



— YOUTUBE RESEARCH SUMMARY

Research Summary: Perimenopause and Neuroinflammation

As featured in Dr. Kenny Mittelstadt's video: [Perimenopause Symptoms Nobody Warns You About \(And What They Mean\)](#)

— Research Context

Perimenopause is widely framed as a hormone story, but the research tells a more layered picture. The symptoms that tend to be most confusing, including tinnitus, palpitations, joint pain, mood shifts, skin sensations, and changes across mucosal surfaces, point to something broader: a systemic shift in how the nervous system, immune system, and microbiome operate when the hormonal baseline they have been depending on becomes unpredictable. This week's research examines what that shift looks like at the tissue level, why symptom burden varies so dramatically from woman to woman, and what the standard workup is often missing.

— Key Findings from the Research

STUDY 1 • PMID 33097048

McCarthy and Raval (2020) reviewed how the perimenopause transition affects the brain and nervous system at a structural level. Perimenopause triggers a pro-inflammatory shift that extends well beyond fluctuating hormone levels. Estrogen has direct regulatory effects on the brain's innate immune response and plays a direct role in keeping mitochondria in brain and nerve cells running efficiently. When estrogen signaling becomes volatile, both systems come under load simultaneously. The result is a nervous system recalibrating under stress, which helps explain why mood changes, cognitive shifts, pain sensitivity, and immune reactivity often cluster together. What each woman's nervous system was already carrying before the transition shapes how disruptive that recalibration becomes.

STUDY 2 • PMID 15908899

Genazzani and colleagues (2005) mapped what happens to the brain's pain-processing system as estrogen withdraws during the menopausal transition. Key signaling systems in the limbic region, the area involved in both emotion and pain regulation, shift meaningfully during this period. Specifically, the systems that use serotonin, noradrenaline, and the body's natural opioid signals all change as estrogen declines. The nervous system's threshold for detecting and amplifying sensory signals can drop during perimenopause, making the brain more sensitive. Symptoms like tinnitus, skin sensations, and heightened joint or connective tissue pain may reflect this shift in sensitivity rather than a new structural problem at each individual site.

STUDY 3 • PMID 36749328

Crandall, Mehta, and Manson (2023) conducted a large review published in JAMA on the management of perimenopause symptoms. Even the most well-recognized perimenopause symptom, hot flashes and other vasomotor symptoms, affects somewhere between 50 and 75 percent of women going through this transition. A meaningful portion of women, roughly 1 in 4 to 1 in 2, do not experience perimenopause through the textbook picture at all. The variation in who experiences what, and how severely, goes beyond what hormone levels alone can explain. This validates what many women already sense: that their experience does not fit neatly into a single story and that the standard framework may not capture the full picture of what is driving their symptoms.



— Functional Medicine Connections

Estrogen functions as a baseline signal across multiple body systems simultaneously. The nervous system, immune system, connective tissue, microbiome, and cardiovascular system have all been operating with estrogen as part of their regulatory environment. When that baseline becomes unstable during perimenopause, each of those systems has to adapt. This adaptation is a legitimate physiological recalibration happening in real time. Because estrogen receptors are present throughout the brain, spinal cord, auditory pathways, and peripheral sensory nerves, the shift in hormonal signaling registers at every one of those sites. The brain's pain-processing and mood-regulating systems shift together, which is why symptoms at the level of sensory experience, emotional regulation, and physical sensitivity tend to cluster: they are reading from the same changed input.

Estrogen has been actively regulating immune responses, including keeping certain inflammatory responses in check. As that regulation becomes less consistent, immune reactivity that was previously well-managed can become more noticeable. This is part of why some women see flares of conditions that were quiet, or new sensitivities that seem to appear without an obvious trigger, during this transition. The microbiome layer adds another dimension that is often overlooked. Estrogen regulates the integrity of mucosal surfaces across the body, including the gut lining, the oral cavity, the vaginal tract, and the skin. These surfaces each have their own microbial communities, all influenced by the same hormonal signal. When that signal shifts, changes can appear across multiple surfaces simultaneously in ways that look unrelated but share a single upstream cause.

How the body processes and clears estrogen matters as much as how much estrogen is present. Estrogen moves through a multi-stage clearance process involving the liver and the gut. When any part of that process is sluggish, estrogen metabolites that should be leaving the body can linger or re-enter circulation. A community of gut bacteria called the estrobolome plays a direct role in regulating this recycling process. This is one reason why gut health and hormone health are not separate categories in a functional medicine investigation.

— Practical Reflections & Takeaways

If you map your own timeline, what was happening in the years before your symptoms became harder to manage? Were there periods of sustained stress, changes in gut health, immune system challenges, or accumulated load that you were quietly carrying and normalizing? Lived experience is meaningful data, and your timeline often holds more information than a single lab snapshot.

If you have been through the standard workup and been told your numbers look relatively okay, or if treatment helped but left things still unresolved, what does that gap feel like to you? Partial resolution is a clue worth following, not a reason to stop asking questions.

— References

McCarthy, M., & Raval, A. P. (2020). The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. *Journal of Neuroinflammation*, 17(1), 317. doi: 10.1186/s12974-020-01998-9. PMID: 33097048.

Genazzani, A. R., Bernardi, F., Pluchino, N., et al. (2005). Endocrinology of menopausal transition and its brain implications. *CNS Spectrums*, 10(6), 449–457. doi: 10.1017/s1092852900022835. PMID: 15908899.

Crandall, C. J., Mehta, J. M., & Manson, J. E. (2023). Management of menopausal symptoms: A review. *JAMA*, 329(5), 405–420. doi: 10.1001/jama.2022.24140. PMID: 36749328.

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