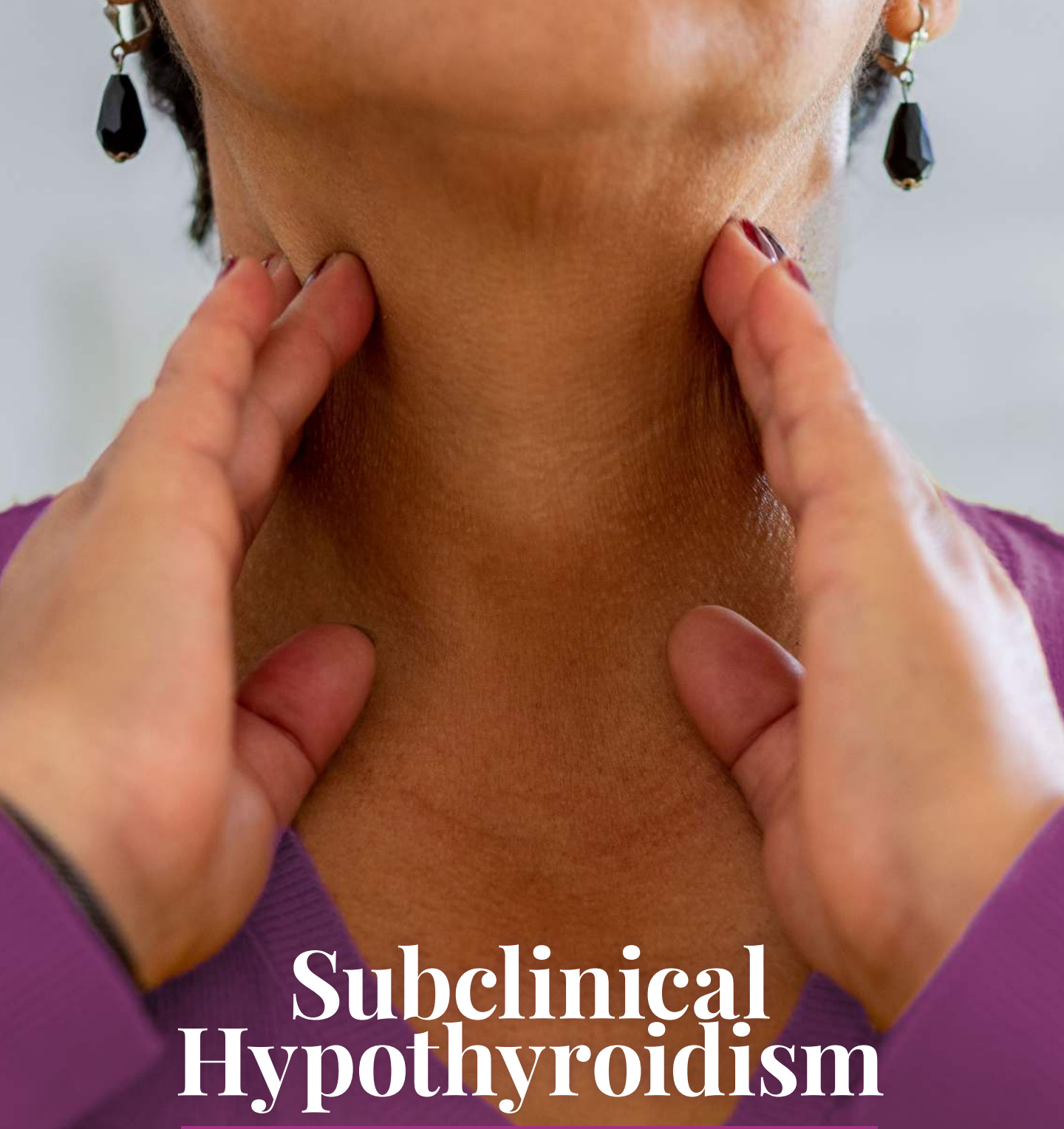

Subclinical Hypothyroidism

UNNECESSARY TREATMENT MAY BE PUTTING YOUR BRAIN HEALTH AT RISK

You may have noticed tabloid headlines at the supermarket checkout proclaiming fatigue, weight gain, and brain fog are caused by an under-active thyroid, a condition known as hypothyroidism, and that hormone replacement therapy is the solution.

Levothyroxine, the medication for treating hypothyroidism, is the second-most prescribed drug in Canada and the United States. The percentage of individuals taking levothyroxine is two times greater than the frequency of the condition, indicating that it is over-prescribed.

One of the key drivers of its extensive use has been an increase in treating people with a controversial condition called subclinical hypothyroidism (SCH), a grey area of reduced thyroid function that shares some overlapping symptoms with perimenopause and menopause. Once initiated, levothyroxine is typically taken daily for life.

A growing body of research shows levothyroxine has little to no impact on SCH symptoms, and at the same time, is associated with an increased risk of dementia, atrial fibrillation, stroke, and fractures.

Mind Over Matter® spoke with two leading thyroid experts studying SCH overtreatment. Dr. Jennifer Mammen, an endocrinologist at the Johns Hopkins Bayview Medical Center and Assistant Professor at the Johns Hopkins School of Medicine in Baltimore, Maryland, is investigating how to distinguish whether decreases in thyroid function in older adults are signs of thyroid failure that needs treatment or protective mechanisms associated with aging.

Dr. Spyridoula Maraka, an endocrinologist at the Central Arkansas Veterans Healthcare System and Associate Professor of Medicine in the Division of Endocrinology and Metabolism at the University of Arkansas for Medical Sciences in Little Rock, Arkansas, is conducting a novel clinical trial to determine whether it's safe and feasible to discontinue levothyroxine prescribed for SCH.

THYROID HORMONES

Your thyroid gland is a small, butterfly-shaped organ that sits at the front of your windpipe below your Adam's apple. It produces hormones that regulate metabolism and affect almost all tissues in your body. ⟶

Hypothyroidism is ten times more common than hyperthyroidism. Hypothyroidism is much more common in women than in men.

Thyroid hormones are also essential for brain development and function. During fetal development, thyroid hormones influence the growth and organization of neurons, glial cells, synapses, and the insulating myelin sheath around nerves.

Worldwide, many pregnant women and newborns are screened to identify thyroid hormone problems as soon as possible because thyroid hormone deficiency during critical transition periods of fetal brain maturation can cause intellectual deficits and neurological impairments in babies.

IN ADULTS, IMBALANCES IN THYROID HORMONES CAN CAUSE CONFUSION, MOOD DISORDERS, DEMENTIA, AND PERSONALITY CHANGES.

The thyroid is controlled by your pituitary gland, a pea-sized organ located behind the nose at the base of the brain. It detects the level of thyroid hormone in your blood and adjusts the level of thyroid stimulating hormone (TSH) it secretes, which in turn tells the thyroid how much of two hormones called thyroxine (T4) and triiodothyronine (T3) to produce.

"A good metaphor for understanding the role of TSH is driving a car," said Dr. Mammen. "TSH is the pressure on the gas pedal. It looks at the thyroid hormone in circulation the way you look at your speedometer and adjusts TSH to maintain your target speed, your metabolic rate."

THYROID DISORDERS

Hyperthyroidism is a disorder that occurs when the thyroid produces too much T4 and T3. The pituitary gland eases up on the gas pedal and lowers TSH, trying to tell the thyroid gland to reduce T4 and T3 production.

Symptoms of hyperthyroidism may include weight loss despite an increased appetite, more bowel movements, irritability, fatigue, vision problems, light menstruation, increased sweating, nervousness, shaking hands, and insomnia. The most common cause of hyperthyroidism is Graves' disease, an autoimmune disorder.

Hypothyroidism, on the other hand, is a disorder that occurs when the thyroid doesn't produce enough T4 and T3. The pituitary gland presses harder on the gas pedal, increasing TSH to tell the thyroid gland to make more T4 and T3.

SYMPTOMS OF HYPOTHYROIDISM MAY INCLUDE WEIGHT GAIN, CONSTIPATION, FATIGUE, DRY SKIN AND HAIR, HEAVY MENSTRUATION, INTOLERANCE TO COLD, JOINT AND MUSCLE PAIN, AND A SLOWED HEART RATE.

Hypothyroidism is associated with depression, bipolar affective disorders, and decreased cognitive function. The most common cause of hypothyroidism is Hashimoto's thyroiditis, an autoimmune condition that destroys thyroid tissue.

Thyroid disorders are diagnosed with a blood test that evaluates TSH, T4, and sometimes T3 and the presence of autoimmune antibodies. Reference ranges may vary slightly between different lab tests.

OVERT VS. SUBCLINICAL HYPOTHYROIDISM

Overt hypothyroidism, indicated by high TSH and low T4, is rare, occurring in less than half of a percent of the general population. Treatment is essential to reverse memory problems, slowed thinking, and sluggish physical movements. All diagnostic guidelines for dementia include screening for thyroid dysfunction because if overt hypothyroidism is causing the symptoms, it is easy to address them with treatment.

However, defining SCH and determining whether it should be treated, especially in older adults, is controversial. "So-called 'subclinical hypothyroidism,' found in about 11 to 15% of older adults, is really a laboratory definition, not a disease," said Dr. Mammen.

"We mostly see isolated elevated TSH readings between 4.5 mIU/L and the upper end of the reference range, around 10 mIU/L, with T4 levels that look fine." Only about 2 to 5% of subclinical hypothyroidism cases may progress to overt hypothyroidism annually.

Keep in mind that your TSH level may be affected by many factors. Just as the pituitary gland controls the thyroid, the hypothalamus, a structure located at the base of the brain, controls the pituitary gland.

"The hypothalamus adds another regulatory layer to thyroid hormone production for maintaining metabolic homeostasis. It integrates many factors, including whether you've recently eaten or fasted, gained or lost weight, slept sufficiently, or are stressed, healthy, or sick," said Dr. Mammen. "That information also determines how much TSH the pituitary makes."

Therefore, an elevated TSH caused by factors other than thyroid problems may return to normal after those issues resolve, so your physician should consider your whole health history and not prescribe treatment based on one somewhat elevated TSH result.

QUESTIONABLE TREATMENT BENEFITS

Once initiated, levothyroxine is taken daily and requires not consuming any food containing calcium or iron within four hours. However, evidence shows that it provides no benefit in improving symptoms and quality of life and little to no benefit in improving cardiovascular events or mortality when taken for SCH.

Three randomized, placebo-controlled blinded studies of levothyroxine in patients with SCH showed no improvement in depression or psychological distress measures, according to a review by Dr. Mary Samuels, an endocrinologist at the Oregon Health & Science University, in Portland, Oregon, published in *Endocrinology & Metabolism Clinics of North America* in 2014.

A large, double-blind, randomized, placebo-controlled trial led by Dr. David Stott at the Glasgow Royal Infirmary in the United Kingdom found that levothyroxine provided no benefits for older adults with SCH defined as TSH between 4.6 and 19.99 mIU/L and T4 within the reference range. There were no differences in hypothyroid symptoms, tiredness, or cognitive function measures between those who received treatment compared with those who took a placebo. The study was published in *The New England Journal of Medicine* in 2017.

OVER-TREATMENT RISKS

Studies have shown that over-treating hypothyroidism is associated with harms. For example, about 40% of patients over 65 taking levothyroxine develop hyperthyroidism, increasing the risk of irregular heart rhythms, stroke, bone loss, and fractures.

A retrospective population study of Taiwanese adults ages 65 years and older found that a history of hypothyroidism was associated with an 81% increased risk of having dementia, and taking thyroid hormone replacement therapy was associated with a three-fold increased risk of having dementia. Dr. Chien-Hsiang Weng, a family medicine physician with Lifespan health system and Clinical Assistant Professor at the Warren Alpert Medical School of Brown University in Providence, Rhode Island, led the large case-control study published in *Neurology* in 2022.

> **WHILE THIS STUDY DID NOT CAPTURE DATA ON THE SEVERITY OF THE HYPOTHYROIDISM FOR WHICH THYROID HORMONE REPLACEMENT WAS PRESCRIBED, IT STILL SERVES AS A WARNING SIGN ABOUT THE POTENTIAL HARMS OF OVER-TREATING OLDER ADULTS.**

More research is needed to tease out the mechanisms that may explain these findings.

CHANGES IN AGING

An elevated TSH is more common with aging. However, determining whether an increasing TSH signals hypothyroidism that needs treating or is a protective adaptation is a current area of investigation.

Dr. Mammen and colleagues analyzed data from the Baltimore Longitudinal Study of Aging (BLSA) to examine relationships between functional mobility, fitness, fatigue, and normal free T4 (FT4), defined as between 0.76 and 1.5 ng/dL.

They discovered that older adults at the lower end of the normal FT4 range had better mobility, fitness, and fatigue profiles than those at the higher end. Their findings, published in the *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* in 2016, added further weight to a growing body of evidence showing that declining thyroid function may align with healthy longevity.

Since 2019, Dr. Mammen has been leading a multi-year research grant funded by the U.S. National Institute of Aging exploring changes in the hypothalamic-pituitary-thyroid axis in aging adults. The project aims to identify markers for determining which individuals truly require thyroid hormone treatment by looking at TSH activity, the ability of the pituitary gland to respond to stimulation, the presence of antibodies, and other blood tests.

> **“THIS WORK IS IMPORTANT BECAUSE TREATMENT DOES NOT SEEM TO IMPROVE COGNITIVE FUNCTION AND OVER-TREATMENT HAS THE POTENTIAL TO WORSEN COGNITIVE FUNCTION. OVER-TREATMENT ALSO INCREASES THE RISK OF IRREGULAR HEART RHYTHMS AND BONE LOSS IN AN ALREADY VULNERABLE POPULATION OF AGING ADULTS,**

Dr. Mammen said. The research has produced some important findings. For example, she and her colleagues found that among 1,295 adults in the BLSA who were followed for nine years, those with normal TSH levels while taking levothyroxine had an 81% increased risk of mortality compared to those with normal TSH levels not taking the medication. Their study was published in the *Journal of the American Geriatrics Society* in 2021.

They also discovered that FT4 may be a useful marker for differentiating whether a transient, isolated elevated TSH is due to early development of SCH or represents an adaptation to age-related stress. Dr. Mammen and her team identified that FT4 levels in the lowest quartile of the reference range were associated with developing hypothyroidism due to thyroid failure, whereas higher and rising FT4 readings were found in older adults with evidence of an aging adaptation in the analysis of their hypothalamic-pituitary-thyroid axis. Their study was published in *Frontiers in Endocrinology* in 2022.

Currently, TSH reference ranges for adults apply to people ages 18 and up, with no separate range for those 65 and older. →

"We should probably be using different reference ranges for older adults that are a bit higher, just as we have lower reference ranges for pregnancy, and also evaluate FT4 to ensure caution when deciding to initiate treatment in older adults," said Dr. Mammen.

"The third National Health and Nutrition Examination Survey suggests a TSH of about 5.6 to 5.9 at the upper end is more appropriate for adults 65 and older, whereas most lab tests have it somewhere between 3.5 and 4.5 for all adults."

IS DEPRESCRIBING POSSIBLE?

In a systematic review and meta-analysis of clinical outcomes after discontinuing thyroid hormone replacement, Dr. Maraka and colleagues found evidence in 17 observational studies that suggested up to one-third of patients remained at normal TSH levels after discontinuing treatment.

They also found that a higher percentage of those who had an initial diagnosis of SCH remained at normal TSH levels after discontinuing treatment, compared to those with overt hypothyroidism. The paper was published in *Thyroid* in 2021.

Next, Dr. Maraka led a double-blind, placebo-controlled clinical trial to determine the impact of stopping levothyroxine in adults treated for mild SCH with an elevated TSH no greater than 10 mIU/L. She presented the interim trial results at the American Thyroid Association's 2022 Annual Meeting.

Study participants were primarily older men, including 20 who continued to take their usual dose of levothyroxine (25 to 75 micrograms daily) and 20 who received a placebo. There were no differences between groups for TSH, FT4, antibody positivity, or clinical symptoms at baseline.

However, after eight weeks, only 36.8% of participants in the placebo group developed SCH, much lower than expected, with an average TSH of 5.5 mIU/L. By contrast, 10% of those who kept taking levothyroxine developed SCH, with an average TSH of 2.7 mIU/L in the group overall.

Notably, there were no significant differences between groups in patient-reported symptoms, quality-of-life measures, or tiredness, and no reports of hypothyroidism or cardiovascular events, such as stroke, heart failure, atrial fibrillation, bone fractures, or deaths.

> **IT IS UNCLEAR WHY SO MANY PHYSICIANS HAVE TREATED PATIENTS FOR SUBCLINICAL HYPOTHYROIDISM OR WHY MANY PATIENTS ARE UNAWARE OF THE REASONS WHY THEY WERE PRESCRIBED LEVOTHYROXINE IN THE FIRST PLACE. OUR FINDINGS SUGGEST THAT IT IS FEASIBLE AND SAFE TO DISCONTINUE LEVOTHYROXINE IN PATIENTS WITH A HISTORY OF SUBCLINICAL HYPOTHYROIDISM. HOWEVER, THE DECISION REQUIRES CAREFUL CONSIDERATION AND DISCUSSION.**

Dr. Maraka and her research team will report the final results after analyzing six months of data. They are also planning to conduct a larger, multisite trial in the future.

"Doctors should explore other factors first before jumping to start thyroid hormone replacement for patients experiencing difficulties losing weight, fatigue, or memory loss," said Dr. Maraka. "There is a great need for patient-centred care and shared decision-making, with a full review of symptoms and discussion about the anticipated benefits and long-term side effects of levothyroxine treatment."

THE BOTTOM LINE

The benefits of taking levothyroxine for SCH are questionable and may put your physical and brain health at risk, especially as you age. If you think you may be unnecessarily treated for SCH, speak to your doctor.

Any changes to your medication, such as reducing your dose or discontinuing treatment, will require close medical supervision.

You can also request a referral to an endocrinologist for a more complete thyroid health evaluation and management of treatment plan changes.