bias
- MHT Type

Legend: Premarin (50% estrone (E1) + 3% estradiol (E2))

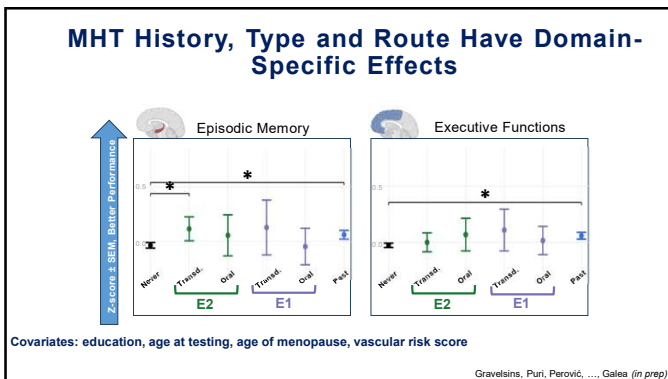
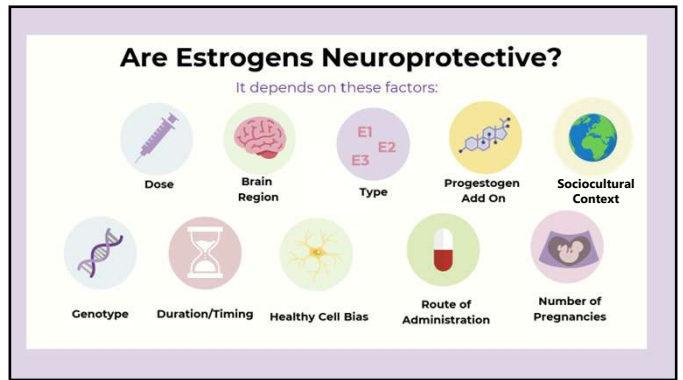




CLSA MHT Groups

Variable	None (N=4218)	E2 Transdermal (N=228)	E2 Oral (N=76)	E1 Transdermal (N=48)	E1 Oral (N=100)	Past Use (N=1823)	Overall
Age (years)	63.6 ± 9.2	62.4 ± 7.9	62.7 ± 8.3	65.6 ± 7.6	63.3 ± 9.0	68.4 ± 7.7	64.9 ± 9.0
Education (years)	14.8 ± 2.6	15.5 ± 2.6 ^a	15.3 ± 2.6	15.6 ± 2.5	15.1 ± 2.8	14.6 ± 2.5	14.8 ± 2.6
Vascular Risk Score	0.3 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.2
Age at Menopause	50.5 ± 4.3	50.8 ± 4.1	49.2 ± 4.9	50.6 ± 4.2	48.0 ± 4.9	49.5 ± 5.0	50.2 ± 4.5
Age at MHT Initiation	NA	53.1 ± 5.6	50.5 ± 5.2 ^{b,c}	53.9 ± 6.1	48.8 ± 5.2 ^{b,c}	50.2 ± 5.5	50.5 ± 5.6
Time Since Menopause	13.1 ± 10.1	11.5 ± 8.8	13.4 ± 8.9	14.9 ± 8.9	15.3 ± 10.2	18.9 ± 8.7	14.7 ± 10.0
# Biological Children	1.9 ± 1.4	1.8 ± 1.2	1.6 ± 1.3	1.7 ± 1.2	1.8 ± 1.2	2.0 ± 1.3	1.9 ± 1.3
MHT Duration	NA	6.7 ± 7.3	11.6 ± 8.8	6.3 ± 5.7	13.1 ± 9.9	5.6 ± 5.7	6.3 ± 6.5
POC, n (%)	250 (5.9%)	8 (3.5%)	0 (0.0%)	0 (0.0%)	5 (5.0%)	66 (3.6%)	329 (5.1%)
Income ≥ \$50,000, n (%)	2694 (69.5%)	170 (80.6%)	58 (77.3%)	36 (81.8%)	70 (74.5%)	1080 (66.1%)	4108 (69.2%)

^a vs Never, *p* < 0.05 ^c vs E1 transdermal, *p* < 0.05
^b vs E2 transdermal, *p* < 0.05 ^d vs E2 oral, *p* < 0.05
^e vs E1 oral, *p* < 0.05



Interpreting Null Effects of Estradiol on Cognition in Randomized Trials

KEEPS-Cogs
Gleason et al., (2015)

ELITE-Cogs
Henderson et al., (2016)

Yaffe et al., (2006)

Conclusions
The KEEPS-Cogs findings suggest that for recently postmenopausal women, **MHT did not affect cognition** as hypothesized. However, beneficial mood effects with small to medium ESs were noted with 4 y of o-CEE, but not with 4 y of t-E2. The generalizability of these findings is limited to recently postmenopausal women with low cardiovascular risk profiles.

Conclusions:
Estradiol initiated within 6 years of menopause does not affect verbal memory, executive functions, or global cognition differently than therapy begun 10+ years after menopause. **Estradiol neither benefits nor harms these cognitive abilities** regardless of time since menopause.


Conclusion Postmenopausal treatment with ultra-low-dose unopposed **transdermal estradiol for 2 years had no effect on change in cognitive function** or in health-related quality of life over 2 years of treatment.

MENO WARS
Fiona Clark

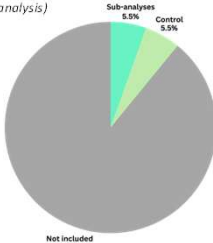
Contextualizing RCTs

Review of 55 MHT randomized control studies (ongoing analysis)

Only 5.5% include APOE4 as predictor



Mateja Perović




Sub-analyses 5.5%
Control 5.5%
Not included 89.3%

Perović et al. (in prep)

We need to make sure women are heard

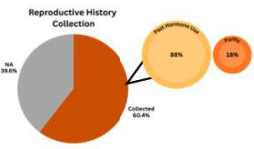
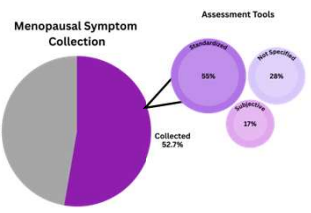
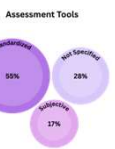

Self-Censorship and Fear of Dismissal

- 58% of women reported downplaying their health concerns
- 77% carefully consider which symptoms are worth mentioning
- 55% worry about not being heard when discussing their health with their doctor
- 51% delay seeking care because they have other responsibilities
- 39% put off seeking healthcare because they are too busy




WOMEN'S HEALTH SURVEY SUMMARY | OCTOBER 2025

Review of 55 MHT randomized control studies reveals lack of reproductive variable reporting (ongoing analysis)

Mateja Perović

Are your menopausal symptoms bothering you?




VIEWPOINT - Volume 13, Issue 1, P10-14, January 2025 [Download Full Issue](#)

Is it time to revisit the recommendations for initiation of menopausal hormone therapy?


Sasha Taylor, MBBS* · Prof Susan R Davis, MBBS, PhD [ORCID](#)

"Estrogen is the most effective treatment available to relieve bothersome symptoms of menopause." Casper 2025, UpToDate

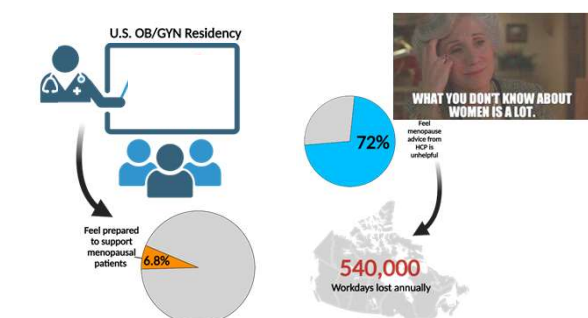


Self-Reported Reasons for MHT Reflect Diverse Menopausal Symptoms

Gravelsins, Perović, ..., Galea (in prep)



The impact of insufficient menopause education



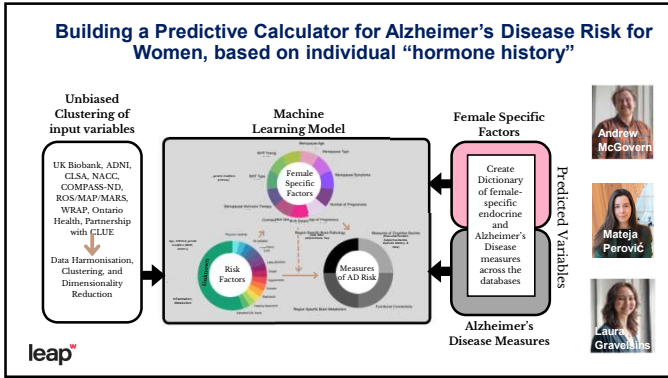
U.S. OB/GYN Residency

72% Feel menopause advice from HCP is unhelpful

6.8% Feel prepared to support menopausal patients

540,000 Workdays lost annually

WHAT YOU DON'T KNOW ABOUT WOMEN IS A LOT.

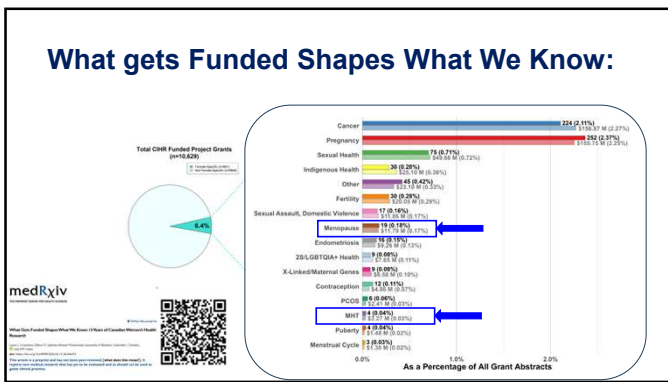


Conclusions

- Menopause is an important inflection point for Aging
- Embrace complexity: Precision Medicine (not one size fits all): Heterogeneity matters (HT type, menopause type, pregnancy type)
- Study Women+!

BE CURIOUS, NOT JUDGMENTAL

camh womenmind, CIHR IRSC, WOMEN'S HEALTH RESEARCH CLUSTER



Acknowledgements

Current and some past members of the Galea Lab:

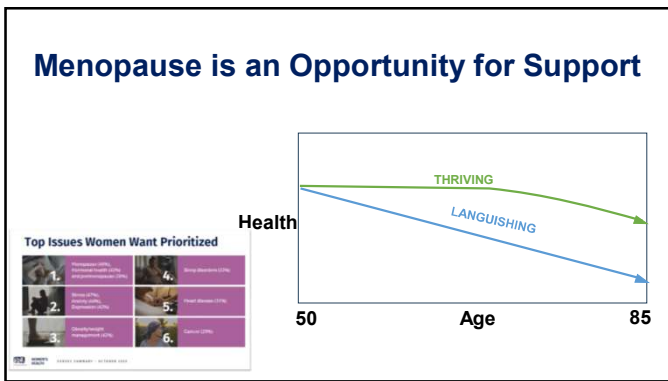
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camh womenmind, leap, CIHR IRSC, NSERC CRSG, Foundation for Research in Menstrual Health



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 1100 members, 11 research teams

More information and registration: <https://bit.ly/camh2026>

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