Estrogen Brain Protector

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Cache Country Dementia Trials

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University of Arizona Dementia Insurance Study

- 379,352 women insurance records by Univ. of Arizona
- FU time 5.1 years
- Foun women on hormone therapy were up to 58% less likely to develop neurodegenerative diseases including Alzheimer's disease, and reduction of risk varied by type and route of hormone therapy and duration of use. The findings could lead to the development of a precision medicine approach to preventing neurodegenerative diseases.
- Women who underwent menopausal hormone therapy for six years or greater were 79% less likely to develop Alzheimer's and 77% less likely to develop any neurodegenerative disease.
- Formulations containing natural steroids 17β-estradiol and/or progesterone were associated with greater reduction in NDD risk
- Oral- HT users showed significantly reduced RRs (0.42, 0.41-0.44, $P < 0.001$) for combined NDDs compared to non-HT users.
- The RRs for transdermal-HT users were significantly decreased for all-cause dementia (0.73, 0.60-0.88, $P = 0.001$) and MS (0.55, 0.36-0.84, $P = 0.005$).
- Greatest reduction in risk of NDD, AD, and dementia emerged in patients aged 65 years or older.
- Further, the protective effect of long-term therapy (>1 year) on combined NDDs, AD, PD, and dementia was greater compared to short-term therapy (≤1 year).

- Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy. Alzheimers Dement (N Y). 2021 May 13;7(1):e12174. doi: 10.1002/trc2.12174. PMID: 34027024; PMCID: PMC8118114.

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Other Huge Brain Studies

- Cache County
- 7 Million Medicare NIH Study

4

Estrogens Brain

- During menopause, decline in circulating estrogen is coincident with decline in brain bioenergetics and shift towards a metabolically compromised phenotype.
- Compensatory bioenergetic adaptations, or lack thereof, to estrogen loss could determine risk of late-onset Alzheimer's disease.
- Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol. 2014 Jan;35(1):8-30. doi: 10.1016/j.yfrne.2013.08.001. Epub 2013 Aug 29. PMID: 23994581; PMCID: PMC4024050.

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Estrogen Lowers IL-6 & Delirium

- Delirium-- a change in mental abilities that includes a lack of awareness of one's surroundings -- is a common problem in older women with UTIs (urinary tract infections).
- All medical students are taught that if an older woman comes to a hospital and she's confused, one of the first things to check is whether the patient has a UTI.
- **Interleukin 6 (IL-6)**
- Past studies have shown that delirium risk is increased by a pro-inflammatory protein called interleukin 6 (IL-6).
- Multiple potential events, such as lung injury from a severe virus, pneumonia, or even a UTI, make the body produce IL-6.
- This local IL-6 then travels through the blood to the brain.
- IL-6 in the brain causes symptoms such as disorientation and confusion.
- *Estrogen is a known suppressor of IL-6.*
- Thus, investigators designed experiments to test giving estrogen to reduce UTI-induced delirium. By tamping down IL-6.
- Studies in mice and the lab in petri dishes flush with UTI bacteria and brain neurons, estrogen tamps down IL-6.
- **Estrogen is a brain protector.**
- Aging is a pro-inflammatory state. I test IL-6 on the first intake of most of my patients. Many are elevated in it. But with integrative medical interventions, we can bring this damaging molecule down to normal levels.
- This research suggests that estrogen therapy makes sense to protect our brains as we age. Why just worry about getting cognitive decline? Why wait for one pharmaceutical to treat Alzheimer's when we have hormonal therapies that when natural steroids are used, not synthetic, have been consistently shown to protect the brain?
- 17β-estradiol ameliorates delirium-like phenotypes in a murine model of urinary tract infection. *Scientific Reports*, 2022; 12 (1) DOI: 10.1038/s41598-022-24247-w

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All new very ill patients

- Measure IL-6 most PRO inflammatory
- Measure IL-10 most ANTI inflammatory
- Estrogen tamps down IL-6
- Boosts IL-10
- So does oxytocin
- L. reuteri BioGaia

7

Hippocampal Volume Is Where Memory Is At, So What Really Fluffs It Up?

- Cognitive decline and other horrific neurodegenerative diseases are on the increase, causing the loss of our loved ones as we know them. Understandably, the rush is on to figure out how to stop this. How to protect our loved one's cognitive abilities.
- **The Hippocampus**
- Memories are "stored" in the hippocampus.
- Our sense of who we have been, who we now are, motivations, and orientations, come from this small anatomical brain region.
- The hippocampus is akin to a "physiologic" version of our ***soul***. *It's our sense of self.*
- When the hippocampus shrinks, our identity shrinks. Cognitive decline emerges. Our loved one as we knew them, horrifically falters.
- The big question becomes, what enlarges or reboots or protects "hippocampal volume"?
- With thinking and memory, size matters. The volume of your hippocampus has everything to do with you staying cognitively… YOU!
- **The MEDEX Trial**
- Yale School of Medicine took this challenge on, using intense mindfulness versus physical exercise, to see if either could reboot the hippocampus. And thus protect memories and slow down the aging of the brain.
- This study, appearing in *JAMA*, is known as the MEDEX trial.
- The design was a randomized trial where participants were randomized to a mindfulness intervention, an exercise intervention, both, or neither.
- Mindfulness, Exercise Strike Out in Memory Trial - *Medscape* - Dec 13, 2022.

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Hormones are More powerful than meditation and exercise on memory

- The interventions were intense.
- The exercise group did a total of 300 minutes of weekly exercise. That's a lot.
- The mindfulness program was characterized by 8 weekly classes of 2.5 hours each as well as a half-day retreat and 60 additional minutes daily, to teach mindfulness and meditation. That's a lot.
- **What happened to the hippocampus?**
- That's the thousand-dollar question.
- Did exercise or mindfulness boost its volume and protect cognition?
- **NO!**
- How did they figure this out? Researchers used MRIs to measure the hippocampal volume. In both groups.
- Neither the VERY intense mindfulness nor exercise protected hippocampal volume.
- In fact, hippocampal volume *decreased* a bit in "all" groups.
- What blows my mind is that the Department of Psychiatry at McGill University "many" years ago had won a coveted award proving that estrogen re-volumizes hippocampal volume in postmenopausal women. Even when their hippocampus has started to shrink. Proven by functional MRIs.
- *They had shown that hippocampal shrinkage, which is at the core of cognitive decline, is reversible with hormone replacement!*
- This has been known for years!
- Still, if you mention this to gerontologists you get the deer in the headlight look.
- This is very frustrating. How many of our loved ones could have been "saved" if the experts truly follow this science?

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- Catherine Lord Ph.D. from the Department of Neuroscience at McGill University wrote in 2007, in Chapter 3 of her thesis for her Ph.D.:
- "HIPPOCAMPAL VOLUMES ARE LARGER IN POSTMENOPAUSAL WOMEN USING ESTROGEN THERAPY COMPARED TO PAST USERS, NEVER USERS AND MEN: A POSSIBLE WINDOW OF OPPORTUNITY EFFECT!"
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.
- Sexy Brain Berkson DL Awakened Medicine Press
- Safe Hormones, Smart Women Berkson DL Awakened Medicine Press
- The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline, Penguin Random House (2017)

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Estrogen Supports Cognition

- Two U.S. departments of neuroscience and cognitive medicine wrote that estrogen administration following menopause has been shown to support h
- A number of previous studies have examined the effect of estrogen on the hippocampal structure to determine the mechanism underlying estrogen's effects on hippocampal function.
- We examined the effect of short-term estradiol administration on hippocampal gray-matter volume in a prospective study with multiple doses of estradiol (placebo, 1 mg, and 2 mg).
- Following 3 months of estradiol administration, bilateral posterior hippocampal voxel-based gray-matter volume was "increased" in women who received 2-mg estradiol.
- There were no significant differences in total hippocampal volume and no significant effects on gray-matter volume in women who received a placebo or 1-mg estradiol.

- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.

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Dose Matters

- Case report
- Gynecologist
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.

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Dale Bredesen Ph.D.

- Dale Bredesen Ph.D., a neurologist from UCLA, has been publishing in peer review, training doctors who are replicating his work and writing books, but no one seems to listen. Why? Dr. Bredesen's answers for Alzheimer's disease are not pharmaceutical medication. They are hormones and other lifestyle modifications. Including dietary interventions.

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More Life Time Estrogen Exposure Less Risk of Stroke

- People with a higher cumulative estrogen exposure throughout their life may have a lower risk of stroke, according to a new study published in the February 1, 2023, online issue of *Neurology*®, the medical journal of the American Academy of Neurology. The lower risk was found for both ischemic stroke and intracerebral hemorrhage.

- **Lifetime Cumulative Effect of Reproductive Factors on Stroke and Its Subtypes in Postmenopausal Chinese: A Prospective Cohort Study**. *Neurology*, 2023; 10.1212/WNL.0000000000206863 DOI: 10.1212/WNL.0000000000206863

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Stroke Prevention

- "Our study suggests that higher estrogen levels due to a number of reproductive factors, including a longer reproductive life span and using hormone therapy or contraceptives, are linked to a lower risk of ischemic stroke and intracerebral hemorrhage," said study author Peige Song, PhD, of the Zhejiang University School of Medicine in Hangzhou, China.
- "These findings might help with new ideas for stroke prevention, such as considering screenings for people who have a short lifetime exposure to estrogen."
- The study involved 122,939 postmenopausal female participants with a median age of 58 living in China without stroke at the start of the study.

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Estrogen Window Stroke Prevention - Timing

- **Methods and findings:**
- Data on HT use reported by the participants in 5 population-based Swedish cohort studies, with baseline investigations performed during the period 1987-2002, were combined in this observational study.
- In total, 88,914 postmenopausal women who reported data on HT use and had no previous cardiovascular disease diagnosis were included.
- During a median follow-up of 14.3 years, 6,371 first-time stroke events were recorded; of these, 1,080 were haemorrhagic.
- **Conclusions:**
- When initiated early in relation to menopause onset, HT was not associated with increased risk of incident stroke, regardless of the route of administration, type of HT, active ingredient, and duration.
- Generally, these findings held also for haemorrhagic stroke.
- Our results suggest that the initiation of HT 0-5 years after menopause onset, as compared to never use, is associated with a decreased risk of stroke and haemorrhagic stroke.
- Late initiation was associated with elevated risks of stroke and haemorrhagic stroke when conjugated equine oestrogen was used as single therapy. Late initiation of combined HT was associated with haemorrhagic stroke risk.
- Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. PLoS Med. 2017 Nov 17;14(11):e1002445. doi: 10.1371/journal.pmed.1002445. PMID: 29149179; PMCID: PMC5693286.

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CEE (Premarin) vs. Estradiol - Stroke

- This study aimed to evaluate the risk of ischemic stroke (IS) in hormone therapy (HT) with oral conjugated equine estrogen (CEE) and estradiol (E2) in postmenopausal women in Taiwan.
- A retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database, a population-based healthcare claims dataset.
- Eligible women, aged 40-65 years, who received HT with E2 and CEE orally were enrolled. The primary outcome was IS.
- After adjusting for age and comorbidities, the incidence of IS was 1.17-fold higher in the women treated with CEE than in those treated with E2 (4.24 vs. 3.61/1000 person-years), with an adjusted HR (aHR) of 1.23 (95% confidence interval [CI] 1.05-1.44).
- Moreover, HT with CEE initiated within 5 years of menopause had a higher HR than E2 (aHR = 1.20; 95% CI 1.02-1.42).
- In conclusion, HT with oral CEE might be associated with a higher risk of IS than E2 in postmenopausal Taiwanese women.
- The use of HT with CEE should be cautioned with the risk of IS.
- Conjugated equine estrogen used in postmenopausal women associated with a higher risk of stroke than estradiol. Sci Rep. 2021 May 24;11(1):10801. doi: 10.1038/s41598-021-90357-6. PMID: 34031535; PMCID: PMC8144437.

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Stroke

- The incidence of stroke increases substantially after menopause, and in the United States it is the third leading cause of death.
- Data exist suggesting that women have worse outcomes for stroke than do men.
- Trials of aspirin use further suggest that there is a gender difference regarding stroke. While men may have a coronary benefit from aspirin, postmenopausal women do not; yet ischemic stroke may be decreased in women but not in men.
- Among the traditional risk factors for stroke (such as smoking, hypertension, diabetes, obesity), hormonal therapy (HT) has been suggested to be a risk as well, although the data are not consistent.
- At the same time, a recent body of evidence from basic science studies has reaffirmed the neuronal and stroke protective effects of estrogen.
- Recent trials in older women with osteoporosis have suggested an increased risk of stroke with tibolone and of stroke mortality with raloxifene.
- In conclusion, the current data suggest no increased risk of stroke with hormone therapy in younger (50-59 years) normotensive postmenopausal women, particularly when lower doses are prescribed soon after menopause.
- Menopause and stroke and the effects of hormonal therapy. Climacteric. 2007 Oct;10 Suppl 2:27-31. doi: 10.1080/13697130701550903. PMID: 17882669.

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Route of delivery, type of estrogen, type of progesterone Stroke

- HRT, consisting of estrogens alone, or in combination with a progestogen, is widely used for the relief of symptoms in postmenopausal women. Early observational studies have suggested that HRT might be associated with a reduced risk of cardio- and cerebro-vascular events.
- These encouraging results prompted randomized controlled trials assessing the risks and benefits of HRT in primary and secondary prevention of arterial vascular events. However, these clinical trials and further observational studies did not confirm the protective effect of HRT; it is now established that HRT increases the risk of stroke. This increased risk is mainly related to an increased risk of ischemic stroke.
- Oral estrogen alone and combined with progestogen are associated with a similar increased risk, which may be dose dependent.
- Conversely, a low dose of transdermal estrogens with or without a progestogen does not seem to be associated with such an increased risk of stroke, whereas the impact of tibolone, a synthetic steroid, remains uncertain. In summary, there is now a large amount of evidence demonstrating that HRT is associated with increased risk of stroke, in particular, ischemic subtype.
- Hormone therapy administration in postmenopausal women and risk of stroke. Womens Health (Lond). 2011 May;7(3):355-61. doi: 10.2217/whe.11.28. PMID: 21612355.

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The Pill - stroke

- Women using low-dose oral contraceptives are at an increased risk for a heart attack or stroke while taking the pill -- however the risk disappears after discontinuation, according to a Virginia Commonwealth University study published in the July issue of the *Journal of Clinical Endocrinology and Metabolism July 7 2005*

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Newest Version Of "The Pill" Confers Same Stroke Risk As Old Pill

- The first major study of ischemic stroke in women taking the latest form of low-estrogen birth control pills finds that they still have about double the stroke risk of women not taking the pill.
- In absolute terms, the number of women likely to have stroke from taking “the pill” rises from about three women to six per 10,000 a year,
- AN ANTONIO, Feb. 7 – The first major study of ischemic stroke in women taking the latest form of low-estrogen birth control pills finds that they still have about double the stroke risk of women not taking the pill. These findings were reported today at the American Stroke Association’s 27th International Stroke Conference. The American Stroke Association is a division of the American Heart Association.
- These findings were reported today at the American Stroke Association’s 27th International Stroke Conference. 2002

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Stroke Risk Is Greater For Migraine Sufferers, Especially Those On Oral Contraceptives

- The risk analysis came from a review conducted by a group of Canadian, Spanish, and United States scientists of 14 studies on the link between migraines and stroke. The review suggests that migraine may be an independent risk factor for stroke, according to Dr. Ali Samii, associate professor of neurology at the University of Washington (UW), who did the study along with Dr. Mayhar Etminan of Montreal's Royal Victoria Hospital and with other collaborators from Spain. Samii practices at the Veterans Affairs Puget Sound Health Care System and UW Medical Center.

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The risk is small, though — at **most, 10 in 10,000 people per year develop** these clots as a result of being on birth control pills.

- The absolute rate of venous thromboembolism in young women is low, but the use of combined oral contraceptives increases this rate three- to five-fold, with an even higher rate in the presence of associated risk factors such as thrombophilia.[4]
- Gronich and colleagues[2] focus our attention on women 12 to 50 years of age taking hormonal contraceptives and attempt to quantify the relative difference in risk of venous thromboembolism attributable to the type of oral contraceptive prescribed.
- The reported incidence of venous thromboembolism in users of oral contraceptives is about 0.06 per 100 pill-years,
- Risk of venous thromboembolism with oral contraceptives. CMAJ. 2011 Dec 13;183(18):E1278-9. doi: 10.1503/cmaj.111614. Epub 2011 Nov 7. PMID: 22065358; PMCID: PMC3255133.
- Cleveland Clinic

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Hypercoagulability - OCPs increase procoagulants while decreasing anticoagulants.

- ral contraceptive (OCP) induced changes on coagulation are complex with high inter-individual variability. The precise reason for differences in this variability is unknown. We hypothesized that global coagulation assays better delineate these changes and variability in hypercoagulability may be the result of differences in estrogen metabolism and thrombophilia. Fifty-two adolescents initiating OCPs were prospectively enrolled; 33 subjects completed the study. Samples were analyzed prior to and after OCPs for procoagulant and anticoagulant factor activities and thrombin generation (TG) +/- thrombomodulin. Participants were genotyped for common thrombophilia and estrogen receptor-α (ESR-α) single nucleotide polymorphisms (SNPs). SNP genotypes were compared to coagulation parameters; TG parameters and differences pre and post OCPs were examined. At baseline, a striking finding was elevated FVIII levels. FVL was absent in all and F2 G20210A was present in one participant. The ESR-α polymorphism was present in heterozygous state in 59% and homozygous state in 21% participants. There were no differences in VWF levels and FVIII: C after being on OCPs. Protein S levels decreased with OCPs. Sixty percent of participants showed evidence of hypercoagulability on TG testing on OCPs. Higher thrombin peak and endogenous thrombin potential (ETP) were seen on TG after OCPs. With thrombomodulin, ETP and thrombin peak did not decrease after OCPs, signifying 'thrombomodulin resistance'. We demonstrated that OCPs induce a state of "variable" hypercoagulability in adolescents, predominantly through the protein S pathway. Genetic and nongenetic factors may account for the variable increase in hypercoagulability. Further research is needed to understand this. Am. J. Hematol. 90:725–731, 2015. © 2015 Wiley Periodicals, Inc.
- **Introduction**
- Modern birth control pills offer excellent contraceptive and noncontraceptive benefits to users. In 2013, oral contraceptives (OCPs) ranked among the top 200 generic drugs prescribed in the U.S. **1** and were reportedly used by over hundred million women worldwide **2**. National Survey of Family Growth 2006–2010 estimated that 56% of U.S. teenage girls between the ages of 15–19 years described OCPs as the most commonly employed method used for contraception **3**. Moreover, the U.S. birth rate for females 15–19 years in 2009 was at a historic low, reflecting an overall increased and consistent use of reliable methods of contraception, including OCPs **3**.
- Adolescence is one of the peak ages for venous thromboembolism (VTE) in the pediatric age group **4**; early pregnancy and OCP use in girls being largely responsible for most events in this age group **5**. The incidence of VTE in 15–19 year old girls on OCPs was reported as 4.2 events per 10,000 exposure years as compared to 0.7 events in nonusers in a large Danish cohort study **6**. While the absolute risk remains low (0.05% per year) in this age group, a majority of VTEs in young women are attributable to OCPs. Despite the convincing association of hypercoagulability with resultant VTE in older women **7**, the biology of OCP induced VTE in adolescence remains, for the most part unknown. OCPs increase procoagulants while decreasing anticoagulants. It is plausible that the interplay of estrogen dose and the type of progesterone in OCPs,
- Hypercoagulability in adolescent girls on oral contraceptives-global coagulation profile and estrogen receptor polymorphisms. Am J Hematol. 2015 Aug;90(8):725-31. doi: 10.1002/ajh.24064. PMID: 26014094.

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Oral Contraceptives

- Increase risk of higher blood pressure
- Increase risk of stroke
- Decrease all hormones signals
- Increase risk of SHBG
- Decrease oxytocin, bonding and relationship decisions
- Effect developing younger brain
- Yet offered for women up to 50's as HRT = malpractice

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OCP – disordered brain signals

- New rodent research links synthetic hormones found in birth control pills, patches, and injections with "disordered signal transmission" between cells in the prefrontal cortex, an area of the brain that continues to develop throughout adolescence.
- Reproductive health experts consider hormonal contraceptives good choices for adolescents because they're safe and highly effective at preventing pregnancy.
- But it appears since hormones rule the brain (thus my last book was called SEXY BRAIN, as sex steroid hormones like estrogen, progesterone, and testosterone highly influence brain tissue and function), these synthetic hormones might modify the teenage developing brain. And perhaps not in an optimal way.
- Compared to control rats, animals receiving hormonal contraceptives had glitches in their brain signals. And also produced higher levels of the stress hormone corticosterone, which is similar to cortisol in humans.
- The Ohio State University scientists launched this line of study in the prefrontal cortex, a region where mood is regulated.
- This is because previous research associated early adolescent use of hormonal contraceptives with the risk for **depression** in adulthood.
- An estimated 2 in 5 teenage girls in the United States have sexual intercourse between ages 15 and 19, and the vast majority use a contraceptive -- condoms in particular.
- 5% use hormonal contraceptives. That's what we are talking about here.
- Birth control pills are also widely used to treat Poly Cystic Ovarian Syndrome (PCOS) which is occurring in 1 out of 10 young women globally.
- Birth control pills are also used to treat **acne, migraines, POTS** (dysfunction of the autonomic nervous system called *Postural Orthostatic Tachycardia Syndrome*) and other health issues.

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Increase Cortisol

- The researchers gave a combination of synthetic estrogen and progesterone typically found in hormonal contraceptives to female rats for three weeks beginning about a month after they were born, an age equivalent to early adolescence in humans.
- Blood samples showed the treated rats were producing more corticosterone than untreated animals, a sign that they were stressed.
- **This means that birth control pills put human physiology under a "constant state of stress".**
- And after being subjected to and recovering from an experimental stressor, the treated rats' corticosterone levels remained high.
- Their **adrenal glands were also larger**, suggesting their stress hormone production was **consistently higher** than that of control animals.
- An analysis of gene activation markers in the animals' prefrontal cortex showed a decrease in excitatory synapses in rats treated with birth control hormones.
- The loss of only excitatory synapses in the prefrontal cortex has been linked to exposure to chronic stress and **depression** (in previous research).
- This may set the scene for depression and mood dys-regulation later in life. And the need for more meds, like **anti-depressants.**
- Research poster presented Tuesday, Nov. 15, 2022 at Neuroscience 2022, the annual meeting of the Society for Neuroscience.
- Ohio State University. "How hormonal birth control may affect the adolescent brain: Research in rats hints at increased stress, signaling changes." ScienceDaily. ScienceDaily, 15 November 2022.

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OCPS lower T which increase risk of autoimmune diseases

- This study was done on 68 female athletes.
- Athletes ranged from intercollegiate soccer, volleyball, and softball team players, to women skaters from a team competing in an amateur roller derby league.
- The researchers, from the Department of Psychology, at Emory University took saliva samples before warm-up and immediately after the completion of one or more sanctioned competitions.
- They found that women using oral contraceptives had a significantly lower mean level of saliva testosterone than non-users.
- Anyone performing robust exercise had an increase in testosterone.
- Unless they were on oral contraceptives (OCs).
- OC users had significantly lower saliva T levels than non-users before and after the competition.
- Testosterone, in both genders, is needed for healthy memory, bone, gut immunity (to ward off auto-immune diseases), and much more.
- Testosterone is especially needed for healthy muscle maintenance and response to exercise. In ladies, but also men.
- T is especially important to make SIgA to protect against autoimmune diseases.

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Block Muscle Mass Development

- The Department of Health and Kinesiology, Texas A&M University School of Education, and the Health Professions and Human Development, University of Houston-Victoria found that oral contraceptives block muscle building in young women using them.
- Many active young women use oral contraceptives, yet the effects on body composition and exercise performance have not been thoroughly studied
- These researchers examined the effects of OCs on muscle responses to a standardized resistance exercise training program.
- They looked at two groups of young healthy women 18-29 years old, 38 not on OCs, and 34 on OCs, doing strength training for 10 weeks.
- Women on OCs had higher stress hormones (cortisol). But lower male and growth hormones (DHEA, DHEAS, Testosterone, and IGF-1) compared to females not taking birth control pills.
- Women taking birth control pills grew less muscle in response to the muscle-building exercises.
- Oral contraceptives impair lean mass gains in exercising young women.
- By impairing the release of male and growth hormones.
- Progestins (used in oral contraceptives as well as IUDs, etc.) may bind to androgen (male) receptors and inhibit their normal function.

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Less Serotonin More Anxiety and STress

- Canadian and Swedish researchers looked at the effects of OCs on mood.
- They found that young women on OCs had lower levels of serotonin receptors, which explains the molecular link between OC use and increased risk of depressive episodes.
- OCs blunt hormones in young girls. Neurotransmitters follow hormones. The blunted ovarian hormonal state among OC users explains a higher rate of possible depression and anxiety.
- Progesterone is an anti-anxiety, anti-depression, and memory booster hormone. But not its synthetic version, progestins.

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Less Serotonin

- A collaboration of Chinese and NY scientists looked at saliva levels of young females on birth control pills, showing they had lower progesterone levels.
- This could also explain a higher risk of anxiety and depression when on OC.
- **This collaborative study found:**
- Healthy women who use oral contraceptives have 9–12% lower global brain serotonin 4 receptor binding potential compared to non-users.
- The lower serotonin 4 receptor binding potential provides a plausible molecular mechanism by which oral contraceptive use can be associated with an increased risk of developing depression.
- Compared to previous studies, the effect size of oral contraceptive use is almost twice as big as the effect size of selective serotonin reuptake inhibitors (SSRIs) on serotonin 4 receptor binding potential. This raises the question of if concomitant oral contraceptive use affects SSRI antidepressant efficacy. Meaning, if on OC, does this nullify the benefit (or need) of being on SSRI anti-depressants?

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Migraines + Aura

- A large collaboration of European scientists systematically reviewed data about the association between migraine, ischemic stroke, and hormonal contraceptive use.
- Available data suggest that combined hormonal contraceptives may increase the risk of ischemic stroke, especially in females that have a history of migraines specifically, migraines with aura.
- Have a history of migraines? Think twice about OCs.

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Citations

- Results of intra-individual salivary progesterone analysis indicated that caution should be exercised when using progesterone concentrations in predicting ovulation for females who are under treatment with birth control pills/devices or has body a weight of > 90 kg.
- Oral contraceptives decrease saliva testosterone but do not affect the rise in testosterone associated with athletic competition. Horm Behav. 2009 Aug;56(2):195-8. doi: 10.1016/j.yhbeh.2009.01.008. Epub 2009 Jan 31. PMID: 19470364.
- Noninvasive detection of human dehydroepiandrosterone, progesterone, and testosterone using LC-MS/MS revealed effects of birth control pills/devices and body weight on ovulatory prediction. J Chromatogr B Analyt Technol Biomed Life Sci. 2021 Jun 1;1174:122716. doi: 10.1016/j.jchromb.2021.122716. Epub 2021 Apr 21. PMID: 33946036.
- Oral Contraceptive Use Impairs Muscle Gains in Young Women. J Strength Cond Res. 2022 Nov 1;36(11):3074-3080. doi: 10.1519/JSC.0000000000004059. Epub 2021 May 14. PMID: 33993156.
- Oral contraceptives and the serotonin 4 receptor: a molecular brain imaging study in healthy women. Acta Psychiatr Scand. 2020 Oct;142(4):294-306. doi: 10.1111/acps.13211. Epub 2020 Jul 21. PMID: 33314049; PMCID: PMC7586815.
- Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). J Headache Pain. 2017 Oct 30;18(1):108. doi: 10.1186/s10194-017-0815-1. Erratum in: J Headache Pain. 2018 Sep 10;19(1):81. PMID: 29086160; PMCID: PMC5662520.

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OCP + Obesity

- The European Society of Cardiology's new study demonstrates that obese women who use oral contraceptives containing estrogen and progestin have a 24-fold increased risk of venous thromboembolism (VTE) - compared with non-obese women not using the drugs.
- Study author Professor Giuseppe Rosano of the IRCCS San Raffaele Pisana, Rome, Italy said: "It is well established that both obesity and oestrogen-containing contraceptives are risk factors for VTE.
- Despite this, obese women continue to receive these drugs.
- The scientific evidence indicates that obesity and combined oral contraceptives have a synergistic effect on VTE risk and this should be considered in prescribing decisions.
- Obesity and contraceptive use: impact on cardiovascular risk. *ESC Heart Failure*, 2022.

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Case Report

- One patient: 56 presently and on warfarin since 41 when had pulmonary embolism. She had been on birth control pills for 24 years, was obese, was a smoker, and had some autoimmune markers.
- Now 56, brain fog, osteoporosis, anxiety, severe weight gain, fatigue and no longer a smoker and no one will give her HRT.
- Obesity and contraceptive use: impact on cardiovascular risk. *ESC Heart Failure*, 2022.

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OCP highly linked to IBD

- Slides

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Estrogen Brain

- HorEstrogen Therapy (ET) may protect against age-related cognitive decline and neuropsychiatric disorders (e.g. Alzheimer's disease). The biological basis for this putative neuroprotective effect is not fully understood, but may include modulation of cholinergic systems. Cholinergic dysfunction has been implicated in age-related memory impairment and Alzheimer's disease. However, to date no one has investigated the effect of long-term ET on brain cholinergic muscarinic receptor aging, and related this to cognitive function.
- We used Single Photon Emission Tomography (SPET) and (R,R)[(123)I]-I-QNB, a novel ligand with high affinity for m(1)/m(4) muscarinic receptors, to examine the effect of long-term ET and age on brain m(1)/m(4) receptors in healthy females.
- We included 10 younger premenopausal subjects and 22 postmenopausal women; 11 long-term ET users (all treated following surgical menopause) and 11 ET never-users (surgical menopause, n=2).
- Also, verbal memory and executive function was assessed in all postmenopausal subjects.
- Compared to young women, postmenopausal women (ET users and never-users combined) had significantly lower muscarinic receptor density in all brain regions examined.
- ET users also had higher muscarinic receptor density than ET never-users in all the brain regions, and this reached statistical significance in left striatum and hippocampus, lateral frontal cortex and thalamus. Moreover, in ET users, (R,R)[(123)I]-I-QNB binding in left hippocampus and temporal cortex was significantly positively correlated with plasma estradiol levels. We also found evidence for improved executive function in ET users as compared to ET never-users. However, there was no significant relationship between receptor binding and cognitive function within any of the groups.
- In healthy postmenopausal women use of long-term ET is associated with reduced age-related differences in muscarinic receptor binding, and this may be related to serum estradiol levels.
- Estrogen therapy and brain muscarinic receptor density in healthy females: a SPET study. Horm Behav. 2007 Feb;51(2):249-57. doi: 10.1016/j.yhbeh.2006.10.007. Epub 2006 Dec 14. PMID: 17173920.

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Estrogen Brain

- long with advanced age and apolipoprotein E (APOE)-4 genotype, female sex is a major risk factor for developing late-onset Alzheimer's disease (AD).
- Considering that AD pathology begins decades prior to clinical symptoms, the higher risk in women cannot simply be accounted for by their greater longevity as compared to men.
- Recent investigation into sex-specific pathophysiological mechanisms behind AD risk has implicated the menopause transition (MT), a midlife neuroendocrine transition state unique to females.
- Commonly characterized as ending in reproductive senescence, many symptoms of MT are neurological, including disruption of estrogen-regulated systems such as thermoregulation, sleep, and circadian rhythms, as well as depression and impairment in multiple cognitive domains.
- Preclinical studies have shown that, during MT, the estrogen network uncouples from the brain bioenergetic system.
- The resulting hypometabolic state could serve as the substrate for neurological dysfunction. Indeed, translational brain imaging studies demonstrate that 40-60 year-old perimenopausal and postmenopausal women exhibit an AD-endophenotype characterized by decreased metabolic activity and increased brain amyloid-beta deposition as compared to premenopausal women and to age-matched men.
- This review discusses the MT as a window of opportunity for therapeutic interventions to compensate for brain bioenergetic crisis and combat the subsequent increased risk for AD in women.

- Female Sex and Alzheimer's Risk: The Menopause Connection. J Prev Alzheimers Dis. 2018;5(4):225-230. doi: 10.14283/jpad.2018.34. PMID: 30298180; PMCID: PMC6198681.
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Estrogen Brain

- Neurological aging is frequently viewed as a linear process of decline, whereas in reality, it is a dynamic non-linear process. The dynamic nature of neurological aging is exemplified during midlife in the female brain.
- To investigate fundamental mechanisms of midlife aging that underlie risk for development of Alzheimer's disease (AD) in late life, we investigated the brain at greatest risk for the disease, the aging female brain.
- Outcomes of our research indicate that mid-life aging in the female is characterized by the emergence of three phases: early chronological (pre-menopause), endocrinological (peri-menopause) and late chronological (post-menopause) aging.
- The dismantling of the estrogen control of glucose metabolism during mid-life aging is a critical contributor to the shift in fuel systems and emergence of dynamic neuroimmune phenotype.
- The shift in fuel reliance, puts the largest reservoir of local fatty acids, white matter, at risk for catabolism as a source of lipids to generate ketone bodies through astrocytic beta oxidation.
- APOE4 genotype accelerates the tipping point for emergence of the bioenergetic crisis.
- Preclinical and clinical evidence indicate that midlife endocrine aging can also be a transitional bridge to autoimmune disorders.
- Collectively, the data indicate that endocrinological aging is a critical period "tipping point" in midlife which can initiate emergence of the prodromal stage of late-onset-Alzheimer's disease. Interventions that target both immune and metabolic shifts that occur during midlife aging have the potential to alter the trajectory of Alzheimer's risk in late life. Further, to achieve precision medicine for AD, chromosomal sex is a critical variable to consider along with APOE genotype, other genetic risk factors and stage of disease.
- A tale of two systems: Lessons learned from female mid-life aging with implications for Alzheimer's prevention & treatment. Ageing Res Rev. 2022 Feb;74:101542. doi: 10.1016/j.arr.2021.101542. Epub 2021 Dec 17. PMID: 34929348; PMCID: PMC8884386.

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Age, APOE and sex: Triad of risk of Alzheimer's disease

- Age, apolipoprotein E ε4 (APOE) and chromosomal sex are well-established risk factors for late-onset Alzheimer's disease (LOAD; AD).
- Over 60% of persons with AD harbor at least one APOE-ε4 allele.
- The sex-based prevalence of AD is well documented with over 60% of persons with AD being female.
- Evidence indicates that the APOE-ε4 risk for AD is greater in women than men, which is particularly evident in heterozygous women carrying one APOE-ε4 allele.
- Paradoxically, men homozygous for APOE-ε4 are reported to be at greater risk for mild cognitive impairment and AD.
- Herein, we discuss the complex interplay between the three greatest risk factors for Alzheimer's disease, age, APOE-ε4 genotype and chromosomal sex.
- We propose that the convergence of these three risk factors, and specifically the bioenergetic aging perimenopause to menopause transition unique to the female, creates a risk profile for AD unique to the female.
- Further, we discuss the specific risk of the APOE-ε4 positive male which appears to emerge early in the aging process.
- Evidence for impact of the triad of AD risk factors is most evident in the temporal trajectory of AD progression and burden of pathology in relation to APOE genotype, age and sex. Collectively, the data indicate complex interactions between age, APOE genotype and gender that belies a one size fits all approach and argues for a precision medicine approach that integrates across the three main risk factors for Alzheimer's disease.

- Age, APOE and sex: Triad of risk of Alzheimer's disease. J Steroid Biochem Mol Biol. 2016 Jun;160:134-47. doi: 10.1016/j.jsbmb.2016.03.012. Epub 2016 Mar 8. PMID: 26969397; PMCID: PMC4905558.

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APOE4

- Age-related changes in testosterone are believed to be a key component of the processes that contribute to cognitive aging in men.
- The APOE-ε4 allele may interact with testosterone and moderate the hormone's association with cognition.
- The goals of the present study were to examine the degree to which free testosterone is associated with episodic memory in a community-based sample of middle-aged men, and examine the potential interaction between free testosterone and the APOE-ε4 allele.
- Data were used from 717 participants in the Vietnam Era Twin Study of Aging.
- Average age was 55.4 years (standard deviation = 2.5).
- Significant positive associations were observed between free testosterone level and verbal episodic memory, as well as a significant interaction between free testosterone and APOE-ε4 status.
- In ε4 carriers free testosterone was positively associated with verbal episodic memory performance (story recall), whereas no association was observed in ε4 noncarriers.
- Results support the hypothesis that APOE-ε4 status increases susceptibility to other risk factors, such as low testosterone, which may ultimately contribute to cognitive decline or dementia.
- Interaction of APOE genotype and testosterone on episodic memory in middle-aged men. Neurobiol Aging. 2014 Jul;35(7):1778.e1-8. doi: 10.1016/j.neurobiolaging.2013.12.025. Epub 2013 Dec 27. PMID: 24444806; PMCID: PMC3980008.

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Interaction between testosterone and apolipoprotein E epsilon4 status on cognition in healthy older men

- **Context:** Reduced testosterone levels have been implicated as a potential causative factor in cognitive decline with older age. Men who possess the apolipoprotein E (APOE) epsilon4 allele have an increased risk of developing Alzheimer's disease; however, no studies have examined whether the influence of testosterone on cognition in healthy older men may be modulated by this genetic predisposition.
- **Objective:** The objective of the study was to investigate the association between serum testosterone concentrations and cognitive performance in healthy older men, taking into account APOE epsilon4 status.
- **Design:** This was a cross-sectional study conducted from 2003 to 2004.
- **Setting:** The study population consisted of community-dwelling males residing in Perth, Western Australia.
- **Participants:** Healthy men over 55 yr, free of cognitive impairment and dementia (n = 45), were included in the study.
- **Main outcome measures:** Participants had fasting early morning blood samples for testosterone and SHBG and were assessed for mood as well as indices of general cognition, verbal and visual memory, executive functioning, working memory, and attention.
- **Results:** There was a significant interaction between calculated free testosterone (FT) and APOE epsilon4 on general cognition ($P = 0.01$) and executive functioning, working memory, and attention ($P < 0.01$).
- Higher levels of FT were associated with better general cognition in non-epsilon4 carriers ($P = 0.01$).
- By contrast, in epsilon4 carriers higher FT levels were associated with lower scores on tests of executive functioning, working memory, and attention ($P = 0.02$).
- In men at increased risk for Alzheimer's disease, higher testosterone levels were not associated with better cognitive function.
- **Conclusions:** Cross-sectional and prospective studies of testosterone and cognition in older men should take into account APOE epsilon4 status.
- Interaction between testosterone and apolipoprotein E epsilon4 status on cognition in healthy older men. J Clin Endocrinol Metab. 2006 Mar;91(3):1168-72. doi: 10.1210/jc.2005-1072. Epub 2005 Dec 20. PMID: 16368754.

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APOE3

- Though a small percentage of Alzheimer's cases arise from genetic mutations that cause obvious disease before the age of 65, the vast majority of people who develop the condition do so later in life from undefined triggers, some thought to be genetic.
- In 1993, scientists found that people who inherit a gene variant called apolipoprotein E4 (*APOE4*) are more prone to the common form of Alzheimer's that strikes in late life.
- There's also a "risk-neutral" variant (*APOE3*) and a much rarer version of the gene (*APOE2*) that decreases a person's risk for Alzheimer's.
- Shortly thereafter, other research groups replicated the finding and some data hinted that *APOE4* raises Alzheimer's risk more in women than in men.
- Indeed, when scientists combed through a massive data set containing 5930 Alzheimer's patients and 8607 dementia-free elderly from 40 independent studies, they reported in 1997 that females with the *APOE4* variant were four times more likely to have Alzheimer's compared with people with the more common, neutral form of the gene.
- Less free T than males.
- Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56. PMID: 9343467. ever, in men, *APOE4* seemed virtually harmless.

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This is why want to track T in ladies

- **Conclusions and relevance:** Contrary to long-standing views, men and women with the APOE ε3/ε4 genotype have nearly the same odds of developing AD from age 55 to 85 years, but women have an increased risk at younger ages.

- Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease: A Meta-analysis. JAMA Neurol. 2017 Oct 1;74(10):1178-1189. doi: 10.1001/jamaneurol.2017.2188. PMID: 28846757; PMCID: PMC5759346.

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Less T Higher Tau in APOE4 regardless of gender

- Women show greater pathological Tau biomarkers than men along the Alzheimer's disease (AD) continuum, particularly among apolipoprotein ε-E4 (APOE4) carriers; however, the reason for this sex difference in unknown. Sex differences often indicate an underlying role of sex hormones.
- We examined whether testosterone levels might influence this sex difference and the modifying role of APOE4 status.
- Analyses included 172 participants (25 cognitively normal, 97 mild cognitive impairment, 50 AD participants) from the Alzheimer's Disease Neuroimaging Initiative (34% female, 54% APOE4 carriers, aged 55-90).
- We examined the separate and interactive effects of plasma testosterone levels and APOE4 on cerebrospinal fluid phosphorylated-tau181 (p-Tau) levels in the overall sample and the sex difference in p-Tau levels before and after adjusting for testosterone.
- A significant APOE4-by-testosterone interaction revealed that lower testosterone levels related to higher p-Tau levels among APOE4 carriers regardless of sex.
- As expected, women had higher p-Tau levels than men among APOE4 carriers only, yet this difference was eliminated upon adjustment for testosterone.
- Results suggest that testosterone is protective against p-Tau particularly among APOE4 carriers.
- The lower testosterone levels that typically characterize women may predispose them to pathological Tau, particularly among female APOE4 carriers.
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- Alzheimer's Disease Neuroimaging Initiative. Sex differences in Alzheimer's-related Tau biomarkers and a mediating effect of testosterone. Biol Sex Differ. 2020 Jun 19;11(1):33. doi: 10.1186/s13293-020-00310-x. PMID: 32560743; PMCID: PMC7304096.

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Less T More Memory Loss

- Despite some inconsistencies [24, 25], a wealth of evidence indicates an association between low testosterone levels, poorer cognitive function [26,27,28,29,30], and greater odds or risk for AD [18, 20,21,22,23, 31, 32], with these associations more clearly defined in men [18, 20,21,22,23, 26,27,28,29, 31, 32] than in women [26, 27].
- Suggestive of a more causative than consequential role for testosterone on AD-related outcomes, longitudinal studies have shown that low free and/or total testosterone levels precede development of AD dementia [23] and cognitive dysfunction on measures of global cognition [26, 29] and episodic memory [29]. Furthermore, exogenous testosterone supplementation led to improved performance over time in a range of cognitive domains including global cognition [19, 33], psychomotor speed [33], executive function [33], and spatial and verbal memory [34, 35], although not always [36].
- Animal and human studies demonstrate that the effects of testosterone may depend on APOE genotype. The APOE4 allele is associated with lower testosterone levels in men [31], and with downregulation of androgen receptors in mice, resulting in reduced binding of testosterone [37]. Experimental manipulations of testosterone levels in male and female mouse models relate to changes in cognitive function more so among APOE4 carriers than APOE3 carriers [37, 38], suggesting that APOE4 carriers are more sensitive to the effects of testosterone on the brain. In humans, the direction of the APOE4 by testosterone interaction is less consistent, whereby Panizzon et al. found that low testosterone levels in men related to smaller hippocampal volumes and poorer episodic memory among APOE4 carriers only [39, 40], whereas Hogervorst et al. found that low testosterone levels related to a greater likelihood of an AD diagnosis among APOE4 non-carriers only [31]. The APOE4 by testosterone interaction has yet to be examined either in women or in relation to hallmark AD pathologies.
- Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004;62(2):188–93.
- Endogenous sex hormones and cognitive function in older adults: a systematic review. West. J. Nurs. Res. 2014.

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T and AD

- Furthermore, exogenous testosterone supplementation led to improved performance over time in a range of cognitive domains including global cognition [19, 33], psychomotor speed [33], executive function [33], and spatial and verbal memory [34, 35], although not always [36].
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- Our results suggest that higher levels of p-Tau in women versus men are likely capturing an association between the low testosterone levels that are commonly seen in women and higher p-Tau.
- In fact, we found that the higher p-Tau levels in female APOE4 carriers versus male APOE4 carriers was eliminated when adjusting for testosterone suggesting that differences in testosterone between men and women is a central mechanism underlying this sex difference.
- These findings may have implications for the well-evidenced higher AD risk in women considering that Tau pathology is closely tied to neurodegeneration and clinical symptomology.
- Our findings also challenge the concept that testosterone is a "male hormone" in which the implications of low levels on AD-related outcomes are mostly circumscribed to men despite women having lower testosterone levels than men overall as well as age-related declines.
- Our results offer a potential mechanism for the strongly, yet not consistently [72] supported finding of a stronger effect of APOE4 in women versus men on AD risk [6,7,8, 72].
- If APOE4 has a stronger effect on AD-related outcomes in the context of low testosterone levels, as suggested by our data, then this would lead to a greater susceptibility of women to these effects.
- Our findings may also help to explain inconsistencies in the literature regarding an effect of APOE4 on Tau. Other biomarker [73], neuroimaging [74], and autopsy [75] studies found a more robust association between APOE4 and Tau in women versus men, whereas studies that did not compare by sex have shown inconsistent findings in the APOE4 and Tau link [73, 76,77,78,79,80].
- Alzheimer's Disease Neuroimaging Initiative. Sex differences in Alzheimer's-related Tau biomarkers and a mediating effect of testosterone. Biol Sex Differ. 2020 Jun 19;11(1):33. doi: 10.1186/s13293-020-00310-x. PMID: 32560743; PMCID: PMC7304096.

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Low T More Tau

- Findings suggest that the lower testosterone levels in women are a significant contributor to their higher levels of p-Tau compared to men.

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- Furthermore, we hypothesized that the higher p-Tau levels in female versus male APOE4 carriers will diminish upon adjustment for testosterone.

- TR may be AD protective.

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T AZ

- **Background:** Sevoflurane anaesthesia induces phosphorylation of the microtubule-associated protein tau and cognitive impairment in neonatal, but not adult, mice. The underlying mechanisms remain largely to be determined. Sex hormones can be neuroprotective, but little is known about the influence of testosterone on age-dependent anaesthesia effects.
- **Methods:** Six- and 60-day-old male mice received anaesthesia with sevoflurane 3% for 2 h daily for 3 days. Morris water maze, immunoassay, immunoblotting, co-immunoprecipitation, nanobeam technology, and electrophysiology were used to assess cognition; testosterone concentrations; tau phosphorylation; glycogen synthase kinase-3β (GSK3β) activation; binding or interaction between tau and GSK3β; and neuronal activation in mice, cells, and neurones.
- **Results:** Compared with 60-day-old male mice, 6-day-old male mice had lower testosterone concentrations (3.03 [0.29] vs 0.44 [0.12] ng ml^{-1}; P<0.01), higher sevoflurane-induced tau phosphorylation in brain (133 [20]% vs 100 [6]% in 6-day-old mice, P<0.01; 103 [8]% vs 100 [13]% in 60-day-old mice, P=0.77), and sevoflurane-induced cognitive impairment. Testosterone treatment increased brain testosterone concentrations (1.76 [0.10] vs 0.39 [0.05] ng ml^{-1}; P<0.01) and attenuated the sevoflurane-induced tau phosphorylation and cognitive impairment in neonatal male mice. Testosterone inhibited the interaction between tau and GSK3β, and attenuated sevoflurane-induced inhibition of excitatory postsynaptic currents in hippocampal neurones.
- **Conclusions:** Lower brain testosterone concentrations in neonatal compared with adult male mice contributed to age-dependent tau phosphorylation and cognitive impairment after sevoflurane anaesthesia.
- Testosterone might attenuate the sevoflurane-induced tau phosphorylation and cognitive impairment by inhibiting the interaction between tau and GSK3β.
- Testosterone attenuates sevoflurane-induced tau phosphorylation and cognitive impairment in neonatal male mice. Br J Anaesth. 2021 Dec;127(6):929-941. doi: 10.1016/j.bja.2021.08.028. Epub 2021 Oct 20. PMID: 34686310; PMCID: PMC9642834.

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