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Mind Over Matter®

VOLUME 20

HELPING YOU PROTECT YOUR BRAIN HEALTH

Ozempic & *Brain Health*

Ovarian Removal at Mid-life

Hope for *Dementia*

Let's Get *Physical*

Childhood Dementia

Wildfire Smoke

Women's Brain Health Initiative

Advancing Women's Brain Health

Through Collaborative Research

In this edition, Mind Over Matter® spotlights two transformative research programs powered by Brain Canada and its partners, Women's Brain Health Initiative (WBHI) and Weizmann Canada, demonstrating a collective commitment to advancing brain health.

Connecting Minds: Pioneering New Frontiers in Brain Health Research, on page 32, features a joint initiative between Brain Canada, the Weizmann Institute of Science, and Weizmann Canada, which is breaking new ground in open science. Through team grants, this novel pilot program is dismantling traditional silos and fostering interdisciplinary research to enhance our understanding of the brain.

Let's Get Physical: Building & Connecting the Brain Through Exercise, on page 47, explores the impact of physical activity on the brain. By considering sex and gender differences and the relationship between different kinds of exercise and brain function, this research, conducted by WBHI Future Leader in Canadian Brain Research Dr. Cindy Barha, is uncovering critical insights into brain aging and resilience.

Although just a sampling of the inspiring work underway to advance women's brain health, these projects illustrate Brain Canada's commitment to enabling research that considers sex and gender differences while improving health for all.

Our work is made possible by the Canada Brain Research Fund (CBRF), an innovative arrangement between the Government of Canada (through Health Canada) and Brain Canada.

We are deeply grateful for our partnership with WBHI. Together, we look forward to making meaningful contributions to advancing brain health for all Canadians.

Sincerely,

Viviane Poupon, PhD
President & CEO, Brain Canada

Editor-in-Chief

Welcome to the 20th edition of Mind Over Matter®! Reaching this milestone is a testament to the ongoing and generous support of our incredible partner, **Brain Canada** – we simply couldn't do it without them.

Their commitment to focusing research on sex and gender differences is crucial for understanding how to better address women's unique needs, ensuring that advancements in brain health research benefit everyone more equitably. Their dedication to advancing brain health research and making knowledge accessible has helped shape **Mind Over Matter®** into the trusted resource it is today.

We're also beyond thrilled to feature **Jann Arden** on this issue's cover. As a celebrated artist and devoted caregiver, Jann's journey is one of resilience, humour, and deep wisdom. Her story reminds us of the profound role caregiving plays in shaping lives, and we're honoured to share her insights with you.

In every edition, our mission remains the same: to bring you the latest research on brain health in a way that's understandable, practical, and engaging.

This issue is no exception. We explore some of the most current findings, including the latest research on Ozempic and brain health, shedding light on its effects beyond weight loss.

We also examine the impact of wildfire smoke on cognitive function, highlighting the emerging evidence on air quality and brain health. Additionally, we delve into the risks associated with ovarian removal at mid-life and its long-term impact on cognitive function.

Exercise remains one of the best tools for brain health, and we explore its continued benefits. We also discuss the positive lifestyle changes we can make today to reduce our risk of cognitive decline – because we have more control than we may realize.

What you eat and what you don't influences your brain, which is why we share delicious recipes from leading chefs in each edition, and this one features recipes from **Celebrity Chef David Rocco**. We also highlight beneficial dietary plans for your brain.

And we're sharing a wonderful tribute to the **Fisher family**, an inspiring entrepreneurial family of women who share their story as they celebrate the **40th anniversary** of their thriving business.

WITH EACH ARTICLE, WE AIM TO EMPOWER YOU WITH KNOWLEDGE AND ACTIONABLE INSIGHTS TO SUPPORT LIFELONG BRAIN HEALTH.

Whether you're a caregiver, a researcher, or someone simply looking to stay sharp and proactive, we hope this issue inspires and informs.

Thank you for being part of this journey with us. Here's to the next 20 editions and beyond!

Warmly,

Lynn Posluns
President and CEO,
Women's Brain Health Initiative

PHOTO: JAYLYN TODD

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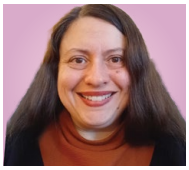


ALEX MLYNEK // MANAGING EDITOR

Alex Mlynek is a Toronto-based journalist who has worked as an editor for *Today's Parent* and *Canadian Business* magazines. Her writing has appeared in a number of publications, including *Reader's Digest*, *Broadview*, *Chatelaine*, *Best Health*, *The Walrus* and *Report on Business*. She loves telling a good story and making copy entertaining and accurate. When she isn't hanging out with her husband and two kids, you will likely find Alex in her garden or with her nose in a book.

WENDY HAAF // WRITER

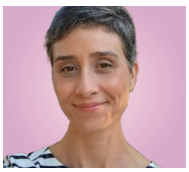
Wendy is a freelance health writer based in London, Ontario. As a longtime contributor to a Canadian retirement magazine, she has regularly covered topics related to healthy aging. A mother of three, including two adult daughters, and grandmother to two granddaughters, she is particularly interested in providing women with evidence-based information about what they can do to protect and maintain their brain health throughout life.

STEPHANIE HAHN // WRITER

Stephanie is a writer and yoga instructor living in Waterloo Region, Ontario. It was through the "gift" of back pain that Stephanie learned to slow down, listen to her body, and rediscover the joys of moving. "Writing for this magazine allowed me to merge my love of writing with my love of spreading the word that stress relief is critical for health."

JANE LANGILLE // WRITER

Jane is a health and medical writer living in Richmond Hill, Ontario, who writes for healthcare organizations, hospitals, and academic health research institutions in Canada and the United States. Having seen close family members deal with progressive supranuclear palsy and Parkinson's disease, she enjoys interviewing experts to learn about the latest advances in women's brain health and sharing evidence-based insights.



ILIMA LOOMIS // WRITER

Vancouver-based Ilima Loomis is a freelance science writer whose work has appeared in publications like *Science, Popular Science, and Discover.* Having seen close family members cope with neurodegenerative conditions like Parkinson's disease and dementia, she is always eager to learn more about brain health, speak with experts, and share information with other women.

SEAN MALLEN // WRITER

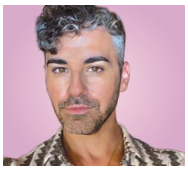
Sean is a Toronto-based communications consultant, media trainer, and writer. Having seen close family members deal with dementia, he is a passionate supporter of WBHI's mission and is inspired by telling the stories of researchers who are expanding our knowledge of women's brain health. Sean's first book, *Falling for London: A Cautionary Tale* from Dundurn Press, is widely available across North America and the United Kingdom.

SUBHA RAMANATHAN // WRITER

Subha is a director and research consultant for Atmoco Ltd., specializing in health promotion through physical activity. With a PhD in public health, Subha helps non-profits collect relevant information, make research findings understandable, and put recommendations into action. She also teaches a university course in sustainable happiness. Writing for Mind Over Matter® unites Subha's knowledge, skills, and desire to share information and strategies that enhance brain health and overall well-being.

VITINA BLUMENTHAL // CREATIVE DIRECTOR

For more than a decade, Vitina – founder of Align Creative Minds – has lent her branding and design expertise to WBHI, aligning her passion for mindful living with the organization's mission to safeguard the mental and brain health of women. Her grandparent's dementia diagnosis brought new meaning to this work, inspiring her to prioritize her own cognitive health and appreciate WBHI's ongoing educational support.



GREGORY CIRA // CREATIVE DESIGNER

Gregory is an established design entrepreneur with an acuity for information design and understands the importance of communicating clearly. Having had family members who suffered from dementia, he has been inspired to raise awareness of the importance of brain health and uses his visual communication skills to help bring that awareness to others.

JANN ARDEN // ON THE COVER

Jann Arden is not only one of Canada's most celebrated musicians, she has also become an eloquent and powerful advocate for care partners. This advocacy grew out of her experience caring for her mother, who passed away from Alzheimer's disease in 2018.

"I've learned more about myself – and became a better version of myself – because of the experience," said Jann in an interview for the cover story of Mind Over Matter®'s landmark 20th edition.

She is also a big supporter of the educational and research programs supported by Women's Brain Health Initiative.

"It's probably one of the most important missions that anybody is on."

WE ARE TRULY GRATEFUL TO:

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Brain Canada recognizes Women's Brain Health Initiative for its role in educating the public about the importance of women's brain health and the role of prevention, but neither Brain Canada nor the Minister of Health or the Government of Canada are responsible for the accuracy of the contents of this magazine.

The production of this magazine has been made possible in part with the financial support of Health Canada, through the Canada Brain Research Fund, an innovative partnership between the Government of Canada (through Health Canada) and Brain Canada. To date Health Canada has invested over $145 million through the CBRF which has been matched by Brain Canada Foundation and its donors and partners.

Ozempic & Brain Health

A Breakthrough or Just Another Trend?

Unless you've been living under a rock lately, you've heard of Ozempic®.

You may think of it as a weight loss medication, but Ozempic is technically only approved for lowering blood sugar and reducing the risk of heart attack and stroke in people with Type 2 diabetes.

It's not your fault for thinking Ozempic is for weight loss. Off-label demand for it soared in 2022 when there were supply shortages of Wegovy®, an approved medication for treating obesity. Wegovy contains semaglutide, the same active ingredient found in Ozempic.

Semaglutide belongs to a class of medications called glucagon-like peptide-1 (GLP-1) agonists. Many celebrities, including Oprah Winfrey, Sharon Osbourne, Whoopi Goldberg, and Kathy Bates, have reported that GLP-1 drugs helped them achieve their weight loss goals.

Part of the success of these blockbuster drugs is that they don't just act on the gut; they also act on the brain.

Researchers are now investigating whether they may provide additional brain health benefits, such as helping people quit cigarette smoking and as a potential treatment for early Alzheimer's disease (AD).

GLP-1 & GLP-1 DRUGS

GLP-1 is an endocrine hormone produced in the small intestine in response to eating. It triggers the pancreas to release insulin, the hormone that allows your body to convert food to energy and lowers blood glucose levels.

GLP-1 produced in the gut communicates with receptors in the brain through the central nervous system. When GLP-1 binds to receptors in the hypothalamus, it activates neurons that promote feelings of fullness and inhibits neurons that produce hunger signals. Scientists have discovered the brain also makes GLP-1.

GLP-1 drugs mimic the GLP-1 hormone, binding to GLP-1 receptors and causing the same effects as natural GLP-1, including enhancing the release of insulin to lower blood sugar, inhibiting the release of glucagon, a hormone that raises blood sugar, delaying gastric emptying, and promoting satiety.

The U.S. Food and Drug Administration approved exenatide (Byetta®), the first GLP-1 drug for treating diabetes, in 2005. More recently, the drug class has expanded significantly

to include several others, such as liraglutide (Saxenda® or Victoza®) and tirzepatide (Mounjaro® for diabetes and Zepbound® for weight loss).

OBESITY IS A BRAIN DISORDER

Experts are increasingly regarding obesity as a brain disorder, not a failure of willpower or just a reflection of personal diet and exercise choices.

"Obesity is now considered a disease not of the intestines or your stomach, but of the brain. It's a huge shift in the way that we think, with huge implications for treatment," said Dr. Sanjay Gupta, CNN Chief Medical Correspondent, in his special report *Is Ozempic Right for You?* that aired on CNN in November 2024. "But these are still early days, and remember, at one time, even depression and addiction were seen as failures of willpower instead of a brain disease. Changing the perception of obesity – that's going to take time."

According to Obesity Canada, obesity is a chronic disease of the brain involving an imbalance in the regulation of energy intake and expenditure to maintain weight.

Complex and powerful interactions between genetic, environmental, behavioural, and social factors cause disruptions in the hypothalamus, the "control centre" deep in the brain that manages hunger, body temperature, heart rate, mood, sleep, and sex drive. The imbalance results in excess body fat that has a negative impact on physical and mental health, as well as quality of life.

GLP-1 DRUGS FOR PEOPLE WHO ARE OVERWEIGHT OR OBESE

The Oscar-winning actress Kathy Bates, 76, told *People* magazine she lost 80 pounds over seven years through diet and lifestyle changes and then used Ozempic to lose another 20 pounds. She was diagnosed with Type 2 diabetes in about 2017.

Like Ozempic, Wegovy is taken once weekly by injection. In the clinical trial that led to its approval for treating overweight and obesity in people without diabetes, Wegovy led to a 15% decrease in body weight (an average loss of 15.3 kg) compared to a drop of only 2.4% (or 2.6 kg) in people who took a placebo over 68 weeks.

The results of the international Phase 3 study, the STEP trial, were published in March 2021 in *The New England Journal of Medicine*. Interestingly, 74% of the study participants were women.

Wegovy comes with some unwanted side effects. In the STEP trial, 74% of people taking the drug experienced gastrointestinal problems like nausea, diarrhea, vomiting, and constipation, compared with 48% in the placebo group. Most of these issues were mild-to-moderate in severity, with nausea being the most common, and mainly emerging during the dose-escalation period.

The study authors wrote, "Weight loss with semaglutide stems from a reduction in energy intake, which is thought to result from direct and indirect effects on the brain." People who have taken semaglutide for weight loss have also reported the drug quiets persistent thoughts about what to eat, called "food noises."

GLP-1 DRUGS FOR SMOKING CESSATION?

About a decade ago, while working as a nurse practitioner in a family practice, Dr. Luba Yammine prescribed GLP-1 medications to patients with Type 2 diabetes. She was surprised when some reported they were no longer craving cigarettes or quit smoking altogether.

GLP-1 DRUGS MAY INDEED HELP PEOPLE STOP SMOKING, ACCORDING TO A GROWING BODY OF EVIDENCE.

For example, semaglutide was associated with a lower risk of nicotine dependence compared to other medications for Type 2 diabetes in an analysis of patient records of 20,000 Americans. Conducted by researchers at the University of Oxford, the study was published in the journal *eClinicalMedicine* in July 2024.

Another study published a month later in *Annals of Internal Medicine* by researchers at Case Western Reserve University School of Medicine in Cleveland, Ohio, found that compared with some other medications for diabetes, semaglutide use was associated with a lower risk of healthcare visits related to tobacco use and fewer prescriptions for smoking cessation therapies and counselling appointments in patients with Type 2 diabetes who smoked at baseline.

These findings were similar for people with and without obesity, and most differences occurred within 30 days of starting the medication.

In the U.S., 77.1% of men are overweight or obese compared to 69.4% of women. In Canada, the rates are somewhat lower at 70% for men and 61.5% for women in 2023.

A study by researchers at the University of Pennsylvania and Cedars-Sinai Medical Center in Los Angeles found that the number of people with overweight or obesity but not diabetes who started taking GLP-1 drugs in the U.S. grew by 700% from 2019 to 2023. Between 2011 and 2023, 60% of new users were women.

"These observational studies provided promising, albeit unproven, signals," said Dr. Yammine, an associate professor in the Department of Psychiatry and Behavioral Sciences at McGovern Medical School at UTHealth Houston.

"We believe that GLP-1 drugs may help with smoking cessation in two primary ways: (1) by modulating the release of dopamine in the reward pathways of the brain and thereby reducing the motivation to smoke; and (2) by causing aversion via acting on the brain area called the habenula, resulting in unpleasant effects. For example, some patients have told me that after starting to take GLP-1 drugs, cigarettes became stale-tasting and smoking made them feel nauseated," Dr. Yammine explained.

These effects are similar to quieting food noises and causing nausea in people taking GLP-1 drugs for overweight and obesity.

"WE THINK THAT THE EFFECTS OF THESE DRUGS ON CONSUMING FOOD AND SUBSTANCES OF ABUSE ARE SIMILAR BECAUSE THE CENTRES IN THE BRAIN THAT ARE RESPONSIBLE FOR FOOD AND DRUG REINFORCEMENT OVERLAP.

Dr. Yammine conducted a pilot study of the GLP-1 drug exenatide in combination with a nicotine patch in 84 people who smoked and had prediabetes and/or were overweight.

Results showed that the treatment combination improved smoking abstinence, reduced withdrawal symptoms and cravings, and decreased post-cessation weight gain compared with the nicotine patch alone. The study results were published in *Nicotine & Tobacco Research* in April 2021.

"Studies show that 80% to 90% of individuals who quit smoking gain an average of five to 15 pounds of body weight by the end of the first year," said Dr. Yammine. "About 14% gain more than 20 pounds, which may have negative health consequences, such as new-onset Type 2 diabetes and other metabolic problems."

"WEIGHT GAIN ASSOCIATED WITH QUITTING SMOKING IS ALSO PROBLEMATIC BECAUSE IT MOTIVATES SOME PEOPLE TO RETURN TO SMOKING JUST TO MAINTAIN A LOWER BODY WEIGHT.

"While the fear of post-cessation weight gain is endemic among women who smoke, it is also a concern among men," she added.

The pilot study results formed the basis for two Phase 2 trials led by Dr. Yammine: a study of exenatide opened in December 2022 at two sites in Houston and a study of semaglutide began April 2024 in Houston and Austin. The trials are evaluating these GLP-1 drugs in the context of smoking cessation in patients who are overweight or obese and/or have elevated blood glucose levels indicative of prediabetes.

In addition to examining whether GLP-1 agonists improve smoking and weight outcomes, the researchers are trying to understand *how* these medications work in the context of smoking cessation.

For example, participants in the exenatide study will undergo electroencephalography testing at the beginning of the study and after several weeks of taking the medication to assess for any changes in how the brain responds to smoking- and food-related images as a result of taking the medication.

"If the research confirms that GLP-1 drugs are beneficial for smoking cessation and prevention of weight gain in those who quit smoking, that would be a game-changer for a whole lot of people.

SEMAGLUTIDE FOR EARLY ALZHEIMER'S?

Researchers are also studying semaglutide as a potential treatment for early AD and mild cognitive impairment (MCI).

"While the field has made much progress with new treatment options for people with Alzheimer's disease, the recently approved drugs for removing amyloid are not a home run. We need to cast a wide net and keep exploring other

treatment avenues," said Dr. Carmela Tartaglia, Site Clinical Research Unit Medical Lead and Director of the Memory Clinical Trials Unit at Toronto Western Hospital, University Health Network, and associate professor in the Temerty Faculty of Medicine at the University of Toronto.

Researchers at Case Western Reserve University School of Medicine studied the association between GLP-1 drugs and a first-time diagnosis of AD in health records.

They found that semaglutide use was associated with a 40% to 70% lower risk of a first-time AD diagnosis compared to seven other diabetes medications, including insulin and other GLP-1 drugs. The findings held regardless of obesity status, gender, and age, suggesting semaglutide may have potential for preventing AD.

In their paper published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in October 2024, these authors noted that semaglutide has demonstrated it can reduce neurotoxicity caused by amyloid buildup, enhance the clearance of dead cells, improve brain glucose uptake, and reduce amyloid-beta plaques and tau tangles in preclinical studies.

"GLP-1 drugs work on receptors all over our bodies, including in the brain," Dr. Tartaglia explained.

EMERGING EVIDENCE ALSO INDICATES SEMAGLUTIDE CAN REDUCE INFLAMMATION AND MAYBE IMPROVE DNA REPAIR, ADDING TO THE COMPELLING RATIONALE FOR STUDYING THEM IN THE CONTEXT OF EARLY ALZHEIMER'S.

At Toronto Western Hospital, Dr. Tartaglia is the principal investigator of two clinical trials testing whether semaglutide may improve cognition in people with early AD or MCI compared to taking a placebo. The hospital is one of 340 international locations participating in the Phase 3 studies, called EVOKE and EVOKE Plus.

Both trials compare oral semaglutide taken once daily to a placebo over a period of 173 weeks (about three years and four months) in adults aged 55 to 85. Eligible participants have a confirmed diagnosis of early AD or MCI, are amyloid positive, and scored 22 or higher on a Mini-Mental State Examination.

Dr. Tartaglia and her team are assessing study participants' cognitive function and their ability to function in daily life activities according to self-reports or reports from their study partner such as a spouse or care partner. They are also looking at the time to progression in AD or MCI disease stage, and inflammation as measured by C-reactive protein in the blood.

A new treatment to help people stop smoking would be a welcome advancement. Despite the fact the percentage of American adults who smoke declined from 42% in 1965 to about 12% in 2022 smoking remained the leading cause of preventable disease and death.

Canadian statistics show similar trends, decreasing from about 50% of adults smoking in 1965 to about 10% in 2020. Tobacco use is the leading modifiable risk factor for disease and death in Canada, according to the Canadian Cancer Society.

"One of the nice things about the EVOKE Plus study is that it includes people with cerebrovascular disease. These individuals are often excluded from Alzheimer's trials, but the two diseases frequently occur together," said Dr. Tartaglia.

> ***Semaglutide may attack the Alzheimer's pathology and also have a positive effect on the cerebrovascular pathology.***

Dr. Tartaglia is cautiously optimistic about the potential of semaglutide for treating early AD and MCI. "The current pipeline of drugs that are being tested for Alzheimer's is very vast, targeting many different pathways," she said. "GLP-1 drugs may show a benefit but we won't know until we see study results in 2025 or 2026. Until then, we're keeping an open mind."

TIME WILL TELL

While obesity, tobacco use disorder, and AD continue to affect the lives of so many people, there is still much to learn about how GLP-1 drugs affect the brain and whether they will prove to be beneficial for these brain health issues. Mind Over Matter® is cautiously optimistic that the clinical research underway may lead to new approved treatments in the future.

FURTHER READING

Magic Pill: The Extraordinary Benefits and Disturbing Risks of the New Weight-Loss Drugs
by Johann Hari

If I Could Turn Back Time

Is Aging Inevitable?

Throughout history, humans have been fascinated with the idea of preventing aging. Tales of a fictional Fountain of Youth, which will restore health and vigour by drinking or bathing in the water, have been told by various cultures over the centuries.

Fascination with the Fountain of Youth myth reflects our desire to reverse, or at least slow, the aging process.

This fascination with eternal youthfulness is evident in the high demand for anti-aging products and services.

According to Statista, spending on anti-aging globally was estimated to be approximately US$47 billion in 2023 and is predicted to rise to nearly US$80 billion by 2032.

The allure of eternal youthfulness is also increasingly evident in the research community. There has been a recent explosion in research, with more than 300,000 academic papers on the topic of aging being published in the past ten years, approximately the same number that were published on the subject in the previous *century*. Also, billions of dollars are being invested in longevity startup companies.

In this article, we'll explore what aging is and what we know about the biology of aging and highlight findings from recent research into anti-aging interventions.

WHAT IS AGING & WHAT ARE ITS UNDERLYING DRIVERS?

The cells in our bodies don't last forever. Their structure and function deteriorate as we age, and this results in increased susceptibility to age-related diseases. This aging process is complex and involves several inter-related bodily mechanisms and systems.

In a 2023 review published in *Cell*, Dr. Carlos López-Otín and colleagues shared 12 underlying drivers of aging, i.e., "hallmarks of aging," that can potentially be prevented, slowed, or reversed to improve health and extend lifespan.

There are some species that don't age, such as tiny freshwater creatures called hydra and the "immortal" jellyfish. They don't actually live forever but hypothetically they could because their bodies don't experience the age-related decline that other species do; instead, they die from other causes, like starvation or being killed.

01 Genomic (DNA) Instability.

Our DNA contains the instructions for all the various cellular functions in the body. It faces constant challenges from external sources, such as ultraviolet radiation and chemical exposure, as well as internal sources, such as replication errors.

This leads to DNA damage that accumulates with age, corrupting the instructions given to the cells. The resulting unhealthy cells either die off or senesce, which compromises tissue and organ function, leading to disease. (You'll learn about cell senescence in another hallmark later on.)

02 Telomere Attrition.

Our DNA is housed in chromosomes, which have protective telomeres on the ends, which look much like the caps on the ends of shoelaces. Each time a cell divides and duplicates our DNA information, a little bit of telomere gets chopped off, damaging the DNA. Eventually, the telomere is all used up, and the cell can no longer divide, so it dies or senesces.

03 Epigenetic Alterations.

The two previous hallmarks involve damage to the DNA itself, i.e., the instructions. Epigenetic alterations are different; they don't change the instructions, but instead affect *which* instructions are followed, i.e., which genes are turned on or off.

Epigenetics change over time in response to environmental factors such as exposure to external stressors and lifestyle choices. So, as we age, more of the "wrong" genes are turned on, increasing the risk of developing age-related diseases.

04 Loss of Proteostasis.

Our cells use the instructions from our DNA to create proteins that are then folded into their functional shape. This process is prone to error, so our bodies have mechanisms in place to fix or remove any of these protein-related errors. However, as we age, these mechanisms don't work as well, leading to the accumulation of dysfunctional, toxic proteins – which contribute to age-related diseases like Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).

05 Disabled Macroautophagy (Autophagy).

Each of our cells contains multiple parts that, over time, can become defective or stop working. Our bodies use a process called autophagy to clean up these unwanted

cell parts, and the effectiveness of the autophagy process declines with age.

06 Deregulated Nutrient-Sensing.
Because our intake of nutrients varies, our bodies have multiple nutrient-sensing pathways that help ensure our cells get just the right amount of each nutrient at the right time and keep the nutrient levels in our bloodstream within a safe range.

This nutrient-sensing allows the body to respond appropriately – sometimes absorbing and metabolizing nutrients, sometimes converting nutrients from one form to another, and sometimes storing nutrients when they are abundant and then accessing those stores later when nutrients are scarce. Deregulation of these nutrient-sensing pathways plays a key role in the aging process.

07 Mitochondrial Dysfunction.
Mitochondria are the part of cells commonly referred to as the "powerhouse" because their primary function is to produce the energy needed to power the cell.

As we age, mitochondria tend to become unhealthy, and unhealthy mitochondria produce chemicals that damage cells (i.e., oxidative stress), and trigger inflammation and, eventually, cell death.

08 Cellular Senescence.
When cells are damaged, they enter a senescent state where they stop dividing and start to secrete pro-inflammatory molecules and tissue-degrading enzymes. Senescent cells accumulate as we age and contribute to chronic inflammation, which is linked with many age-related diseases.

09 Stem Cell Exhaustion.
Stem cells are a special type of cell that can develop into many different cell types, allowing them, in some cases, to fix damaged tissues. As we age, though, stem cells' regenerative capacity is impaired so that when tissues are damaged, they can no longer be properly repaired.

10 Altered Intercellular Communication.
Information is transferred from one cell to another through intercellular signalling. This communication can happen through direct contact between cells, or via the release of a substance (e.g., neurotransmitter or hormone) that is then taken up by another cell. Aging is associated with compromised intercellular communication.

11 Chronic Inflammation.
Two of the aging hallmarks already mentioned – dysfunctional mitochondria and senescent cells – contribute to inflammation. Chronic inflammation that tends to get worse with increasing age is linked with age-related decline in the immune system and increased risk of numerous age-related diseases as well as all-cause mortality.

12 Dysbiosis (Gut Microbiome Alterations).
The human body is host to trillions of microbes – including bacteria, fungi, and viruses – most of which reside in our gut. (Collectively, the microbes on/in the human body are known as the microbiome.)

While some microbes can make us sick, others play an important role in keeping us healthy, handling a number of essential and beneficial functions in the human body, including nutrient digestion and absorption, and protection against pathogens.

The composition and activity of the gut microbiome shifts gradually during aging, leading to an overall decrease in microbiome diversity.

"The 12 hallmarks of aging that we've identified each represent a potential target for interventions to prolong life or improve health over the lifespan," explained Dr. López-Otín, a professor at the University of Oviedo in Spain.

> ***"All of the hallmarks are strongly inter-related, so if an intervention affects one of the hallmarks positively, it often benefits other hallmarks as well.***

"Human *aging* is inevitable because it is a biological process that is part of our molecular and evolutionary essence. In contrast, *longevity* is plastic and there are some opportunities to extend it, albeit modestly," shared Dr. López-Otín.

"In my view, the main purpose of aging and longevity research should be to try to understand and ameliorate human diseases associated with aging, not to chase a dream of immortality."

RESEARCH TO FIND ANTI-AGING INTERVENTIONS

Researchers are using what is known about why and how we age to guide the search for interventions to slow, reverse, or even prevent some of the typical age-related changes in the body.

Much longevity and anti-aging research to date has been conducted with animals, and while findings from that research certainly inform additional research, they do not on their own indicate which, if any, of the tested interventions could be effective and safe in humans.

Some human trials have been conducted, and Dr. Leonard Guarente and colleagues recently reviewed the research from those trials and shared a summary of the results in *Cell Metabolism* in 2024.

In total, they looked at eight promising drugs and natural compounds that have been tested in humans for their potential to prevent or improve age-associated diseases like diabetes, cardiovascular disease, neurodegenerative diseases, and cancer:

- **metformin** – a drug used to treat diabetes that may help with anti-aging, too;
- **NAD⁺ precursors** – supplements that replenish a small molecule within each cell called nicotinamide adenine dinucleotide (NAD^+) that becomes depleted with age;
- **glucagon-like peptide-1 (GLP-1) receptor agonists** – drugs that mimic the action of GLP-1, a hormone produced in the intestines in response to ingesting food;
- **TORC1 inhibitors, e.g., Rapamycin** – a highly-used drug for immunosuppression;
- **spermidine** – a natural metabolite (i.e., a substance produced during metabolism);
- **senolytics** – compounds that selectively kill senescent cells; examples include the natural flavanol fisetin, the drug dasatinib used in combination with the flavonol quercetin, and the osteoporosis drug zoledronate;
- **probiotics** – oral supplements and fecal transplants of favourable bacterial species; and
- **anti-inflammatories** – drugs including corticosteroids, analgesics such as Aspirin and ibuprofen, and monoclonal antibodies.

Much of the research to date on these eight drugs/ supplements has been exploratory, and although some of them show potential, no miracle drugs or treatments have yet been found that are proven effective and safe in humans for slowing or reversing the aging process.

"After reviewing the evidence from research to date in human clinical trials of anti-aging interventions, we concluded that at this point no drug can be recommended for human use. The leading candidates we looked at in detail show varying degrees of promise and require more research before any firm conclusions can be reached," said Dr. Guarente, a professor at Massachusetts Institute for Technology (MIT).

"At this point, we are very optimistic about the future of anti-aging research. We believe that the next few years will be critical and anticipate that a tipping point will soon be reached where the most viable interventions will become evident, perhaps some of them brand new."

'NOT-SO-SECRET' STRATEGIES FOR AGING WELL

While we wait for researchers to continue their search for an anti-aging drug or supplement, there is much we can do to age well. Simple, old-fashioned, sensible advice about healthy living is the current the "not-so-secret recipe" for living longer and staying well as one ages.

It is well-established that a healthy diet, exercise, and sleep are critical anti-aging "medicines."

These just so happen to be three of the Six Pillars of Brain Health that Women's Brain Health Initiative promotes. It's not surprising that the same actions that will keep your brain healthy as you age are the same actions that will contribute to overall better health in your older years. What's healthy for the brain is healthy for all of the systems and parts in the body!

Creatine: Helpful or Hype?

Can Creatine Supplementation Boost Your Brain?

Have you heard about creatine, a compound your body uses for maintaining cellular energy? Cells in your liver and brain produce creatine. You can also obtain it from your diet or a supplement.

Athletes have been using creatine supplements for decades to enhance muscle mass, performance, and recovery.

A growing number of studies are investigating whether creatine supplementation may help combat a range of brain health issues, such as sleep loss, cognitive fatigue, traumatic brain injury, and even neurodegenerative conditions like Alzheimer's disease (AD).

This article provides an overview of creatine, where it comes from, and a summary of the proven benefits of creatine supplementation for muscle health and emerging evidence on brain health benefits. It also provides some critical caveats to consider before you decide to take a creatine supplement.

WHAT IS CREATINE?

Creatine is a compound produced in your liver and brain from reactions involving the amino acids arginine, glycine, and methionine.

Your liver and brain produce about half of the creatine found in your body. The other half comes from your diet, from foods like red meat, seafood, and poultry.

Almost all of your creatine stores, 95%, reside in your skeletal muscles, and less than 5% are found in your brain. The brain makes creatine and can also bring in creatine produced by the liver or from dietary sources across the blood-brain barrier.

Creatine is essential for high-energy demands during muscle and brain development. Children born with rare genetic errors in making or transporting creatine may develop muscle weakness, gastrointestinal problems, intellectual disabilities, speech delay, and autism-like behaviours.

Depending on the specific genetic defect, oral supplementation with creatine monohydrate can effectively address symptoms if initiated early enough, according to the National Organization for Rare Disorders.

CREATINE HELPS MAINTAIN CELLULAR ENERGY, ESPECIALLY DURING INTENSE PHYSICAL OR MENTAL ACTIVITY.

"Your body uses creatine to regenerate adenosine triphosphate, or ATP, the energy currency used by all cells," said Dr. Austin Perlmutter, a Seattle-based board-certified internal medicine physician, clinical researcher, and *New York Times* bestselling author.

SUPPLEMENTATION FOR MUSCLE HEALTH

Athletes in the Soviet Union and Eastern Bloc countries began using creatine supplements in the 1970s. Elite and recreational athletes worldwide take creatine supplements to enhance muscular strength and recovery.

According to the International Society of Sports Nutrition, creatine monohydrate is a safe, effective, and well-studied supplement for boosting athletic performance, enhancing post-exercise recovery, and helping athletes tolerate heavy training regimens. The U.S. Food and Drug Administration categorizes creatine monohydrate supplements as "generally recognized as safe."

According to the Harvard Medical School, creatine monohydrate supplementation helps muscles rapidly produce energy and may enhance power or bursts of speed during activities such as sprinting and weightlifting. It may also hasten muscle recovery after strenuous activities by providing additional energy for healing.

CREATINE AND SEX-RELATED DIFFERENCES

- **Women can have 70% to 80% less total body creatine stores than men.**
- **Women's brains have lower creatine levels than men, especially in the frontal lobe areas responsible for mood, cognition, memory, and emotion.**
- **Women typically consume significantly less dietary creatine than men.**

It may also help offset the age-related loss of muscle mass, strength, and functional ability, called sarcopenia, along with regular resistance training and a well-balanced diet.

Dr. Darren Candow is Director of the Aging Muscle and Bone Health Laboratory and Director of Research for the Athlete Health and Performance Initiative at the University of Regina in Saskatchewan. His research focuses on developing effective lifestyle interventions that involve creatine supplementation and resistance training for improving muscle, bone, and brain health. He has published numerous review papers summarizing the latest evidence on creatine supplementation.

In a review of the effects of supplementation on women's health across their lifespan, considerable evidence showed that it increases women's strength, power, and athletic performance without a significant change in body weight.

By contrast, men taking creatine monohydrate may rapidly and temporarily gain weight, especially if they use a loading dose strategy or consume it with a recommended 1 g of carbohydrate for every kilogram of body weight.

This research also revealed that creatine monohydrate supplementation may be important for women during life stages that feature increased demand for cellular energy, including during menses, pregnancy, menopause, and after menopause. His paper was published in the journal *Nutrients* in March 2021.

Strong muscles are essential for good brain function. According to Dr. Perlmutter,

"HEALTHY MUSCLES APPEAR TO PROMOTE A HEALTHIER BRAIN IN PART THROUGH THE PRODUCTION OF SIGNALLING MOLECULES CALLED MYOKINES.

Proteins that transmit messages from muscles to other tissues, including the brain, are called myokines. When your muscles contract or grow new cells, myokines released into your bloodstream reach your brain, where they help regulate cognition, mood, and emotions.

Myokines can also help the brain form new neurons and increase the strength of synaptic connections, which in turn improve learning and memory.

SUPPLEMENTATION FOR BRAIN HEALTH?

Processing and transmitting information through electrical signals, the brain's primary activities, requires significant energy. In fact, despite making up only 2% of total body weight, the brain of an average resting adult consumes about 20% of the body's total energy.

Since creatine plays a critical role in maintaining cellular energy during demanding brain activities, researchers have been investigating the potential of creatine monohydrate supplementation in providing brain health benefits.

"Overall, the evidence on whether creatine monohydrate supplementation is beneficial for supporting brain health is in its infancy," said Dr. Candow.

"Average, healthy individuals make enough brain creatine. When brain creatine stores are low, supplementation can increase the levels and may moderately improve cognition and memory in conditions that stress the brain, like sleep deprivation and traumatic brain injury.

Here are some highlights of findings from small studies that explored the effects of creatine supplementation in a range of brain health conditions in humans:

Hypoxia. Brain cells use oxygen to convert ATP into energy. A lack of sufficient oxygen, called hypoxia, is associated with the development of age-related neurodegenerative diseases like AD.

A small study by researchers at the University of Auckland in New Zealand, was the first to demonstrate that creatine monohydrate supplementation could restore cognitive focus after oxygen deprivation.

Normal air contains about 21% oxygen, but in this study, 15 healthy adults, all age 55 or younger, breathed air with only 10% oxygen for 90 minutes after taking a 20 g daily dose of creatine for a week. The paper was published in the *Journal of Neuroscience* in 2015.

Sleep deprivation. A recent small study conducted in Germany found that a high, single dose of creatine monohydrate partly reversed deterioration in cognitive performance due to sleep deprivation compared to a placebo.

A total of 15 healthy adults in their early 20s participated in the study (8 women and 7 men). The creatine dose was 0.35 g per kg of body weight, so a person weighing 70 kg, for example, took 24 g.

The maximum cognitive effect was reached four hours after participants took the creatine monohydrate, and the effect lasted about nine hours. The paper was published in February 2024 in *Scientific Reports*.

> ***"Creatine monohydrate supplementation may help reverse brain fog in a sleep-deprived brain."***

"However, the average young adult getting adequate sleep and nutrition will not notice any magical ability to retain more information when studying for exams, for example," Dr. Candow advised.

Traumatic brain injury (TBI). Altered blood flow in the brain after a TBI leads to an imbalance in the supply and demand for energy in brain cells and reduces brain stores of creatine.

A clinical trial among 39 children and adolescents demonstrated that creatine monohydrate supplementation had promising potential for improving outcomes after TBI.

Taking 0.4 g of creatine per kilogram of body weight daily for six months reduced post-traumatic amnesia, intubation time, and length of stay in intensive care and also improved headaches, dizziness, and cognitive function compared to a placebo. The study was published in 2006 in *The Journal of Trauma and Acute Care Surgery*.

Depression and mood disorders. In a review paper published in *Sports Medicine* in June 2023, Dr. Candow and co-authors noted that lower creatine stores in the prefrontal cortex may be associated with a greater likelihood of

WHAT IS THE OPTIMAL CREATINE SUPPLEMENT DOSE?

"Creatine monohydrate, typically sold in a powdered format, is the most common and most studied creatine supplement. It is similar to what's made naturally in the body and has an exceptional safety profile," said Dr. Candow.

He published a review of the optimal dose of creatine monohydrate associated with various health benefits in *Advanced Exercise and Health Science* in May 2024. Highlights of his findings were as follows:

01 **Skeletal muscle benefits:** **A loading phase of 20 g daily for up to a week, with or without a subsequent maintenance phase of 3 g to 5 g daily, appears sufficient to produce muscle benefits. Alternatively, a daily dosing strategy of 0.10 g to 0.14 g of creatine per kg of body weight is a viable option, especially for healthy older adults.**

02 **Bone benefits:** **A few studies have shown that 0.10 g to 0.14 g of creatine per kilogram of body weight can favourably affect bone biology and structure in healthy older adults participating in exercise training. "The lowest dose that has ever shown bone benefits is 8 g daily," said Dr. Candow.**

03 **Brain health benefits:** **The optimal dose and the duration needed to enhance brain function are unclear. Increasing brain creatine stores likely requires a dose of 20 g daily or higher or 0.3 g per kg of body weight for at least a week, or 4 g or more daily for several months.**

Dr. Candow told Mind Over Matter® that he takes a 10 g dose of creatine monohydrate daily. "A total of 3 g to 5 g daily as a dietary supplement for muscle health is fine, but older adults, especially those looking for bone and brain benefits, may wish to increase their daily dose to 8 g," he said. "Given my body weight, 10 g per day is appropriate. I divide it up into several smaller doses during the day."

Note: Always consult your healthcare provider before taking any supplement to ensure it is right for you.

experiencing depression and anxiety, and that creatine monohydrate supplementation may help alleviate symptoms.

For example, taking at least 20 g of creatine monohydrate daily for 4 weeks or 5 g daily for at least 8 weeks may help ease the symptoms of major depressive disorder.

Memory. Taking creatine monohydrate moderately improved memory in healthy adults compared to a placebo, especially for older people aged 66 to 76, according to a meta-analysis and systematic review by Dr. Candow published in *Nutrition Reviews* in 2022.

"Keep in mind that this finding was based on a small number of clinical trials containing small numbers of participants," said Dr. Candow.

> **WE NEED BIGGER CLINICAL TRIALS WITH HUNDREDS OF PEOPLE TO DETERMINE IF TAKING CREATINE MONOHYDRATE REALLY CAN IMPROVE MEMORY.**

Slowing neurodegenerative disease progression. While there is some evidence that creatine supplementation improves outcomes for people with muscular dystrophy, Dr. Candow's review of the literature found scant evidence suggesting it can slow the progression of neurodegenerative diseases such as Parkinson's, amyotrophic lateral sclerosis, or AD.

> ***Creatine supplementation may help improve brain energy in conditions like dementia or Alzheimer's disease where the brain is begging for help, similar to results we are starting to see with clinical depression. But the evidence is not there yet.***

Dr. Candow continued, "I am planning a clinical trial of creatine supplementation in people with Alzheimer's and dementia, in collaboration with colleagues at the University of Northern Iowa in late 2025."

CREATINE CAVEATS

If you are considering taking a creatine supplement, keep the following caveats in mind:

Determining sufficiency or deficiency is impossible for most people. "Without access to expensive brain imaging technology used in only a few labs worldwide, called magnetic resonance spectroscopy, it's impossible to know if brain creatine stores are sufficient or deficient and whether people may benefit from supplementation," Dr. Candow advised.

Remember the earlier statistic that women can have 70% to 80% less creatine stores than men? One supplement sold in the U.S. is using that claim to imply women are deficient.

> **REMEMBER THAT SEX-RELATED DIFFERENCES IN CREATINE STORES MAY BE JUST DIFFERENCES, NOT PROBLEMS THAT NEED FIXING, ADVISED DRS. PERLMUTTER AND CANDOW.**

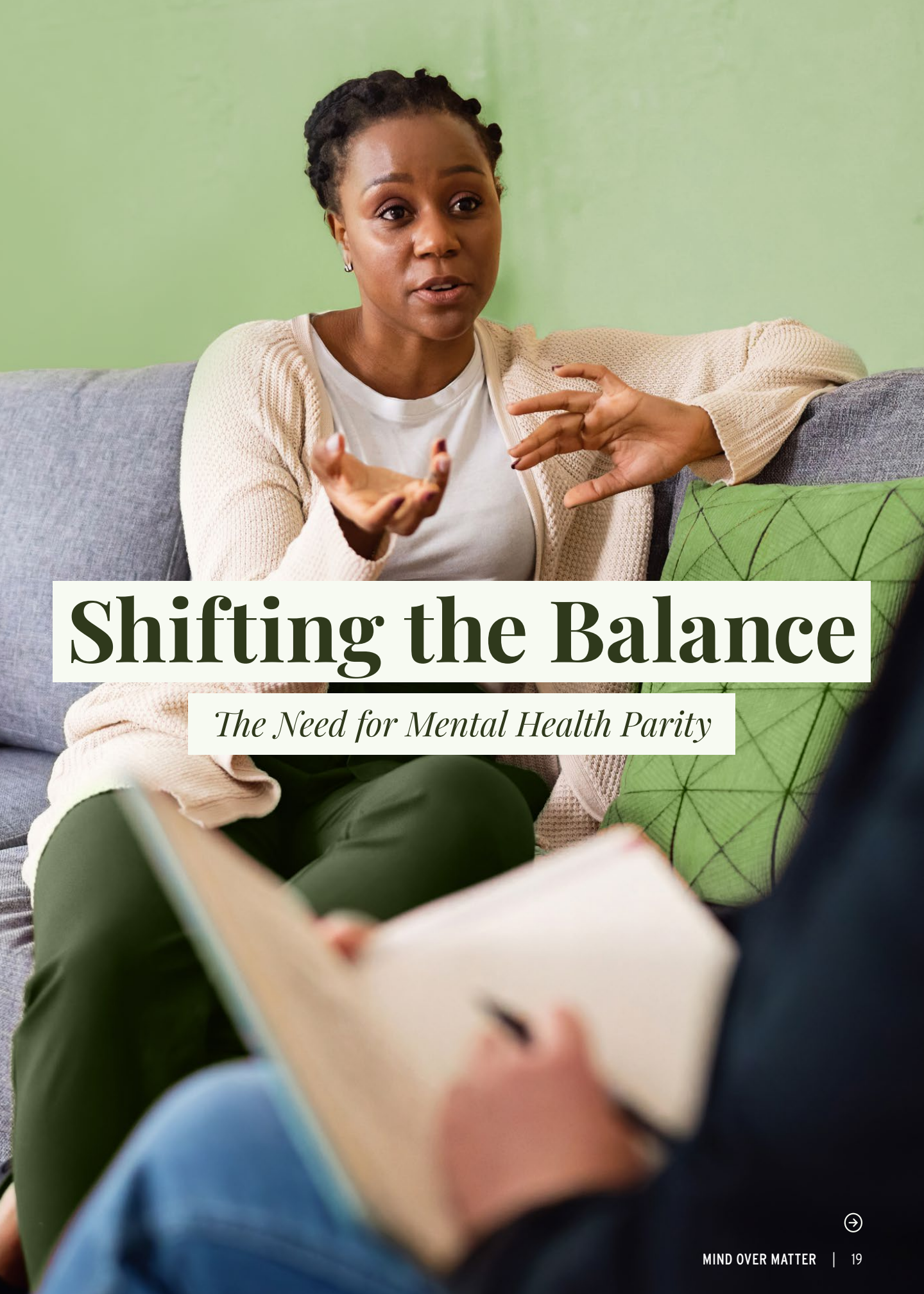
So far, only creatine monohydrate has been proven safe and effective. Supplement manufacturers are now selling other types of creatine, such as creatine hydrochloride. "Some newer products purportedly reach the digestive system and bloodstream quicker than creatine monohydrate, but the truth is that creatine is useless until it gets into the tissue," said Dr. Candow.

"Many people don't realize creatine monohydrate has a proven safety profile. The safety of newer forms of creatine is unknown and no studies yet demonstrate they are superior to creatine monohydrate."

"Creatine hydrochloride may be more quickly absorbed than creatine monohydrate," said Dr. Perlmutter. "However, the mechanism of action of both types of creatine are the same: they contribute to the regeneration of ATP, our cellular energy currency."

Taking a creatine supplement may increase your creatinine lab results. After your body uses creatine, it is broken down to form creatinine, a waste product your blood exports to your kidneys, where it is excreted in urine.

While studies have shown that consuming recommended doses of a creatine supplement does not affect kidney function in healthy people, an increase in your creatinine lab results may lead your doctor to wonder if your kidney function is declining.



Shifting the Balance

The Need for Mental Health Parity

As a pediatrician specializing in mental health, Sharon Burey has more than 30 years of frontline experience in how the system too often fails people in need.

"I've seen first-hand the long wait times and lack of availability of in-patient and outpatient community mental and behavioural health services. I've also witnessed the sometimes-devastating consequences of these lack of services," said Dr. Burey.

"If they (my patients) had cancer or diabetes, they would get help immediately. But if it's depression or anxiety or suicidal thoughts, issues that can be life-threatening, the care just isn't available on a timely basis."

"WE'RE MUCH BETTER AT SPEAKING OPENLY ABOUT MENTAL HEALTH, BUT ACCESS TO NECESSARY IN-PATIENT AND COMMUNITY MENTAL AND BEHAVIOURAL SERVICES JUST HASN'T KEPT PACE.

Dr. Burey is now in a position to do something about it because she is no longer just Dr. Burey, but also Senator Burey, having been appointed as an independent member of the upper house of Canadian Parliament in November 2022.

A few months after arriving in Ottawa, a veteran senator approached her and asked what she wanted to accomplish in the Senate. Her answer was immediate and heartfelt: "I want to work on mental health parity."

"We desperately need an attitude shift, a reorganization of priorities," Sen. Burey told Mind Over Matter®.

The concept of mental health parity exists in a variety of forms in both the U.S. and the U.K.

SOMETIMES REFERRED TO AS "PARITY OF ESTEEM," IT IS A RECOGNITION THAT PEOPLE SUFFERING FROM MENTAL HEALTH ISSUES SHOULD RECEIVE THE SAME LEVEL OF CARE AS PEOPLE WITH PHYSICAL AILMENTS.

It makes a difference. In Britain, 8% of the health budget is devoted to mental health care. By comparison, according to a November 2024 report from the Canadian Mental Health Association (CMHA) on the state of mental health in Canada, the country allocates about 6.3% of its health spending to mental health care.

Many mental health services are not covered by public plans. We're also spending proportionally less than other peer countries (15% in France, 11% in Germany, and 9% in Sweden.) The CMHA report also noted: "In fact, we're not even spending what our national mental health strategy, published 12 years ago, said Canada *should* be spending for mental health care by now (7-9%)."

The need is clear and pressing. Canada has an epidemic of opioid addiction, with a catastrophic cost in human life, including children. Although it is well established that most mental health disorders start in childhood and adolescence, Children's Mental Health Ontario reports that 28,000 kids in Ontario are on wait lists for mental health services and some wait more than two years to access appropriate care.

The number of people living with mental illness in Canada is expected to grow to almost nine million within a generation.

The parity issues also include differences between the sexes.

Sen. Burey has specialized in diagnosing ADHD in children and teens, where studies show that boys are diagnosed up to three times more frequently than girls in the childhood and teen years.

But by adulthood, there is virtually no difference in the prevalence between women and men. There are differences in presentation between the sexes and she believes that this and other underlying factors need further research.

"It means we're missing girls in diagnostic criteria. That relates to the parity of everything. It's for all of us."

Sen. Burey plans to introduce a mental health, substance abuse, and addiction parity bill in the Senate, which she hopes the government will support and then build upon in order to establish national standards.

She has many allies and supporters among experts, activists, and professionals in mental health; people and organizations who have been calling for years for such an initiative. To build momentum for the cause, she invited several leading voices to speak at a roundtable meeting on Parliament Hill last September.

At the event, Dr. Selene Etches, a child and adolescent psychiatrist in Halifax, brought a powerful, first-hand perspective on the disparities between physical and mental health care, drawing from her dual roles at the IWK Health Centre. Part of her time is spent on the medical floors, part of it running an addiction clinic for young people.

Children with medical problems and their families get substantial support, while those coping with addictions must navigate a complex system themselves in search of appropriate treatments, some of which may be unavailable or ruinously expensive.

"Addiction is treatable," Dr. Etches said in an interview with Mind Over Matter®.

"We can't separate mind and body in this way. Most people who have what we deem medical illnesses often have comorbid mental health that isn't addressed. So, we're missing the boat by not treating them both the same," she added.

A 2019 report by the Canadian Association of Social Workers (CASW) called for the introduction of a mental health parity act, saying it is needed not only to address the opioid crisis, but "as a concrete way forward to more holistic well-being for all those who live in Canada: an approach that will address many of the most pressing issues facing our nation."

CASW Executive Director Fred Phelps told Mind Over Matter® that the over 20,000 members of his organization deal with mental health cases more than any other profession in the healthcare system, and they constantly see the disparities in access.

"We believe there really has to be a fulsome study of how to achieve mental health parity in Canada," he said.

Mr. Phelps suggested that the federal government should take the lead, with legislation that could either amend the *Canada Health Act* or be a stand-alone bill. Either way, he said that there should be specific requirements for each province or territory to report on its financial support for mental health, and that Ottawa could exert influence through its transfer payments that help fund the broader system.

"It would bring an accountability that isn't there," said Mr. Phelps.

Margaret Eaton, National CEO of the Canadian Mental Health Association (CMHA), told the roundtable on Parliament Hill: "Parity is more than equally providing mental and physical health care. It means equally valuing care. Parity is not only about better funding, but it is also about who has equal access to the most effective and the safest care and treatment."

The proportion of funding devoted to mental health in Canada has declined over the last decade, even as the demand for care has increased.

The November CMHA report found that mental health care is "grossly underfunded … often a privilege available only to those who can afford it" and that access to care is inequitable "geographically and socio-economically, especially for racialized and Indigenous people."

In an interview with Mind Over Matter®, Ms. Eaton said, "We believe mental health is a fundamental human right. Mental health affects physical health. Ultimately, we believe there'll be cost savings and benefits (with parity).

"We're thrilled that Senator Burey is taking up the cause. She's an extraordinary champion in convening mental health professionals to shine a light on this topic. We would love to see it higher on the political agenda. It should not be a partisan issue."

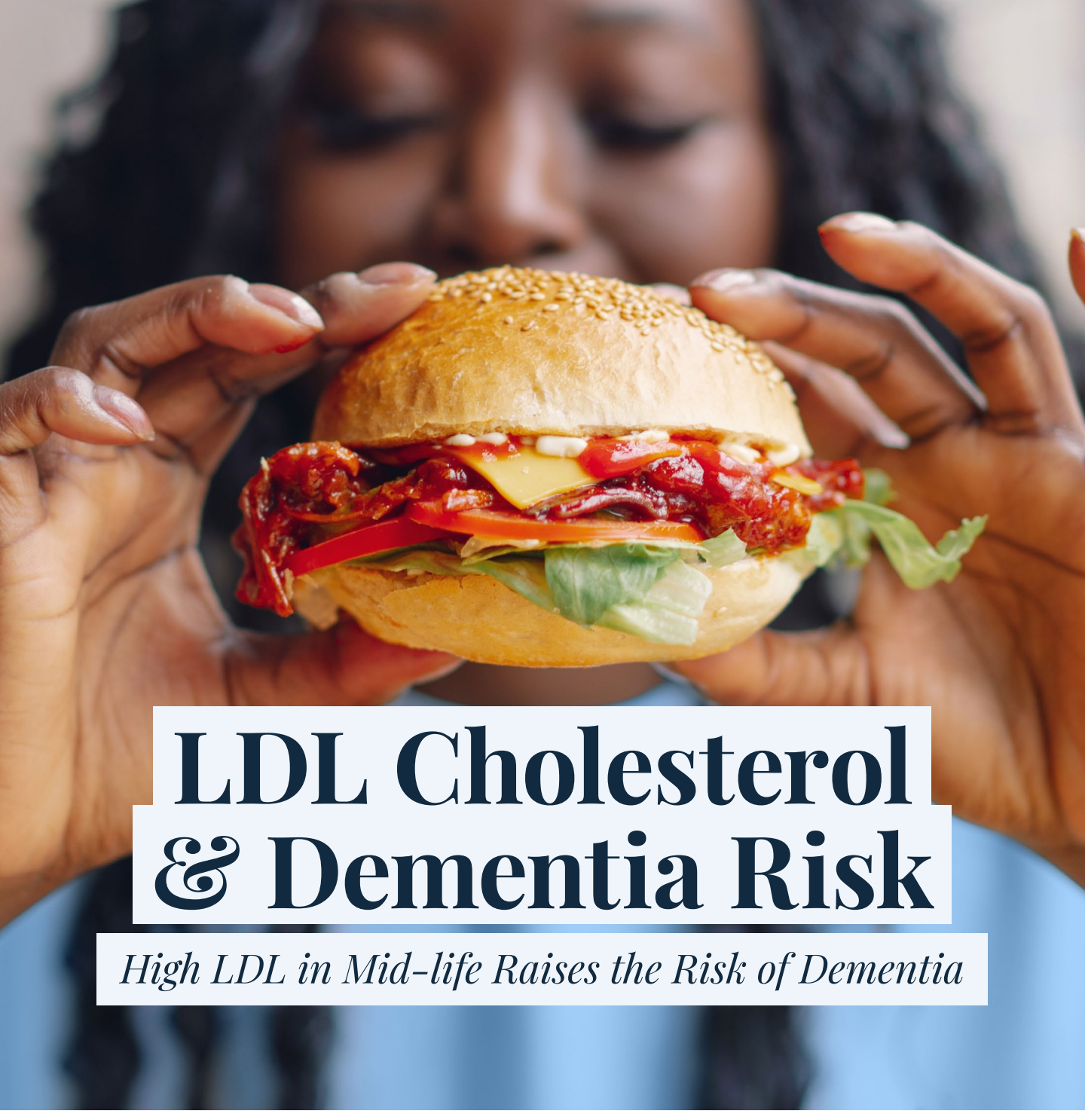
As an independent senator, Sen. Burey is not a member of a political party and has made a point of reaching across the aisle to find supporters among all parties.

The Senate has a history of taking the lead on mental health issues.

A 2006 landmark report, "Out of the Shadows at Last: Transforming Mental Health and Addiction Services in Canada," is credited with opening up the discussion of a topic that was long held to be taboo. It prompted the creation of the Mental Health Commission of Canada in 2007, a not-for-profit corporation that has played an important role in combatting stigma, funding research, and broadening the conversation.

A generation later, Sen. Burey hopes the upper house can again show the way, saying:

"All of us know someone who has suffered mental health problems and who had trouble finding help. We must do better. It's time to do it."



LDL Cholesterol & Dementia Risk

High LDL in Mid-life Raises the Risk of Dementia

If you think keeping your low-density lipoprotein (LDL) cholesterol in check only matters for heart health, think again.

Last August, the *Lancet* standing Commission on Dementia Prevention, Intervention, and Care added high LDL in mid-life as a modifiable dementia risk factor to their previous list of 12 risk factors.

The news underscored the importance of identifying and treating high LDL in mid-life, especially as women have higher LDL cholesterol after menopause yet are less likely to be prescribed cholesterol-lowering medication than men, leading to worse health outcomes.

Mind Over Matter® reviewed the evidence leading to the *Lancet* Commission's decision. We also spoke to leading experts to learn how high LDL cholesterol is linked to dementia and proven ways to lower it to protect brain health and heart health.

LDL CHOLESTEROL

Cholesterol is a waxy substance your body uses to make cell membranes, vitamin D, and many hormones. Your liver makes

The *Lancet* standing Commission's 12 modifiable dementia risk factors are:

- less education;
- hypertension;
- hearing impairment;
- smoking;
- obesity;
- depression;
- physical inactivity;
- diabetes;
- low social contact;
- excessive alcohol consumption;
- traumatic brain injury; and
- air pollution.

all the cholesterol your body needs. The rest found in your blood comes from animal-based foods, such as meat, poultry, and dairy products, and a trace amount from plant-based foods.

Cholesterol is carried in your blood by lipoproteins, spherical particles made of fats (lipids) and proteins.

There are two main types of lipoproteins. LDL cholesterol is sometimes called "bad" cholesterol, but that's not a fair nickname because it plays an essential role in transporting fats in your blood to various cells throughout your body.

The other primary lipoprotein is high-density lipoprotein (HDL), the "good cholesterol," so named because it transports excess LDL in your blood back to your liver, where it is broken down and flushed from the body.

TOO MUCH LDL CHOLESTEROL IS PROBLEMATIC. IT CAN CONTRIBUTE TO PLAQUE BUILDUP IN ARTERIES, INCREASING THE RISK OF CORONARY ARTERY DISEASE, CEREBROVASCULAR DISEASE, PERIPHERAL ARTERY DISEASE, HEART ATTACK, AND STROKE.

Many factors cause high LDL cholesterol, including genetics, aging, eating a diet that's high in saturated fats or trans fats and refined sugar, being overweight or obese, smoking, diabetes, kidney disease, and some medications.

As we age, LDL levels change, and so do sex-related differences. In early life, girls have higher LDL levels than boys. After 19 years of age, premenopausal women have lower LDL cholesterol levels than men.

However, after age 50 and coinciding with menopause, women experience a steep increase in LDL levels that surpasses men's levels. LDL cholesterol levels gradually decline in older age. However, the drop is less pronounced and takes place later in women.

LDL TARGETS

Your LDL cholesterol level is determined through blood work, typically as part of an annual wellness check-up.

Canada - Physicians use a risk calculator, such as the Framingham Risk Score (FRS), to determine your risk of developing cardiovascular disease in the next ten years. The FRS considers your cholesterol results, age, sex, and cardiovascular risk factors like diabetes, blood pressure, kidney disease, and smoking history. According to the Canadian Cardiovascular Society:

- **low risk:** FRS under 10%;
- **intermediate risk:** FRS of 10% to 19.9% and LDL cholesterol 3.5 mmol/L or higher; and
- **high risk:** An FRS of 20% or greater.

Treatment is not required for an FRS under 10%. For patients with an FRS in the intermediate- or high-risk categories, physicians discuss health behaviour changes and options for initiating treatment. If a first drug therapy does not sufficiently lower LDL cholesterol, your doctor may recommend adding on other treatments.

United States - For people without heart disease, the target LDL is 100 mg/dL or lower, and for people with heart disease, the target is 70 mg/dL or lower, according to the American Heart Association.

EVIDENCE LINKING HIGH LDL TO DEMENTIA

The *Lancet* Commission reviewed the latest evidence and concluded, "Overall, high-quality, consistent, biologically plausible evidence exists that high LDL cholesterol in midlife is a risk factor for dementia."

High LDL cholesterol is one of the most significant risk factors for heart conditions and stroke in women, according to the Heart and Stroke Foundation of Canada.

Highlights of some of the study findings that formed the basis of their recommendation are as follows:

- every 1 mmol/L increase in LDL cholesterol was associated with an 8% increase in the incidence of dementia in adults under 65, according to a meta-analysis of health records for 1.1 million adults in the United Kingdom (U.K.) who were followed for more than a year. (*Alzheimer's Dementia (Amst.)*, 2023)

- an LDL cholesterol level of 3 mmol/L or higher was associated with a 33% increased risk of dementia, according to a population study of 1.2 million people. (*PLOS One*, 2023)

- an analysis of health records of more than 1.8 million people in a U.K. databank followed for about 7.4 years showed that having a higher LDL level at the beginning of the study was associated with a 5% increased risk of all-cause dementia for each additional 1 mmol/L. The risk of a dementia diagnosis within ten years and later was 10% greater for people under 65 than for people who were older than 65 at the beginning of the study. (*Lancet Healthy Longevity*, 2021)

The *Lancet* Commission's report stated that 45% of all dementia cases worldwide could be prevented or delayed by addressing these 14 modifiable risk factors across the human lifespan.

Estimated % reduction in dementia cases if each risk factor is eliminated by stage of life:*

EARLY LIFE	
Less education	5%
MID-LIFE	
High LDL cholesterol	7%**
Hearing loss	7%
Depression	3%
Traumatic brain injury	3%
Physical inactivity	2%
Diabetes	2%
Smoking	2%
Hypertension	2%
Obesity	1%
Excessive alcohol consumption	1%
LATE LIFE	
Vision loss	2%**
Social isolation	5%
Air pollution	3%

**Adapted from: Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission.*
*** New in 2024*

THE LINK BETWEEN HIGH LDL & DEMENTIA

Heart health and brain health are intertwined, but how does having a high LDL raise the risk for dementia? The common denominators are vascular disease and inflammation.

Vascular disease is any condition that affects how well blood vessels carry blood throughout your body and brain. A buildup of excess LDL cholesterol in your arteries can cause atherosclerosis, a narrowing that, over time, can become a blockage that causes heart attack or stroke. Ongoing inflammation is part of the atherosclerosis process.

Vascular dementia is a decline in cognitive function caused by reduced or blocked blood flow to the brain. It is the second-most common subtype of dementia after Alzheimer's disease (AD), representing about 15% to 20% of dementia cases in North America and Europe.

"Most people show some degree of vascular damage over time as they age, even when they don't have cognitive deficits," said Dr. Betsy Mills, Assistant Director of Aging and Alzheimer's Prevention at the Alzheimer's Drug Discovery Foundation.

> **"HOWEVER, GROWING EVIDENCE SHOWS THAT VASCULAR DISEASE PROCESSES AND INFLAMMATION ARE MAJOR FACTORS IN MOST FORMS OF DEMENTIA, INCLUDING ALZHEIMER'S.**

"As scientists developed blood biomarkers for Alzheimer's disease, they discovered that cognitive impairment in people with Hispanic or African American ethnicities appears to be driven by vascular-related disease processes more so than amyloid beta deposition," added Dr. Mills.

The *Lancet* Commission report identified lowering high LDL cholesterol as one way to decrease vascular damage and prevent and delay dementia.

"High LDL cholesterol is a proven cardiovascular risk factor," said Dr. Christopher Labos, a Montreal-based cardiologist, epidemiologist, and co-host of the award-winning *The Body of Evidence* podcast. "Anything that decreases the risk of

cardiovascular disease and stroke is also going to lead to a lower risk of vascular dementia."

> **HIGH LDL CHOLESTEROL IN MID-LIFE IS AN IMPORTANT DEMENTIA RISK FACTOR THAT ALL WOMEN SHOULD KNOW ABOUT.**

"We already knew that vascular disease plays a role in dementia and cognitive impairment, but the *Lancet* Commission's news underscores that it's a major driver. We can't yet prevent amyloid plaques and tau tangles, but we can take steps to prevent vascular damage, and that's huge," continued Dr. Mills.

HOW TO LOWER HIGH LDL

The good news is that there are steps you can take to lower high LDL and reduce your risk of dementia and heart disease.

DIET AND EXERCISE STRATEGIES

Harvard Medical School recommends the following diet modifications to help bring down your LDL:

Eliminate trans fats and limit saturated fats. Eliminate trans fats by avoiding foods with "partially hydrogenated" ingredients. Limit foods high in saturated fats, such as red meat, shrimp, lobster, high-fat dairy products, and butter, to small portions every couple of weeks. Note that it's OK to have as many as four egg yolks weekly and egg whites as often as you wish.

Consume more polyunsaturated and monounsaturated fats. Plant-based oils, like olive, canola, and sunflower oil, are good sources of these healthy fats. Seeds, nuts, avocados, soybeans, and fatty fish, including salmon, trout, tuna, herring, and mackerel, are also excellent sources.

Eat a rainbow of fruits and veggies. Colourful fruits and vegetables contain fibre as well as cholesterol-blocking substances called sterols and stanols.

Avoid added sugars and refined grains. Avoid added sugars by spotting sugar, corn syrup, or words ending in "ose" near the top of ingredient lists. Choose whole grain foods as a good source of fibre over those containing refined flour or white rice.

Ensuring you get enough moderate-to-vigorous exercise on an ongoing basis can also lower LDL by boosting HDL cholesterol. According to the Canadian Cardiovascular Society, half an hour to one hour of moderate-to-vigorous intensity exercise daily can raise HDL by 5% to 10%.

EXAMPLES OF EXPECTED BENEFITS OF HEALTH BEHAVIOUR CHANGES TO LOWER LDL*

	% reduction in LDL cholesterol
Reduced saturated fats/dietary cholesterol:	
200 mg or less daily (7% or less of total food energy)**	12-16%
300 mg or less daily (10% or less of total food energy)**	10-12%
Portfolio dietary pattern	8-14%
Weight loss of 5-10% of body weight	11-12%
Dietary pattern with plant sterols/stanols 1-2 g daily	6-12%
Viscous fibre: 10 g or more daily (oats, barley, psyllium, pectin)	5-10%
Pulses: more than 1 serving or 130g daily (beans, peas, chickpeas, lentils)	5%
Low glycemic index dietary pattern	5%
Nuts: more than 30 g daily	5-7%
Soy protein: more than 30 g daily	3-5%
DASH dietary pattern	3%

**Adapted from the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults.*
***National Cholesterol Education Program Step Diet*

Before making changes to your diet, consult with your healthcare provider.

Note that both diet and exercise are essential: a large study of several controlled trials found that dietary changes lowered LDL while exercise alone did not. However, adding aerobic exercise enhanced the lipid-lowering effect of a heart-healthy diet, according to Harvard Medical School.

Dr. Labos gives patients with a borderline intermediate-risk FRS an opportunity to decrease their LDL cholesterol with diet and exercise modifications first.

"A heart-healthy diet and sufficient cardiovascular exercise are important for everyone, whether or not they require cholesterol-lowering medication," Dr. Labos said.

Set nutrition and exercise goals and track your progress with Women Brain Health Initiative's BrainFit™ mobile app, a unique habit tracker designed to help you prolong cognitive vitality.

"However, the reality is that it's very hard to bring down a high LDL with diet and exercise alone. You may be able to lower it by 10% to 15%, but not much more, because most cholesterol produced in the body is determined by genetics.

MEDICATION OPTIONS

There are several medications that effectively suppress the production of excess LDL cholesterol.

Statins are a proven effective class of oral drugs for lowering LDL cholesterol. They work by blocking an enzyme your body needs to make cholesterol. Some common examples are atorvastatin (Lipitor®), rosuvastatin (Crestor®), and simvastatin (Zocor®).

Meta-analyses of observational studies have shown statins have a beneficial impact on dementia risk, according to the *Lancet* Commission. For example, a meta-analysis of 36 cohort studies found that statin use was associated with a 20% lower risk of all-cause dementia and a 32% lower risk of AD compared with untreated high LDL, with no difference between women and men. The study was published in *European Journal of Preventive Cardiology* in 2022.

"Recently, statins have become a focus of Alzheimer's and dementia research due to their anti-inflammatory and antioxidant properties in addition to their cholesterol-reducing benefit," said Dr. Mills.

The side effects of statins may include muscle soreness and short-term brain fog, but these do not occur in most people and can be addressed by switching to a different statin or another medication type, Dr. Labos advised.

Beyond statins, other medication options for lowering LDL cholesterol include ezetimibe, PCSK9 inhibitors, and bempedoic acid.

Ezetimibe is an oral drug that helps prevent the absorption and storage of cholesterol in the liver and improves the cholesterol clearance from your blood. It may be prescribed alone or as an ingredient in a combination medication.

PCSK9 inhibitors, such as alirocumab (Praluent®) and evolocumab (Repatha®), are given by injection every three months. They prevent the breakdown of LDL receptors, especially in the liver, so more LDL receptors work to reduce your LDL cholesterol.

Bempedoic acid (Nexletol®) is an oral non-statin medication that reduces the amount of cholesterol made by the liver. Nexlizet®, made by the same manufacturer, combines bempedoic acid and ezetimibe in the same medication.

KEEP IN MIND

"It is important for women to realize their dementia risk increases starting in mid-life because it usually takes decades to develop. Menopause seems to be a tipping point where the seeds of cardiovascular and dementia-related disease processes get planted, and damage starts building up," Dr. Mills said.

"High LDL is a warning sign that vascular damage and inflammation may be occurring, and women should take action to mitigate their future risk of developing dementia.

"High LDL cholesterol is bad for men. It's bad for women. It's bad for everyone," Dr. Labos said. "The fact that women are under-treated for high LDL cholesterol is a detriment to their heart health and brain health. More women should pay attention to the increased risks associated with high LDL cholesterol and discuss treatment options with their physicians."

Now What?

Steps to Take When You Notice Cognitive Decline

Noticing signs of forgetfulness or cognitive challenges in yourself or a loved one can be unsettling, often raising fears about dementia – a condition many consider one of the most daunting aspects of aging.

But negative cognitive changes do not necessarily indicate the start of dementia. In fact, there are several other possible explanations. For example, cognitive function can be negatively affected by:

- mental health conditions such as depression or anxiety;
- medications;
- stroke;
- urinary tract infections; and
- traumatic brain injury.

That's why diagnosing dementia is such a complex and often lengthy process, requiring careful evaluation to uncover the true cause. The process involves in-depth assessment, often administered by a memory specialist, that in part focuses on ruling out any other potential causes of cognitive decline.

The first step, before diving into a more in-depth evaluation, is usually a brief cognitive screening test.

This helps quickly assess cognitive function and determine if further examination is necessary.

A wide range of cognitive screening tests have been developed over the years. In this article, we highlight some of the most commonly used by healthcare professionals, along with a few that you can try at home.

TESTS ADMINISTERED BY HEALTH PROFESSIONALS

Three cognitive tests that are widely used by health professionals for cognitive screening are the Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), and Mini-Cog.

MINI-MENTAL STATE EXAM (MMSE)

The MMSE was created in 1975 and includes 11 questions/tasks such as counting backward by sevens, stating the date and location, naming and recalling objects in the room, copying a drawing, and writing a short sentence. It takes about five to ten minutes to complete.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

The MoCA is a newer test, validated in 2005, that includes activities such as memorizing a short list of words, reading a list of letters while tapping the hand when saying each letter, naming animals shown in pictures, copying a simple stick drawing of a bed, counting backward by sevens, and naming as many words as possible in 60 seconds that start with a given letter. (You might have noticed that some of these tasks overlap with what's included in the MMSE.) MoCA is available as a paper version or an app and takes about ten to 15 minutes to complete.

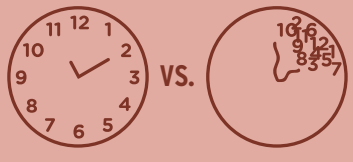
MINI-COG©

The Mini-Cog is a test, introduced in 2000, that is even quicker than the MMSE and MoCA – it takes just three minutes to complete and includes only two components: (1) a three-item recall test for memory and (2) a clock drawing test. The test is administered in three steps:

01 the test-taker is instructed to listen carefully and repeat three words chosen by the test-giver (for example: banana, sunrise, chair)

02 a clock drawing test is administered

03 the test-taker is asked to repeat the three words from step 1



THE CLOCK DRAWING TEST

How it works. The test-taker is given a pre-drawn circle, or, in some cases, they may be asked to draw the circle. They are asked to draw the numbers of a clock in that circle, and then to draw hands on the clock to show ten past 11.

How it's scored and interpreted. When the clock drawing test is used as part of the Mini-Cog©, it is scored as a pass/fail, with the test-taker getting either 0 or 2 points. However, this test is sometimes used on its own (i.e., not as part of the Mini-Cog©) and is scored in a variety of other ways, e.g., assessing specific aspects of the test independently and giving points for things like correct placement and spacing of the numbers, and presence and correct placement of the clock hands.

MINI-COG© SCORING:

Recall Score (1 point for each word correctly recalled in step 3) **+ Clock Drawing Score** (2 points for normal clock or 0 points for abnormal clock) **= Total Score** (from 0 to 5).

A total score of 0, 1, or 2 indicates higher likelihood of clinically important cognitive impairment, while a total score of 3, 4, or 5 indicates lower likelihood of dementia. A score of 3 or more does not, however, rule out some degree of cognitive impairment entirely.

ALZHEIMER'S QUESTIONNAIRE (AQ©)

The three tests described earlier are all completed by the person who is experiencing cognitive difficulties. Another way that health professionals sometimes do initial cognitive screening is by asking a *care partner* questions about the person experiencing cognitive difficulties.

One such "informant-based" test is the Alzheimer's Questionnaire (AQ©). The 21 questions are answered "yes" or "no," with each "yes" getting a score of 1 or 2, and each "no" getting a score of 0.

1. **Does your loved one have memory loss?**
   Y = 1 N = 0

2. **If so, is their memory worse than a few years ago?**
   Y = 1 N = 0

3. **Do they repeat questions, statements, or stories in the same day?**
   Y = 2 N = 0

4. **Have you had to take over tracking events or appointments, or does the patient forget appointments?**
   Y = 1 N = 0

5. **Do they misplace items more than once a month?**
   Y = 1 N = 0

6. **Do they suspect others of hiding or stealing items when they cannot find them?**
   Y = 1 N = 0

7. **Does your loved one frequently have trouble knowing the day, date, month, year, and time; or do they have to use cues like the newspaper or the calendar to know the day and date more than once a day?**
   Y = 2 N = 0

8. **Do they become disoriented in unfamiliar places?**
   Y = 1 N = 0

9. **Do they become more confused when not at home or when travelling?**
   Y = 1 N = 0

10. **Excluding physical limitations, do they have trouble handling money, such as tips or calculating change?**
    Y = 1 N = 0

11. **Excluding physical limitations, do they have trouble paying bills or doing finances?**
    Y = 2 N = 0

12. **Do they have trouble remembering to take medicines or keeping track of medications taken?**
    Y = 1 N = 0

13. **Do they have difficulty driving; or are you concerned about their driving?**
    Y = 1 N = 0

14. **Are they having trouble using appliances, such as the stove, phone, remote control, or microwave?**
    Y = 1 N = 0

15. **Excluding physical limitations, are they having difficulty completing home repair or housekeeping tasks?**
    Y = 1 N = 0

16. **Excluding physical limitations, have they given up or cut down on hobbies such as golf, dancing, exercise, or crafts?**
    Y = 1 N = 0

17. **Are they getting lost in familiar surroundings, such as their own neighbourhood?**
    Y = 2 N = 0

18. **Do they have a decreased sense of direction?**
    Y = 1 N = 0

19. **Do they have trouble finding words other than names?**
    Y = 1 N = 0

20. **Do they confuse names of family members or friends?**
    Y = 2 N = 0

21. **Do they have trouble recognizing familiar people?**
    Y = 2 N = 0

AQ© SCORING:

Add up all the points to get a total score out of 27.

- A score of 4 or less is considered a normal level of cognitive function.
- A score of 5-14 (inclusive) suggests mild cognitive impairment.
- A score of 15 or more suggests the potential presence of dementia.

AT-HOME TESTS

Many cognitive screening tests are marketed for at-home use, but research reveals significant variation in their quality and accuracy.

Here, we highlight a few at-home cognitive screening tests backed by solid research. This list is not exhaustive, and other high-quality options may be available.

Before using any test, ensure it is supported by research that demonstrates its effectiveness.

SAGE (SELF-ADMINISTERED GEROCOGNITIVE EXAM)

In 2010, Dr. Douglas Scharre and colleagues at The Ohio State University developed a pen-and-paper test – the Self-Administered Gerocognitive Exam (SAGE) – that can be completed at home and then taken in to a primary care physician for scoring and interpretation.

SAGE is a 12-question test that assesses multiple types of cognitive function: orientation, language, calculations, abstraction, and visuospatial and executive function. (One of the questions involves clock drawing, described earlier.) It generally takes 15 minutes or less to complete the entire test. Research

SEX DIFFERENCES

Women and men tend to have different strengths when it comes to cognitive performance. For example, among people with basic education, women do better than men on verbal memory tests, while men perform better than women on visuospatial tests.

Research by Dr. Erin Sundermann and colleagues has also shown that even when there are similar levels of physical damage to the brain itself – i.e., pathology associated with amnestic mild cognitive impairment (aMCI) – women have better verbal memory than men. This means that women may not show signs of verbal memory decline until more advanced pathology is present in the brain. These findings were shared in *Neurology* in 2016.

Sex differences in cognitive function and in rates of cognitive decline in the presence of disease have important implications for screening and diagnosis of mild cognitive impairment and dementia.

Given these differences, should the results of cognitive screening tests be interpreted differently for women and men, i.e., should the cut-off score for referral for additional testing be different depending on sex? The answer to that question may depend on which cognitive screening test is being used.

For example, a 2021 study by Dr. Knut Engedal and colleagues suggests that sex does not appear to influence MMSE scores but does impact MoCA scores; women tend to perform better than men on the MoCA test. (These findings were published in *Dementia and Geriatric Cognitive Disorders*.)

In a later paper – published in 2022 in *Journal of Alzheimer's Disease* – Dr. Engedal and other colleagues found that the normative score on the MoCA test varied between 22 and 27 for Norwegian older adults, depending on age, level of education, and sex. So, they concluded that "one size does not fit all" and that "no single cut-off point should be applied" but rather, what is considered a "normal" score needs to be adjusted to take key variables into account, including sex.

More research is needed to uncover recommended normative scores for MoCA differentiated by sex for older adults outside of Norway, and to look at sex differences in other cognitive screening tests.

has found SAGE compares favourably with tests administered by health professionals such as the MMSE and MoCA.

The print version of SAGE is available free of charge at: sagetest.osu.edu. A digital version (eSAGE or BrainTest®) is now available at braintest.com.

XPRESSO BY MOCA

XpressO by MoCA is a self-administered, digital version of the MoCA test. It's taken in the comfort and privacy of home, either at portal.mocacognition.com or using an app installed on any device, and can be completed in a few minutes using simple drag-and-drop tasks.

XpressO by MoCA differs from SAGE in that it automatically calculates a score based on speed and accuracy and provides a simple report that shares whether your performance fell within or below the expected range for cognitive performance.

If your performance is within the normal range, you don't need to take any action. If your performance is below the expected range, then you should book an appointment with your doctor. (With SAGE, you don't get any results at home and have to visit your doctor to get the results.)

According to the XpressO by MoCA website, "serial test results can be tracked," meaning that you can self-monitor your cognition over time and watch for any concerning changes.

KEEP IN MIND

Two important things to keep in mind about cognitive screening:

All of the tests described – both the ones administered by health professionals and the ones you can do at home – are for initial screening only. They are not for diagnosing anything; rather, they just provide a rough idea of cognitive function so that your health professional gets a sense of whether you need additional in-depth testing or not.

It can be stressful to take a cognitive screening test and get the results, especially if your score on the test is poor. Remember that there are several potential causes of cognitive decline besides dementia, many of which are treatable and reversible.

If further testing leads to a dementia diagnosis, it's important to understand that early detection can be highly beneficial. The sooner you know, the sooner you can start medications to slow symptom progression and enhance quality of life. Early diagnosis also gives you more time to plan for the future and actively participate in important decisions about your care, finances, and other aspects of your life.

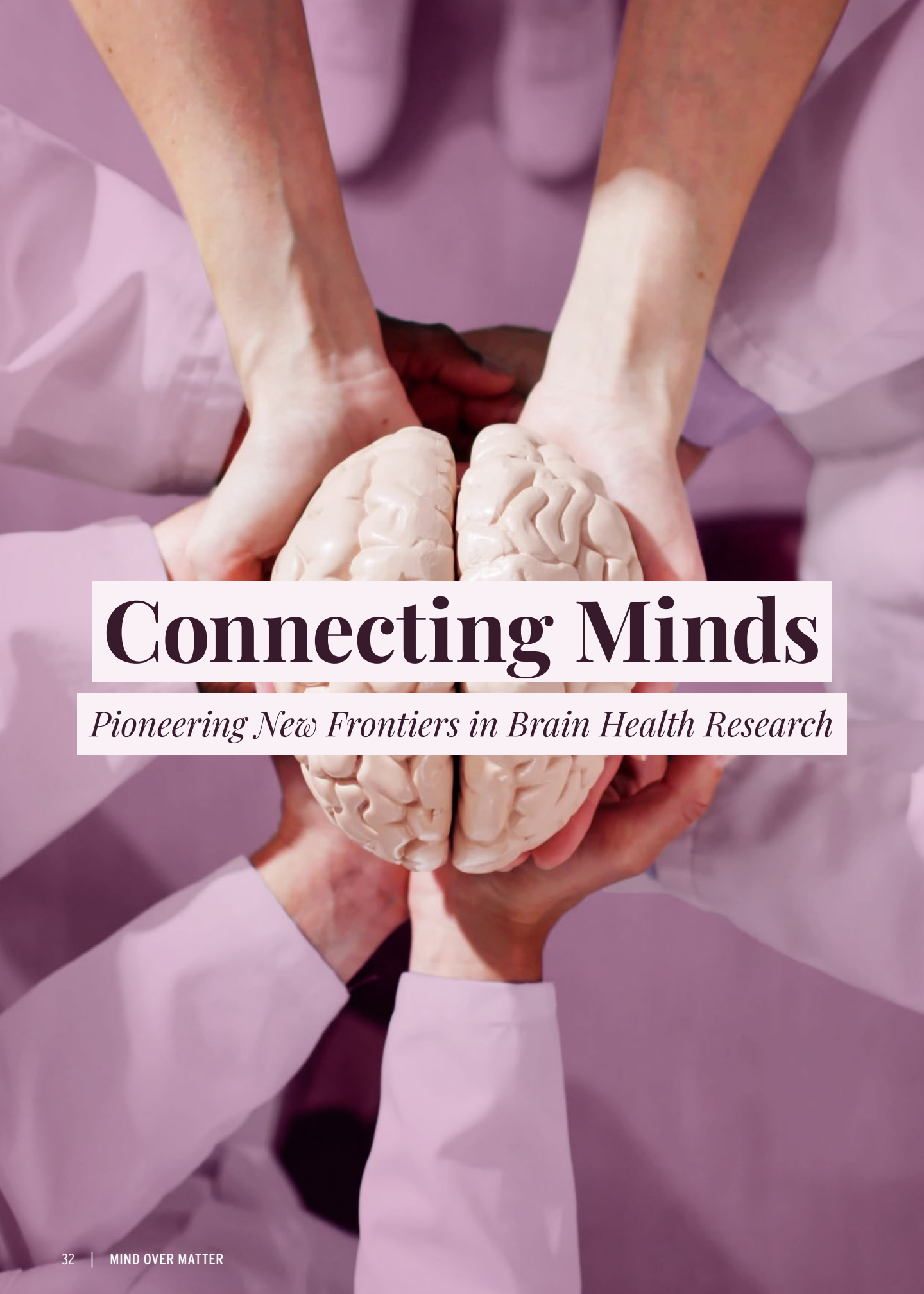
OTHER TESTS USED TO SCREEN FOR COGNITIVE DECLINE

The tests described in this article so far look for signs of impaired cognitive function, but that's not the only way to screen for changes that might indicate early stages of cognitive impairment.

Dementia has negative impacts on many body parts and functions, not just the brain, so there are some other interesting types of tests that are showing promise for screening and early detection: eye, smell, and motor function tests.

You can find out more about these other types of tests in past issues of Mind Over Matter® magazine, which you can read at womensbrainhealth.org/mind-over-matter-magazine.

- "Signs of Compromised Brain Health: Physical Performance Tests That Can Predict Dementia" (volume 3, starting on page 9) describes a variety of physical tests that may help with assessment of dementia risk, such as grip strength, standing balance, timed 4-metre walk, and the ability to do five repetitions of standing up from sitting in a chair without using your hands.
- "The Eyes (and Nose) Have it: Eyes & Nose Might be Key to Early Detection" (volume 2, starting on page 36) shares research on retinal scan testing, and some smell tests such as the ability to identify common scents.
- "Advance Notice: Early Detection of Dementia" (volume 12, starting on page 41) examines research on the "timed up and go (TUG)" motor test, which measures how long it takes a person to rise from seated to standing, walk three metres, turn around and walk back to the chair, and sit down again. This article also revisits the topic of eye and smell tests.



Connecting Minds

Pioneering New Frontiers in Brain Health Research

Prof. Minh Dang Nguyen believes in exploring areas of research where few others go.

"I like to ask questions that nobody asks. And if you ask the right question, then you get answers that nobody expects," said the professor of clinical neuroscience at the University of Calgary.

"It's a risky type of science sometimes, and I would say most of the time it's not funded. But that's what attracts me."

The same is true of his latest research project, in which he hopes to push the boundaries of our knowledge of the brain and the devastating disease amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. And it is funded, thanks to a new pilot program from Brain Canada, Weizmann Canada, and the Weizmann Institute of Science, an initiative that aspires to encourage open science.

"We're very grateful for (the grant) because the research is out of the box. You wouldn't be able to get funding from a traditional funding agency," Prof. Nguyen said in an interview with Mind Over Matter®.

The project is a collaboration with Prof. Eran Elinav of the Weizmann Institute in Israel. They are studying links between the brain and the microbiome – the vast array of bacteria, viruses, and fungi in the gut.

"The project is significant because it addresses a devastating neurodegenerative disorder that has no cure, ALS, and aims to decode the roots of microbiome regulation of this disease," said Prof. Elinav.

Previous research from the Elinav Lab has indicated that gut bacteria can have an impact on ALS, either slowing down or accelerating the progress of the disease. This project will get more specific, exploring whether alterations in the microbiome can affect what is known as the glymphatic system, a newly discovered system that acts to clear waste from the central nervous system.

Using mouse models, the researchers are investigating whether promoting healthy gut bacteria can make the glymphatic system more effective in clearing waste from the brain and, in the process, slow the progression of ALS.

EXPLORING SEX DIFFERENCE IS A KEY ELEMENT OF THE PROJECT. MEN TEND TO GET ALS MORE COMMONLY THAN WOMEN.

The researchers will observe how manipulating the microbiome affects male and female mice differently.

"And hopefully, we want to eventually come up with a strategy to slow down Alzheimer's. It's very exciting because you can modify the microbiome depending on how you eat and sleep," said Prof. Nguyen.

"Results obtained from this study will be harnessed toward future testing in human patients," added Prof. Elinav.

Theirs is one of three projects to be awarded a Brain Canada and Weizmann Institute of Science Team grant. In each case the goal is not only to support exploratory science, but to foster collaboration among researchers with complementary capabilities from different parts of the world.

"AS WITH OTHER 'HIGH-RISK, HIGH-GAIN' PROJECTS, FUNDING VIA 'TRADITIONAL' SOURCES IS OFTEN MET WITH CHALLENGES.

"The opportunity generously provided here will enable the ongoing Canadian-Israeli collaboration to move even faster in achieving the project's scientific and medical goals to the benefit of humanity," continued Prof. Elinav.

BRAIN DEFENCE

"The beauty of this initiative is the ability to bring groups from different disciplines and put them together to make the impossible possible," said grant recipient Prof. Ido Amit of the Weizmann Institute.

He and Prof. Nahum Sonenberg of McGill University are exploring how the brain's immune system could be harnessed to fight Alzheimer's disease (AD), based on a growing body of recent evidence that found a strong connection between the immune system and AD, the most common form of dementia.

They are employing cutting-edge genomic and artificial intelligence technologies to measure and manipulate the mRNA translation machinery to modify immune cells called microglia at the genetic level. Using lab mice, they will see if they can make the microglia more effective in warding off amyloid plaques, which are proteins found in the brain that are associated with AD.

"What's beautiful about activating our own immune system is that it can bring back brain function, without causing damage. This could be the Holy Grail of genetic diseases, and Alzheimer's specifically," Prof. Amit told Mind Over Matter® in an interview from his office at the Weizmann Institute in Israel.

"If we can reactivate the broken resident immune system in the brain, it will make a huge impact on the mental health and

general quality of life of patients who suffer from a whole suite of neurodegenerative diseases, including Alzheimer's."

> *We're hoping to make a breakthrough that will be relevant for both women and men. But for women, it will be even more important, given the higher frequency of the disease.*

Prof. Sonenberg said that using both male and female lab mice will allow their research to contribute to a more complete understanding of the factors associated with AD. "If we have the full picture, we'll have a better idea how to combat the disease," he told Mind Over Matter®.

IMPROVING PRECISION

A greater understanding of the causes of depression is the goal of the third funded project, which is a collaboration between Prof. Ilan Lampl of the Weizmann Institute and Dr. Etay Hay of the Centre for Addiction and Mental Health (CAMH) in Toronto. They are focusing on particular brain cells called somatostatin (SST) interneurons. Autopsies of people who suffered from major depression showed lower levels of SST expression in these cells. The researchers are exploring whether there is a direct link.

"We want to achieve specificity. We want to know if these cells alone can affect depression," said Prof. Lampl.

Using a technique called optogenetics and a mouse model of depression, the team will shine a light on the SST interneurons of mice that have a form of depression and investigate whether this stimulation recovers brain activity to levels seen in non-depressed mice. They will use equal numbers of male and female mice so that they can note any differences between the sexes.

"This will really establish whether that mechanism is relevant for depression, and it will offer insights that could help guide us on what kind of activation or treatment protocols would be effective," Dr. Hay told Mind Over Matter®.

The researchers anticipate that their work could pave the way for future projects that develop treatment protocols using new drugs that treat depression with more precision.

"It's important because the current medications for depression are not specific – they are acting on many cells in different brain regions and therefore have many side effects," said Prof. Lampl.

Recipients applauded the Brain Canada and Weizmann Institute of Science Team Grants program for fostering international collaboration, and for funding projects that otherwise might have difficulty securing support.

"It's a very generous grant, and it's accepting risky projects. It would be hard to fund that kind of project quickly through more conservative channels," said Dr. Hay.

WORKING TOGETHER TO BOOST BRAIN HEALTH

"The selection of these remarkable teams, through our rigorous, independent peer review process, exemplifies the power of international collaboration in advancing our knowledge of the brain," said Dr. Viviane Poupon, President and CEO of Brain Canada.

> **BY UNITING DIVERSE EXPERTISE AND PERSPECTIVES, THESE PROJECTS ARE WELL-POSITIONED TO MAKE STRIDES IN UNRAVELLING THE COMPLEXITIES OF THE BRAIN.**

This program is made possible by the Canada Brain Research Fund (CBRF), an innovative arrangement between the Government of Canada (through Health Canada) and Brain Canada, and Weizmann Canada.

Susan Stern, CEO of Weizmann Canada, is equally enthusiastic about the grant program.

"With this project there is much to celebrate – the high calibre of the neuroscience research being undertaken, its focus on critical areas of brain health that require exploration, and in particular, its collaborative framework. Our Canadian donors give with intent, knowing that the Weizmann Institute of Science partners with the world's best because sharing ideas and expertise strengthens science and innovation for the benefit of all people," she said.

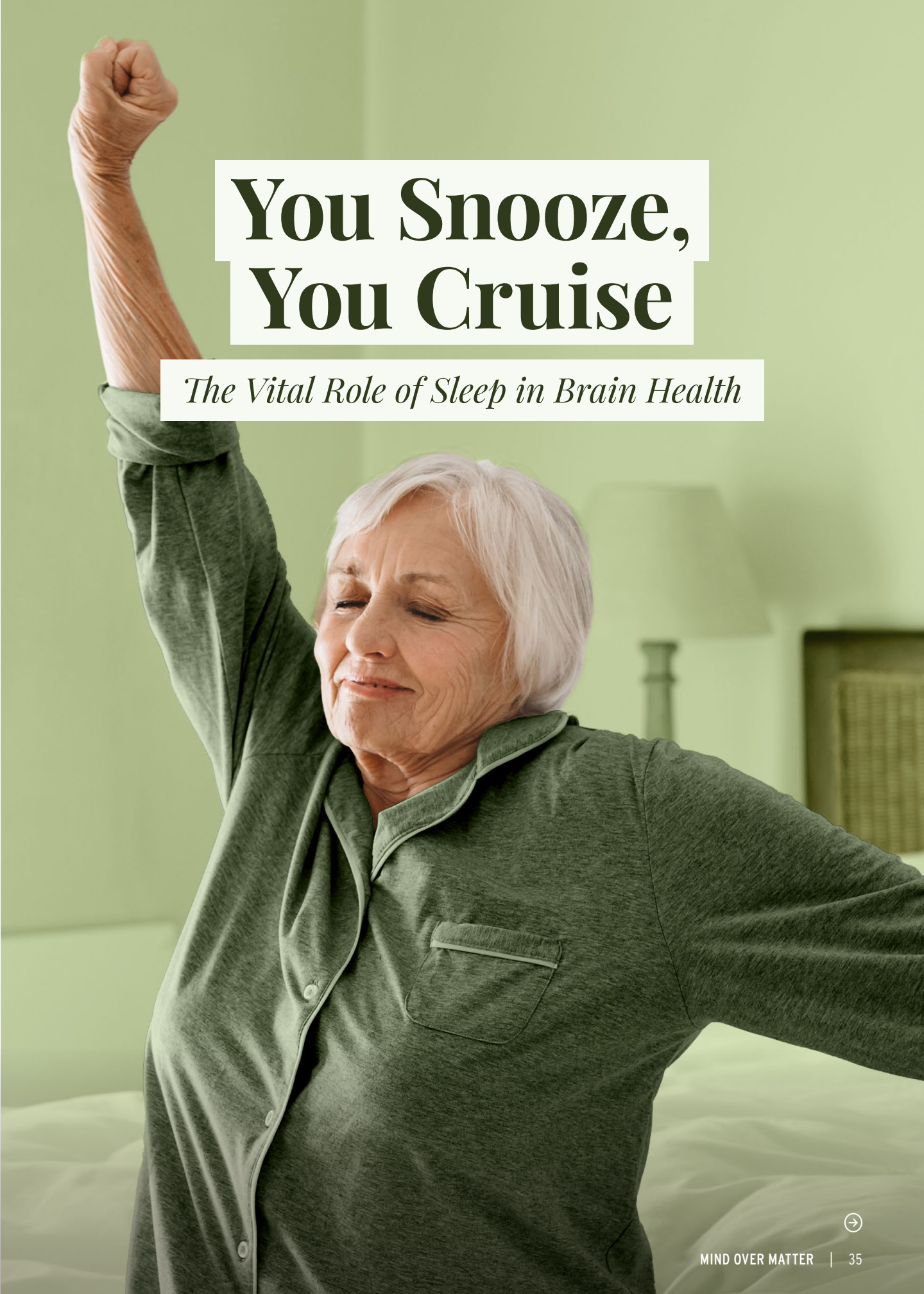
Ms. Stern and Dr. Poupon highlighted the vision of the donors who made the program possible, notably Dr. Daniel C. Andreae and the Larry and Judy Tanenbaum Family Foundation, who played pivotal roles in bringing this pilot program for scientific research to fruition.

Larry Tanenbaum is Vice-Chair at Brain Canada and Founder of the Tanenbaum Open Science Institute (TOSI) at the Neuro (Montreal Neurological Institute-Hospital).

Their support expands the possibilities for brain health and collaborative research.

You Snooze, You Cruise

The Vital Role of Sleep in Brain Health



Sleep is more than a nightly retreat – it is a fundamental pillar of health, essential for survival and optimal functioning of the body and mind. Comparable in importance to nutrition and physical activity, sleep is critical for many functions, from physical recovery to emotional regulation, and cognitive resilience.

Though we may think of sleep as a time of rest, science tells us that it is a period of high cellular activity.

During sleep, the brain consolidates memories, clears toxins, and recharges neural circuits, preparing us to tackle challenges with clarity and focus.

The benefits extend beyond the brain, influencing heart health, immune function, and overall well-being.

Despite its significance, nearly one-third of all adults suffer from sleep disturbances, which can disrupt critical processes and contribute to long-term health risks, including cardiometabolic disorders (e.g., diabetes and heart disease), cancer, accelerated brain aging, and neurodegeneration.

In their 2023 review and editorial in *The Lancet, Public Health*, the World Sleep Society Global Health Taskforce emphasized that the consequences of sleep deficiency are a threat to global health and the health budget of every country. Yet, sleep remains under-recognized in data collection and health policies.

CURRENT EVIDENCE SUGGESTS THAT IF SLEEP IS PRIORITIZED AS A CORE HEALTH-PROMOTING BEHAVIOUR, THIS WILL IMPROVE POPULATION HEALTH AND HELP TO ADDRESS HEALTH INEQUITIES.

SLEEP DURATION RECOMMENDATIONS FOR ADULTS

Experts from the National Sleep Foundation in the United States and the Canadian Society for Exercise Physiology recommend 7-9 hours of sleep for adults aged 18-64 and 7-8 hours of sleep for older adults (65 + years).

ADULT SLEEP CYCLES

HealthLinkBC explains that adults typically progress through the three stages of NREM sleep before entering REM sleep, and the cycle repeats four to six times per night as follows:

- **NREM sleep (~75% of sleep)**
- **N1 – light sleep, usually less than ten minutes**
- **N2 – muscles relax, 30–60 minutes, associated with memory consolidation**
- **N3 – deep sleep, 20–40 minutes, associated with growth and repair, immune function, glymphatic clearance**
- **REM sleep (~25% of sleep)**
- **Dreams most often occur in this phase**
- **Eyes and eyelids flutter, breathing is irregular**
- **The brain temporarily paralyzes your skeletal muscles (sparing the diaphragm and eye muscles), so you do not physically act out your dreams**
- **REM cycles get progressively longer over the course of sleep until we wake up**

STAGES OF SLEEP

Brain cells constantly communicate with each other using electrical impulses. An electroencephalogram (EEG) is a test that measures the amplitude (size) and frequency of the brain impulses and depicts them as brain waves.

Using EEG, sleep has been categorized into two phases: rapid eye movement (REM) characterized by low-amplitude and fast oscillating waves, and non-rapid eye movement (NREM) with high-amplitude and slow oscillating waves. NREM is also referred to as slow-wave sleep and is further differentiated into three stages: N1, N2, and N3.

SLEEP BOOSTS THE BRAIN

Dr. Jean-Philippe Chaput, senior scientist with the Healthy Active Living and Obesity Research Group, and a leading researcher in sleep science, highlights the range of brain health benefits of sleep:

Sleep enhances memory, protects against mental decline, and fosters emotional strength.

MEMORY CONSOLIDATION

Sleep allows the brain to process and organize information from the day. This strengthens neural connections, enhancing learning and transforming short-term memories into long-term ones.

When it comes to big decisions, it looks like the strategy of "sleeping on it" really can help you to weigh information and make informed choices!

A 2023 review in *Neuron* by Dr. Brodt and colleagues explained that while memory consolidation also occurs when we are awake, we are better able to synchronize neural activity with long-term memories encoded in the hippocampus part of the brain when we are asleep.

SYNCHRONIZED BRAIN ACTIVITY HELPS US TO GENERALIZE OUR EXPERIENCES FROM DIFFERENT CONTEXTS, PRODUCING STRONGER MEMORIES THAN THOSE FORMED WHEN WE ARE AWAKE.

Greater demand to integrate learning from daily experiences and form long-term memory is one of the reasons why infants require more sleep than children, and children more than adults.

TOXIN CLEARANCE

The glymphatic system, the brain's waste-removal network, is most active during sleep. Glymphatic clearance filters harmful proteins like tau and beta-amyloid proteins out of the brain and reoxygenates the brain tissues.

A 2020 publication on the glymphatic system by Drs. Reddy and van der Werf in *Brain Sciences* explained there is an 80-90% increase in glymphatic clearance during the N3 stage of NREM compared to when we are awake.

The efficiency of this waste-removal system appears to decrease naturally over the course of aging, aligning with poorer sleeping patterns among older adults. This has prompted the exploration of lifestyle interventions that may be able to enhance glymphatic function, including consumption of omega-3 fatty acids, intermittent fasting, and regular exercise.

Though findings in animal model studies are promising, randomized controlled trials with humans are needed to develop clinically significant recommendations that can boost the function of the glymphatic system with age.

NEURAL PLASTICITY & EMOTIONAL REGULATION

Sleep supports neural plasticity – the brain's ability to adapt and form new connections. This neural plasticity also helps to regulate emotions, reducing stress and anxiety.

Associations between sleep and mental health are well-established, and accumulating evidence supports a causal relationship: improved sleep significantly alleviates mental health disorders.

In 2021, Dr. Scott and colleagues published a systematic review and meta-analysis in *Sleep Medicine Reviews* that examined 65 randomized controlled trials with more than 8,000 participants. Findings showed that interventions to improve sleep had significant positive effects on a composite of mental health outcomes as well as separate positive effects on depression, anxiety, and stress.

Greater improvements led to greater benefits across a variety of sleep interventions and outcomes, providing strong evidence that enhancing sleep quality results in better mental health.

Future research is needed to uncover the mechanisms responsible for this causal relationship and to fine-tune the dose of various sleep characteristics necessary for mental health improvements.

SLEEP DISORDERS & BRAIN HEALTH

Sleep disorders not only disrupt nightly rest but also have long-term implications for brain health by increasing the risk of cognitive decline, emotional dysregulation, and neurodegenerative diseases.

INSOMNIA

Insomnia is when you have difficulty falling asleep or staying asleep. Chronic insomnia can impair memory, concentration, and emotional regulation. It is also associated with increased anxiety and depression.

WOMEN ARE AT A HIGHER RISK OF INSOMNIA COMPARED TO MEN, WITH HORMONAL DIFFERENCES PLAYING A ROLE.

A 2023 review by Dr. Anderson and colleagues in *Frontiers in Sleep*, noted that fluctuations in progesterone and

estrogen are associated with sleep disruption, and among women, those with irregular menstrual cycles have twice the risk of insomnia compared to women with regular cycles.

OBSTRUCTIVE SLEEP APNEA (OSA)

OSA, characterized by repeated interruptions in breathing during sleep, reduces oxygen supply to the brain and impairs toxin clearance through the glymphatic system.

People with sleep apnea tend to spend less time in deep sleep (stage N3), and are at a higher risk of Alzheimer's disease (AD), as well as cardiovascular problems like stroke and hypertension.

OSA APPEARS TO BE MORE COMMON IN MEN THAN IN WOMEN, WITH WIDELY VARYING ESTIMATES OF PREVALENCE IN POPULATION STUDIES.

Research suggests that female sex hormones are protective against OSA because of their role in dilating the airways, however, OSA becomes more common in women after menopause, narrowing differences between women and men.

REM SLEEP BEHAVIOUR DISORDER: AN EARLY WARNING SIGN FOR NEURODEGENERATIVE DISEASES

One sleep disorder that has garnered increasing attention is REM Sleep Behaviour Disorder (RBD). In 2023, the American Academy of Sleep Medicine published a systematic review and meta-analysis in *Journal of Clinical Sleep Medicine* that noted a 1% prevalence of RBD in middle to older adults, affecting approximately 80 million people worldwide. Some studies show a higher prevalence among men than women, while others report no sex differences.

RBD is characterized by acting out dreams, often through shouting, kicking, or punching during sleep. RBD occurs because the natural paralysis of the muscles during REM sleep does not work properly, allowing individuals to move their bodies in response to their dreams.

Vigorous limb movements during sleep can lead to injuries for the person with RBD and even their bed partner, making it important to create a safe sleep environment.

Research links RBD to structural changes in one part of the brainstem called the pons, a critical area for regulating REM sleep. The American Academy of Sleep Medicine explained that abnormal accumulation of a specific type of protein, known as alpha-synuclein protein, often starts in the neurons (nerve cells) of the gut and ascends through the nervous system to the REM sleep generators in the pons, compromising their function.

RBD is more than just a disruptive condition – it is an early marker of neurodegenerative diseases.

A large multi-centre cohort study published in *Brain* in 2019 followed patients around the world with RBD for up to 19 years. At baseline, participants were on average 66 years old and 82.5% were male. Analyses revealed that nearly 74% developed Parkinson's disease, dementia with Lewy bodies, or another neurodegenerative syndrome within 12 years of diagnosis.

The authors suggest that RBD could serve as an important early indicator of brain health issues, making patients with RBD ideal candidates for neuroprotective trials. As well, by studying RBD patients, researchers hope to better understand the pathways that lead to neurodegenerative diseases and develop better preventive measures.

POOR SLEEP CHARACTERISTICS

We all know that it is important to get a good night's rest, but did you know that there's more to it than the time you spend lying in your bed? Sleep duration is just one of several sleep characteristics studied by researchers. Poor sleep characteristics include:

- short sleep duration;
- bad sleep quality;
- difficulty initiating sleep;
- difficulty maintaining sleep;
- early morning awakening; and
- daytime sleepiness.

Sleep disturbances are often reported during menopause, a stage linked to the decline of estrogen in women.

That 2023 review by Dr. Anderson and colleagues in *Frontiers in Sleep* mentioned earlier in this story, showed that 40-60% of menopausal women have trouble initiating and maintaining sleep, and experience early morning awakening.

It is possible that these sleep disturbances, particularly during N3 deep sleep, can affect glymphatic clearance among menopausal women, placing them at higher risk of developing AD.

Sleep disturbances are also associated with sex hormones in men, with more sleep disturbances reported by men with low testosterone, and testosterone production linked to uninterrupted periods of sleep.

The Sleep Regularity Index (SRI) was developed to look at sleep and wake times measured by accelerometers, devices that detect the body's movement. The SRI accounts for variability in several sleep characteristics like the time when someone goes to bed, how often they wake up during sleep, how long they sleep, and when they wake up.

SRI is scored on a scale from 0 (completely random sleep patterns) to 100 (perfectly regular sleep patterns) and can be used to categorize people into regular, moderately irregular, and irregular sleep patterns.

Data from a large prospective cohort study of men and women published in 2024 by Drs. Chaput and Biswas and colleagues in *Journal of Epidemiology and Community Health* found that irregular sleep was strongly linked to major adverse cardiovascular events like heart failure, myocardial infarction (heart attack), and stroke.

Furthermore, findings suggested that an irregular sleep schedule puts you at a higher risk of major adverse cardiovascular events even if you met sleep duration recommendations.

It may be that maintaining a regular sleep routine protects your heart health even more than getting the daily recommended 7+ hours of sleep.

POOR SLEEP & ACCELERATED BRAIN AGING

Emerging research shows that even in the absence of a sleep disorder, there may be a connection between poor sleep habits in mid-life and accelerated brain aging, putting individuals at risk of developing neurodegenerative diseases sooner.

A 2024 study in *Neurology* revealed that 40-year-old adults with three or more poor sleep characteristics – such as short sleep duration, poor sleep quality, or irregular sleep schedules – showed signs of advanced brain aging via MRI brain images.

Dr. Cavaillès and colleagues observed that individuals with poor sleep exhibited brains that were 2.6 years older than those with healthier sleep patterns!

THESE FINDINGS SUGGEST THAT MID-LIFE IS A GOOD TIME TO SET DOWN HEALTHY HABITS THAT IMPROVE SLEEP AND PRESERVE YOUR BRAIN HEALTH.

Sleep is a powerful, yet often overlooked, ally in maintaining brain health. By prioritizing good sleep habits, we can enhance cognitive performance, reduce the risk of neurodegeneration, and enjoy a healthier, more resilient mind.

As Dr. Chaput summarized, "A brain that gets quality and regular sleep functions more effectively, fuelling creativity, improving focus, and safeguarding memories."

PRACTICAL TIPS FOR BETTER SLEEP

Improving sleep quality and regularity doesn't have to be complicated. Here are actionable steps to help you rest better:

01 Exercise During the Day
Physical activity during the daytime can help to reset your circadian rhythm and help your body and brain settle into a restful state as evening approaches.

02 Establish a Sleep Routine
Set consistent bedtimes and wake-up times to regulate your internal clock.

03 Create a Sleep-Friendly Environment
Keep your bedroom dark, quiet, and cool. Avoid light exposure from screens before bedtime.

04 Wind Down Before Bed
Develop a relaxing pre-sleep routine, such as reading, light stretching, listening to soft music, or taking a warm bath.

05 Avoid Sleep Disruptors
Limit caffeine, alcohol, and heavy meals in the evening. Strenuous exercise should also be avoided late at night.

Sharing Their Story

Three Generations of Women Built a Thriving Business & a Mindful Legacy

Even for a relentlessly positive person like Jo-Ann Fisher it was a daring move – opening a women's clothing store with no formal business education after spending most of her adult life as a full-time mom to three daughters. Ask her why she did it, and the answer comes from the heart:

"It was just that I love fashion; let's just open a store."

It was 1985. Jo-Ann had sold Mary Kay cosmetics and was inspired by the story of the founder who built a business from nothing. She attended Mary Kay company conferences, where she learned essential lessons about customer care.

With little money and just an idea about how to streamline dressing for busy women, she partnered with friend Pat Cooper and took the leap. Forty years later her store, Hangar9, is thriving as a fixture in downtown London, Ontario, with a sister store in Toronto, along with an online version.

As with any small business, there were complications in the early days. Her friend Pat had to pull out after a couple of years. Then came big life changes.

"Three years after starting my business, I was surprised to find out I was expecting," said Jo-Ann, speaking in the back room of her bustling Toronto store in the heart of the financial district. It had been 14 years since the arrival of her previous child.

"This was a surprise," she said, gesturing toward her daughter Rachael Doak, who was busily serving a customer in the store.

A couple of years after Rachael's birth, Jo-Ann split up with her husband, meaning she was now not only a small-business person, but a single mother caring for a little one.

She recalled with a laugh how toddler Rachael knocked over the Christmas tree, a misadventure that coincided with the busiest time of the year for retailers. "I looked at it and thought, 'Oh, I can't cope with this right now. Not gonna happen.' I think the tree lay there for three days. It was just like, now is not the time to deal with it; don't stress yourself."

Eldest daughter Denise MacDonald nodded as she listened to the story, observing that the incident speaks to her mom's attitude toward dealing with life's challenges.

"If there's anything bad, she's always able to turn it around and tell me what I should be looking forward to versus what I should be dreading," said Denise, the CFO of the family enterprise. She begins every day with a call to her mother.

"Her perspective is her best mentorship to me. Her positive mindset on life has helped me as a person.

Denise had not planned to work with her mother. She got an MBA and spent several years in the Bay Street corporate world before Jo-Ann asked her to jump aboard for some short-term help with the management.

It meant a substantial pay cut, but with three small children at home and the opportunity for a shorter work week, Denise agreed. It was supposed to be for a few months. That was more than 20 years ago.

"I didn't think I was going to work with Mom, but I sort of feel that I work with her because it was God's way of making me more positive," said Denise.

"I mean, it's a crazy business from a financial metrics standpoint. However, I have an opportunity to work with my family. I speak to all of them every day, and we're building something here, and we're very proud."

Having finished with her client, Rachael joined the conversation. She came into the business right out of college and has the title Chief Operations Officer, Lead Stylist, and Buyer.

"I feel like one of the greatest gifts Mom has given me is this idea that there's no point in getting worked up and upset and unwell over something that is outside of your control. You just have to roll with the punches," she said, noting that she is also raising three children under ten.

"It's not easy, but what's important is that everybody's healthy, happy, alive, and well. You know, we aren't performing brain surgery!" said Rachael.

The second-oldest daughter, Lisa Fisher-Ferguson, has been part of the business from the beginning and now oversees the London store, assisted by her daughter Emily, currently on maternity leave after recently given birth to Jo-Ann's first great-grandchild, a boy named George. (The fourth daughter, Jodi, is not directly part of the Hangar9 team, but is peripherally involved as a wholesaler.)

PHOTO: ARTHUR MOLA

THERE ARE INEVITABLE CHALLENGES IN BEING BOTH BUSINESS PARTNERS AND CLOSE FAMILY MEMBERS. LISA SAID THAT THEY HAVE ARGUMENTS ALL THE TIME BUT HAVE DEVELOPED EFFECTIVE COPING MECHANISMS.

"We're very vocal people. We don't hold things in. We also have the ability to have stern meetings where not everybody agrees but can go for dinner afterwards. It's a talent I'm sure Mom ingrained in us," she said in a phone interview from the London store.

"When we started the business together, we said the moment we can't spend Christmas together the business will be dissolved. Family first."

Not only do they remain partners, but the Fishers recently took a memorable, multigeneration trip to Greece together.

From the outset, Jo-Ann's business plan was to provide an individualized service for busy professionals who might have limited time for shopping. The Hangar9 name refers to the concept of a "capsule wardrobe," a formula in which nine carefully chosen clothing items can be combined to create 36 different looks.

"We really like to cater to a woman who loves the clothes, loves the idea of looking well and feeling confident, but who is busy and doesn't necessarily have much time – a woman who is looking for that kind of personalized individual service," said Jo-Ann.

INVOLVEMENT IN THE MISSION OF WOMEN'S BRAIN HEALTH INITIATIVE (WBHI) WAS A NATURAL OUTGROWTH FOR A STORE THAT CATERS TO WOMEN.

The formula has been a smashing success, with a high retention rate of clients who have been coming back for decades. As they talk about clothes, they also discuss health – stress, menopause, and, yes, dementia. They are hungry for the kind of brain health information and advice disseminated by WBHI and Mind Over Matter®, Jo-Ann said.

"I mean, I'm so involved with women and all their problems, and then all of a sudden, these people are talking about all the problems women have, which is really important. Women want it."

Long before she learned anything about brain health, Jo-Ann instinctively adopted a lifestyle geared toward cognitive vitality. She has always exercised and been socially active. Even though she has now handed over control of the business to her daughters and is well past so-called retirement age, she is in the store most days.

She is part of a book club and a dinner club that sees her regularly meeting friends at restaurants around London. It is a model that her daughters all follow, while she in turn learns lessons from them.

"Now I'm into smoothies and protein shakes because I have a millennial daughter!"

Hangar9 has sponsored a fashion show and luncheon for WBHI, with hopes to do much more. Becoming active in the cause of brain health has a personal resonance for Jo-Ann. Pat Cooper, her friend with whom she launched her business, is now coping with dementia.

"It's really heartbreaking. I think about her all the time," she said.

"That's why it's so important for us to know about all the things that can help us."

Wildfire Smoke

A Greater Impact on Brain Health than Previously Understood

Wildfires. The word evokes frightening images of bright orange flames and smoke filling the sky as millions of hectares of forests, grasslands, and communities burn, as we recently witnessed in California.

As the destruction caused by wildfires has increased due to climate change, wildfire smoke has become a major source of air pollution both within the burn zones and far beyond.

Wildfire smoke is about ten times as toxic as regular air pollution from burning fossil fuels, and there's no safe level of exposure, according to Stanford University experts.

Exposure to wildfire smoke is bad for lung and heart health, especially for people living with chronic conditions like asthma, chronic obstructive pulmonary disease, and congestive heart failure. It can also worsen mental health issues, including anxiety, depression, post-traumatic stress disorder and general distress caused by experiencing a natural disaster.

It's early days for research investigating how wildfire smoke affects brain health, but so far, leading researchers in Canada and the United States have discovered that the impact is more significant than previously understood.

Wildfire smoke exposure is associated with short-term reductions in the ability to pay attention and a longer-term risk of dementia.

Mind Over Matter® spoke with these experts to learn more about their findings. This article also provides helpful information on measures you can take to minimize wildfire smoke exposure.

WHAT'S IN WILDFIRE SMOKE?

> **"TYPICALLY, WE THINK OF WILDFIRE SMOKE AS COMING FROM BURNING FORESTS AND GRASSLANDS. BUT WITH MORE PEOPLE LIVING CLOSER TO FORESTS AND NATURE – THIS IS CALLED THE WILDLAND-URBAN INTERFACE – WILDFIRE SMOKE INCLUDES WHATEVER BURNS, INCLUDING HOMES, ELECTRONICS, AND REFRIGERATORS.**

This description comes from Dr. Stephanie Cleland, a research scientist with the Legacy for Airway Health initiative at the

Vancouver Coastal Health Research Institute and assistant professor at Simon Fraser University in Vancouver.

Wildfire smoke is a complex mix of gases like carbon monoxide and sulphur dioxide; volatile organic compounds like toluene and benzene; and particulate matter (PM).

PM consists of solid and liquid droplets suspended in the air. The size of PM particles is measured in microns. Most of the PM in wildfire smoke, about 90%, consists of fine particles that are 2.5 microns in diameter or smaller, known as $PM_{2.5}$. Each $PM_{2.5}$ particle is tiny and invisible to the naked eye: about 30 can fit across the width of a human hair.

Compared to larger particles, $PM_{2.5}$ particles pose the greatest threat to human health because they can travel deep into the lungs, enter the bloodstream, and find their way into the brain, where they cause inflammation and oxidative stress. $PM_{2.5}$ can also move into the brain through the olfactory nerve in the nose.

"Wildfire $PM_{2.5}$ contains organic carbon but may also contain worse contaminants like lead or zinc, which might make it more harmful to health than non-wildfire $PM_{2.5}$, such as emissions from coal-fired power plants, which are mostly sulphates," said Dr. Joan Casey, an associate professor in the Department of Environmental and Occupational Health Sciences in the University of Washington's School of Public Health.

CLUES FROM ANIMAL STUDIES

Since conducting human clinical trials of a known toxic substance in humans and evaluating how it affects brain health is challenging, scientists often rely on animal studies.

For example, a team of researchers from the University of New Mexico Health Sciences Center studied the brain health consequences of exposure to wildfire smoke that occurred naturally in California, Arizona, and Washington in 2020. They exposed mice to wildfire smoke-derived $PM_{2.5}$ for four hours daily for 20 days in a mobile lab far from natural fires.

In their paper, published in *Toxicological Sciences* in December 2021, the researchers reported they found numerous changes consistent with the development of Alzheimer's and related dementias, including significant neuroinflammation, a reduction in molecules related to protecting against aging, and an increase in the accumulation of amyloid-beta protein.

SHORT-TERM EFFECT ON ATTENTION

While working on her PhD at the University of North Carolina, Chapel Hill, Dr. Cleland led a study together with Dr. Ana Rappold, a statistician and Branch Chief in the Public Health and Integrated Toxicology Division at the U.S. Environmental Protection Agency (EPA) in North Carolina, and Dr. Sarah Henderson, Scientific Director of Environmental Health Services at BC Centre for Disease Control in Vancouver.

"This study was born out of growing anecdotal reports of brain fog during wildfire smoke events," said Dr. Cleland.

> ***"Our study was one of the first, if not the first, to consider the cognitive effects of wildfire smoke.***

For their study, published in *Environmental Health Perspectives* in June 2022, Dr. Cleland and colleagues evaluated the associations between daily and hourly $PM_{2.5}$ and wildfire smoke exposure and cognitive function.

They obtained scores from 20 plays of the attention-training game Lost in Migration by Lumosity for more than 10,000 American adults. The mobile app game asks users to identify the lead bird in a moving image of a flock of birds while ignoring surrounding distractions.

Dr. Cleland and colleagues also collected data on daily and hourly $PM_{2.5}$ and wildfire smoke exposures from multiple sources, including monitoring station observations from the EPA's Air Quality System database and smoke plume density data from satellite imaging provided by the U.S. National Oceanic and Atmospheric Administration.

Their analysis revealed some surprising findings:

- daily and hourly $PM_{2.5}$ exposure was associated with significant decreases in scores for all game players, especially among those living in the wildfire-impacted western U.S.;
- a 10 microgram per cubic metre increase in $PM_{2.5}$ in the three hours before game play was associated with a 21-point drop in game score. Dr. Cleland said that a 10 microgram per cubic metre increase in $PM_{2.5}$ is fairly large, similar to the rise between each level on the Canadian Air Quality Health Index (AQHI);
- heavy smoke exposure the day before game play was associated with a 117-point decrease in score compared to no smoke exposure, and
- $PM_{2.5}$ exposure over 20 game plays was associated with a 3.7% drop in the final score.

"While these score decreases were not huge given that average scores ranged from 9,000 to 14,000 points, the changes we observed were measurable and significant, confirming that experiencing brain fog after wildfire smoke exposure is likely a real phenomenon," said Dr. Cleland.

A REDUCED ABILITY TO PAY ATTENTION DUE TO WILDFIRE SMOKE EXPOSURE PALES IN COMPARISON TO MORE IMMEDIATE PROBLEMS LIKE HOSPITALIZATIONS AND MORTALITY, BUT THOSE OUTCOMES AFFECT A SMALLER PROPORTION OF PEOPLE. A DECREASED ABILITY TO PAY ATTENTION AFFECTS EVERYONE EXPOSED AND CAN HAVE A BIG IMPACT ON THE ABILITY TO NAVIGATE DAILY LIFE.

Interestingly, about 70% of game users were women, and the associations between wildfire smoke exposure and scores tended to be stronger for men, especially those exposed to heavier smoke levels.

"We don't know what led to this gender-related difference, and it's a complicated question to answer," said Dr. Cleland. "Men may be more likely to work or be active outdoors, there may be biological differences, or both factors may play a role. At a minimum, identifying at-risk groups could lead to targeted protective measures."

THE MAIN TAKEAWAY FROM OUR STUDY IS THAT WILDFIRE SMOKE POSES A RISK TO COGNITIVE HEALTH, AS EARLY AS WITHIN HOURS OR DAYS OF EXPOSURE. WE HOPE KNOWING THIS WILL ENCOURAGE MORE PEOPLE TO PROTECT THEMSELVES DURING WILDFIRE SMOKE EVENTS.

In the future, Dr. Cleland plans to conduct new studies examining the relationships between multi-year wildfire smoke exposure, cognitive decline, and the risk of developing chronic neurological conditions.

LONGER-TERM LINK TO DEMENTIA RISK

Dr. Casey was the lead author of the first study to investigate the association between longer-term exposure to wildfire $PM_{2.5}$ and the likelihood of a first-time dementia diagnosis. The paper was published in *JAMA Neurology* in November 2024.

"Previous air pollution studies have found that long-term exposure to $PM_{2.5}$, a major component of wildfire smoke, is associated with an increase in the incidence of dementia," said Dr. Casey. "Since wildfire events are intensifying globally, we looked at the relationships between wildfire and non-wildfire $PM_{2.5}$ and the risk of new-onset dementia diagnoses."

Dr. Casey and colleagues analyzed ten years of electronic health records for more than 1.2 million members of the healthcare plan provider Kaiser Permanente Southern California. They only included data for people over age 60 who had not been diagnosed with dementia at the beginning of the study.

Next, they used air quality monitoring data, satellite imagery, and machine learning methods to estimate wildfire and non-wildfire $PM_{2.5}$ exposures. Finally, they determined each individual's exposure to both types of $PM_{2.5}$ according to their addresses and compared that information with dementia diagnoses that arose over time.

"We were quite surprised to find a much stronger relationship between wildfire $PM_{2.5}$ and dementia diagnoses than with non-wildfire $PM_{2.5}$. Additionally, we found even stronger associations for different subgroups, including non-Hispanic Asian, non-Hispanic Black, and Hispanic members, and those living in high-poverty areas compared to low-poverty areas."

EVERY INCREASE OF 1 MICROGRAM PER CUBIC METRE IN THE THREE-YEAR AVERAGE EXPOSURE TO WILDFIRE $PM_{2.5}$ WAS ASSOCIATED WITH AN 18% INCREASE IN THE ODDS OF A DEMENTIA DIAGNOSIS.

By comparison, the same increase in exposure to non-wildfire $PM_{2.5}$ was only associated with a 1% increase in the odds of a dementia diagnosis.

"It's important to recognize this was not a causal effect; it was an association. Dementia has multiple causes," Dr. Casey cautioned. "However, it gives a strong reason to believe long-term exposure to wildfire $PM_{2.5}$ is worse than other sources of $PM_{2.5}$ for brain health."

In terms of sex-related differences, 53% of the study population was female, and there was a stronger association between wildfire $PM_{2.5}$ and a dementia diagnosis in men.

Mind Over Matter® is the first to ask about sex-related differences in our findings, so I spoke to some sociologists to inquire further.

"They were not surprised with these results since in other qualitative work, they have found women are more likely

to take health protective measures during smoke events, such as staying indoors, wearing masks, or running air filters, whereas men are more inclined to go about their usual activities unfazed," Dr. Casey continued.

Dr. Casey hopes her research will lead to a broader awareness of the importance of paying attention to air quality and checking air quality the same way we check the daily weather forecast before venturing outdoors, especially during wildfire season.

She is planning new studies together with first author Dr. Holly Elser, a resident in the neurology program at the University of Pennsylvania. "Dr. Elser is very interested in learning more about relationships between wildfire $PM_{2.5}$ and different dementia types, hopefully tying in brain imaging data. If we find a stronger relationship to wildfire smoke for one dementia type compared to others, that could shed light on what's driving the increased risk."

KEY TAKEAWAYS

While much research work lies ahead, it's clear that wildfire smoke is terrible for both short- and long-term brain health.

In an opinion piece published in *BC Medical Journal* in April 2024, Dr. Henderson and co-authors noted that wildfire smoke gets a lot of attention when $PM_{2.5}$ concentrations are extreme during large fires but causes much more harm at lower concentrations occurring more frequently.

"If we focus our attention on the extreme events and ignore the more moderate impacts, we miss most of our opportunity to protect health. We should collectively start to manage exposures whenever wildfire smoke is affecting air quality," they wrote.

PROTECT YOURSELF FROM WILDFIRE SMOKE

01 Confirm air quality is safe before you head outdoors. Check a weather app or refer directly to Canada's Air Quality Health Index (AQHI) at **www.canada.ca/en/environment-climate-change/services/air-quality-health-index.html** or the U.S. Air Quality Index (AQI) at **www.airnow.gov/aqi/aqi-basics**.

Firesmoke.ca, an initiative of the Weather Forecast Research Team at the University of British Columbia, provides an interactive map showing forecasts of hourly and daily $PM_{2.5}$ wildfire smoke particles across North America.

02 During a wildfire smoke event, stay indoors as much as possible with windows closed. If you must go outdoors, wear an N95 mask. According to the U.S. National Institute for Occupational Safety and Health, a properly fitting N95 mask can filter out 95% of smoke particles.

03 The EPA recommends keeping your home air filtration system up to date and using a portable air cleaner or high-efficiency filter to remove $PM_{2.5}$ from the air during a wildfire smoke event.

WILDFIRE TRENDS

CANADA

2023 was Canada's most destructive wildfire season ever recorded, with 7,131 fires burning more than 17 million hectares, significantly higher than the ten-year average of 5,350 fires and 2.7 million hectares burned.

According to a report published in *Nature Communications* in August 2024, from April to late October 2023:

- **millions of Canadians were exposed to hazardous air quality from wildfire smoke;**
- **on average, Canadians experienced eight days of poor air quality; and**
- **in some regions, wildfire smoke polluted the air for more than 60 days, including some areas with 18 times the $PM_{2.5}$ level required to trigger an air quality warning.**

The 2024 wildfire season was not as devastating as 2023, but as of October, it was on track to be the second-worst season in the last 20 years, according to CBC News.

U.S.

2024 was the 7th most destructive year in U.S. wildfire history, during which more than 61,000 fires burned about 8.8 million acres (about 3.6 million hectares).

In January 2025, a series of devastating wildfires broke out in Los Angeles. Hurricane-strength winds drove flames through dry vegetation that had gone months without rain, causing massive destruction in several communities.

The area burned by wildfires each year has increased since the 1980s. The proportion of burned land with severe damage has ranged from 5 to 22% of the total area burned each year from 1984 to 2021, according to the U.S. Environmental Protection Agency.

Let's Get Physical

Building & Connecting the Brain Through Exercise

The intricate relationship between physical exercise and brain health is a subject of growing interest in the scientific community. Research consistently shows that regular physical activity, particularly heart-pumping aerobic activity, is related to cognitive function, mental well-being, and overall brain health.

Guidelines from the Canadian Society for Exercise Physiology recommend at least 150 minutes of moderate- to vigorous-intensity aerobic activity weekly, coupled with strength and balance exercises. What we don't yet know are specifics about who benefits the most and how we can tailor exercise to maximize benefits.

Evidence suggests that the brain responds differently to exercise across the lifespan and varies based on individual factors like biological sex and genetics.

These connections are underpinned by complex physiological and psychological processes that affect how the brain operates and adapts to various stimuli.

This article explores the transformative effects of exercise on the brain, incorporating insights from Dr. Cindy Barha, assistant professor in the Faculty of Kinesiology at the University of Calgary, Canada Research Chair (Tier II) in Neuroscience, Brain Health and Exercise, member of the Hotchkiss Brain Institute, and the first Women's Brain Health Initiative Future Leader in Canadian Brain Research. Future Leaders in Canadian Brain Research is one of Brain Canada's signature capacity building programs and has funded more than 100 early career researchers to date.

"Brain Canada is thrilled to see how our signature Future Leaders program has grown, enabling us to provide increased support to researchers during this pivotal stage of their careers," said Dr. Viviane Poupon, President and CEO of Brain Canada. "As a leading research funder focused specifically on the brain, we are thrilled to advance the field of sex and gender brain science and support Dr. Barha's work, together with our partner, Women's Brain Health Initiative."

EXERCISE AS A CATALYST FOR NEUROGENESIS & STRUCTURAL CHANGES

One of the most groundbreaking discoveries in neuroscience is the brain's ability to generate new neurons, a process known as neurogenesis, in adulthood. Exercise plays a pivotal role in this phenomenon, specifically in the hippocampus, a brain region associated with memory and learning.

A 2024 review published in *Trends in Neurosciences* by Dr. Nárlon C. Boa Sorte Silva and colleagues presented evidence from systematic reviews and meta-analyses showing that physical activity promotes structural and functional brain adaptations, such as increased gray matter volume and enhanced white matter integrity.

Dr. Barha, a co-author on this review, highlighted, "When it comes to healthy aging, brain adaptations linked to exercise not only improve memory but also enhance higher-order cognitive functions, such as the brain's capacity to manage multiple tasks simultaneously."

The review further highlighted that brain changes were seen in healthy individuals and those with mild cognitive impairment, though effects were modest.

When comparing the effects of different types of exercise in the brain, aerobic exercises (e.g., running, cycling, and swimming) emerge as particularly effective in supporting neuron growth and survival via the production of brain-derived neurotrophic factor (BDNF).

As it turns out, when your heart pumps faster and increases blood flow during physical activity, there are corresponding increases in proteins like BDNF delivered to the brain and made within the brain.

> **BDNF IS LIKE A VITAMIN FOR YOUR BRAIN. REGULAR PHYSICAL ACTIVITY BOOSTS ITS LEVELS, CREATING AN ENVIRONMENT WHERE NEURONS CAN THRIVE, AND CONNECTIONS CAN STRENGTHEN. THIS IS CRUCIAL FOR MAINTAINING COGNITIVE VITALITY AS WE AGE.**

BOOSTING COGNITION THROUGH MOVEMENT

In addition to neurogenesis and structural changes, BDNF can also support cognitive functions such as focusing attention, planning tasks, ignoring distractions, and consolidating memory.

A 2019 review of research by Dr. Magdalena Miranda and colleagues from the Laboratory of Memory Research and Molecular Cognition in Argentina explained that aging, development of Alzheimer's disease (AD), and chronic stress can decrease levels of BDNF, however, exercise can elevate BDNF and enhance cognition both during and after a bout.

Published in *Frontiers in Cellular Neuroscience*, the evidence showed that BDNF is elevated rapidly during exercise, stays consistent with regular exercise, and remains elevated for several days.

Furthermore, interventions that combine exercise with cognitive demands may have the greatest impacts on the brain. For instance, cited research showed that a dancing program that required more coordination and cognitive processing resulted in greater increases in gray matter than a traditional sports program.

Different types of exercise training appear to influence different types of brain function.

Dr. Barha and colleagues examined the types of exercise protocols used in randomized controlled trials in older adults and their effects on the brain.

Their influential 2017 review and meta-analysis in *Frontiers in Neuroendocrinology*, which has been cited by both the WHO Guidelines on Risk Reduction of Cognitive Decline and Dementia and the *Lancet* Commission, showed that aerobic training, resistance training, and multimodal training that combined aerobic and resistance training all enhanced visuospatial function (e.g., distance perception) and executive functions, but only multimodal training improved episodic memory (e.g., recall events and experiences).

Moreover, aerobic training was more beneficial for global cognitive function and executive functions than resistance training, and multimodal training was even better than aerobic training across several areas: global cognitive function, episodic memory, and word fluency.

These findings align with the Canadian physical activity guidelines recommending that older adults should engage in combinations of aerobic, strength, and balance exercises.

THE ROLE OF EXERCISE IN NEUROPROTECTION IN MID-LIFE

Exercise acts as a powerful neuroprotective agent with multi-system effects like reducing inflammation, lowering oxidative stress, and improving vascular health. These benefits contribute to brain resilience and offer hope for those at risk of or living with neurodegenerative conditions.

"Exercise strengthens the brain's defences," Dr. Barha asserted.

> **"EXERCISE PREVENTS DAMAGE AND AIDS RECOVERY FOR INDIVIDUALS WITH BRAIN INJURIES AND CAN SLOW DOWN DAMAGE FROM NEURODEGENERATIVE DISEASES.**

One important consideration highlighted by Dr. Barha is that brain health status can impact exercise levels. People with cognitive impairments can have challenges with organizing their time, planning exercise into their day, setting goals, and adhering to exercise recommendations.

A 2017 study by Drs. Varma and Watts in *Journal of Alzheimer's Disease* showed that daily physical activity levels declined among people in early stages of AD prior to any declines in mobility and physical function.

Building social supports into exercise programs (e.g., exercise buddies or group classes) or creating exercise programs that can be done with caregivers or family members from the earliest signs of cognitive impairments might help to promote exercise adherence and slow down the progression of disease.

Exercise indirectly benefits brain health as well by preventing and mitigating effects of diabetes and hypertension, known risk factors for neurodegenerative diseases.

Efforts to prevent these chronic conditions takes on greater importance when adults approach mid-life, and this may be especially the case for women.

"Mid-life, that is, about age 45 to 60, is a critical window for intervention because it is a critical window for brain vulnerability," explained Dr. Barha.

When it comes to women, around mid-life, they typically go through perimenopause where there are fluctuations in hormone levels like estradiol, and changes in neuroinflammation and even changes in the brain's energy sources that can damage the brain's white matter can start to be seen.

"By intervening in mid-life, we can hopefully use exercise to bolster the brain and reduce damage, reduce risk for dementia or severity of dementia later in life," said Dr. Barha.

SEX DIFFERENCES IN EXERCISE & BRAIN HEALTH

Although we know that exercise is beneficial for brain health, there are some inconsistent findings, that is, variability in outcomes like memory and executive function. As Dr. Barha explained, "The source of variability between studies could be related to the who, the what, and the how of exercise."

In Dr. Barha's lab, they are focusing on the "who" sources of variability in brain health outcomes from exercise by looking at sex differences between males and females, and how previous reproductive experiences change the way the female brain ages, as well as how the brain responds to exercise as an intervention for cognition.

Few studies have looked at the ways that biological sex influences the brain's responses to exercise, and even fewer studies have been done on women only, posing challenges for understanding how men and women's brains respond to exercise.

In her 2017 meta-analysis in *Frontiers in Neuroendocrinology,* data showed that while exercise enhanced executive functions for both older men and women, there were larger effect sizes in studies with a higher percentage of women in the sample. She's also found this same sex difference favouring women across populations and study designs.

THIS SUGGESTS THAT PHYSICAL ACTIVITY IS MORE PROTECTIVE OF COGNITION IN WOMEN THAN IN MEN, AND THAT WOMEN MAY BENEFIT MORE FROM BEING PHYSICALLY ACTIVE THAN MEN.

In a follow-up study, Dr. Barha has shown that this may be related to a greater increase in the brain "vitamin" BDNF from exercise in women compared to men.

Reproductive history also plays a role in how the brain ages, lifetime risk of developing dementia, and how the brain responds to exercise.

"When looking at studies with older women, it's fascinating that pregnancy experiences from decades earlier have changed their brains in such a way to put certain groups – women who have had five or more complete pregnancies (multiparous), and women who have had zero complete pregnancies (nulliparous) – at higher risk of developing dementia," shared Dr. Barha.

Fortunately, these data published in *The Journals of Gerontology Series A* in 2023 have shown the strongest positive relationships between physical activity levels and cognition for multiparous and nulliparous women, suggesting that exercise as an intervention could be most effective in these two at-risk groups.

As we learn more about these interactions, targeted exercise interventions and specific exercise recommendations for nulliparous and multiparous women later in life could help to mitigate risks of cognitive decline.

Dr. Barha explained, "We are trying to fine-tune and understand which groups need to be targeted, which groups are most at risk for cognitive decline and brain health decline, and how we can best support their brains as they age."

As the body of research grows on biological sex, exercise, and brain health, Dr. Barha is hopeful that more personalized recommendations for exercise will emerge based on combinations of factors.

JUST DO IT

Though we do not yet know the exact dose, type, and timing of exercise needed to maximize cognitive benefits, research clearly shows that there is a positive relationship between exercise and brain health.

From neurogenesis to neuroprotection, regular physical activity serves as a cornerstone for a resilient, healthier brain, and all movement is cumulative and beneficial.

"You just have to move your body," advised Dr. Barha. "Any movement counts, and you need to incorporate it into your everyday life." Whether it's a daily walk or joining a community fitness class, the key lies in consistent, enjoyable movement to support your brain.

Dr. Barha's WBHI Future Leader in Canadian Brain Research grant is made possible by the Canada Brain Research Fund, an innovative arrangement between the Government of Canada, through Health Canada, and Brain Canada, and WBHI.

FIVE SIMPLE WAYS TO MOVE MORE

- Take the stairs instead of the elevator, even for just one flight
- Spend more time outside
- Park farther away when doing errands to get some extra steps in
- Have a "walking meeting" with friends or colleagues
- Do active chores like sweeping or vacuuming more often

Hope for Dementia

Almost Half of Cases May Be Avoided

The idea that lifestyle factors can influence the risk of dementia won't be news to Mind Over Matter® readers who are familiar with the Six Pillars of Brain Health – exercise, mental stimulation, social activity, nutrition, sleep, and stress management. But what proportion of cases could potentially be prevented by addressing modifiable risk factors?

WHILE AN EXPERT *LANCET* COMMISSION HAS BEEN ISSUING GLOBAL ESTIMATES SINCE 2017, NO SIMILAR RESEARCH HAD BEEN DONE TO LOOK SPECIFICALLY AT CANADA – THAT IS, UNTIL NOW.

Two studies published in 2024 offer evidence that dementia cases in Canada could be cut by up to half by addressing 12 modifiable risk factors. The research also identified which lifestyle risk factors are the leading contributors to dementia for Canadians, and how our country compares to other regions of the world.

A TALE OF TWO STUDIES

"The main aim of (our) study was to measure dementia prevention potential in Canada, because it had been estimated worldwide by the *Lancet* Commission, and it had been estimated in other countries, like the U.S., Denmark, and China, but it hadn't been done in Canada," said Surim Son, a researcher at the Lawson Research Institute and St. Joseph's Health Care London in London, Ontario.

Ms. Son is also a PhD candidate in the Department of Epidemiology and Biostatistics at Western University, supervised by Dr. Mark Speechley and Dr. Manuel Montero-Odasso, and lead author of one of the studies, which was published in *The Journal of Prevention of Alzheimer's Disease* in June 2024.

A group of researchers at McMaster University in Hamilton, along with those from other Canadian institutions, conducted the other study, which appeared in *Canadian Journal of Public Health* in July 2024.

Both Ms. Son's group and the second team of researchers, working independently, used data from the same group of approximately 30,000 people enrolled in the Canadian Longitudinal Study on Aging (CLSA). Each of them also based their approach on that of the 2020 *Lancet* Commission on dementia prevention, intervention and care. Both teams focused on 12 well-established dementia risk factors.

Those covered in the study led by Dr. Aaron Jones, an assistant professor in the Department of Health Research

Methods, Evidence and Impact at McMaster University mirrored those in the *Lancet* report.

The list: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. The Lawson researchers opted to replace air pollution with sleep disturbances.

"I did not include air pollution because when I designed the study, I wanted to include risk factors that we can improve with our daily actions, and that are easy to measure," Ms. Son explained. "I also wanted to include risk factors that can be targeted in clinical trials," she added.

"Currently, there are many lifestyle intervention trials going on across Canada, often targeting sleep disturbance along with other risk factors. However, addressing air pollution in clinical trials is hard, as it requires a provincial or national-level approach." (One of Ms. Son's research supervisors, Dr. Manuel Montero-Odasso, is a site principal investigator for one such study: the SYNERGIC 2.0 trial, as part of the Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia or CAN-THUMBS UP.)

POPULATION ATTRIBUTABLE FRACTION EXPLAINED

Both papers rely on a concept known as weighted population attributable fraction or PAF. "This approach was first introduced in the 1950s for lung cancer and cigarette smoking," Ms. Son explained.

"The measure incorporates both prevalence – how common the risk factor is – and the strength of the risk factor's association with dementia. This allows us to infer how many dementia cases can be avoided if we could eliminate a given exposure or risk factor from the population."

Ms. Son's and Dr. Jones' teams used different methods of calculating what's called "communality value," which is based on the degree to which each risk factor is correlated with every other risk factor. This is one reason the weighted PAFs differ across the two papers.

In contrast to the 2020 *Lancet* Commission report, which estimated that 40% of dementia cases were linked to 12 risk factors, Ms. Son's study placed that number at 49.2%. That means the proportion of potentially preventable cases in Canada could be even greater than half, since an updated 2024 *Lancet* Commission report, which added high LDL cholesterol and vision loss to the existing list of risk factors, estimated the expanded list accounted for an estimated 45% of dementia cases.

> ***The research suggests there is significant prevention potential in Canada through making changes in our daily lives.***

And since the prevalence of many risk factors tends to be higher among people belonging to historically marginalized groups (including racialized individuals and those living in rural areas), and CLSA participants are mostly white urban dwellers, "I think our estimate will be conservative if we consider Canada as a whole," Ms. Son said.

LEADING LIFESTYLE FACTORS

In Ms. Son's research, the four risk factors with the greatest influence on risk were physical inactivity (10% of cases), hearing loss (6.5%), obesity (6.0%), and hypertension (6.0%).

Overall, "83% of people had physical inactivity, which means they were not meeting the World Health Organization guidelines," which recommend a minimum of 150 minutes per week of moderate- to vigorous-intensity physical activity, said Ms. Son.

While the figures in the study led by Dr. Jones were slightly different, "overall, I think the papers tell similar stories," he said.

> **WE CAN ESTIMATE THAT 40% TO 60% OF DEMENTIA CASES IN CANADA CAN BE ATTRIBUTED TO 12 MODIFIABLE RISK FACTORS, WITH PHYSICAL INACTIVITY, OBESITY, AND HYPERTENSION BEING HIGHLY IMPACTFUL.**

Ms. Son's research found that while the combined population attributable risk was similar in men and women, "prevalence of the most common risk factors differed across sexes," the study authors wrote. "Among women, 80% had physical inactivity and 20.8% had depression, as compared to 72.8% and 11.8% in men."

Two other key findings from that study, Ms. Son said, are as follows. "Over 95% of Canadians had at least one of the dementia risk factors that were listed in the *Lancet* report, which is huge, because we have participants starting from age 45. That means we should start prevention earlier, because almost all Canadians have risk factors at an early age. And over 80% of Canadians had four or more risk factors."

According to Ms. Son's study, more than 80% of Canadians were not meeting physical activity guidelines, one in three had obesity or hypertension, and one in five showed hearing loss.

HOW CANADA COMPARES INTERNATIONALLY

How does Canada stack up to other countries when comparing the modifiable risk factors examined in the 2020 *Lancet* Commission report? Here are some highlights of Ms. Son's comparison of estimates reported in the U.S., New Zealand, Australia, Denmark, India, Latin America, China, and Brazil. (Estimates for only nine of the 12 risk factors were available for all of these regions.)

Compared to other countries, weighted population attributable fractions (PAFs) in Canada were:

- Smaller for later life smoking and social isolation.
- Larger for later life physical activity, traumatic brain injury and excessive alcohol use.

Compared to low- and middle-income countries, Canadian PAFs were:

- Smaller for less early-life education and mid-life hypertension.
- Larger for mid-life obesity.

Compared to other high-income countries, Canadian PAFs were:

- Larger for less education in early life, mid-life hypertension, and later-life depression.

COMBINED PAFs

	ALL RISK FACTORS	NINE RISK FACTORS
Latin America	55.9%	55.9%
Canada	49.2%	40.9%
New Zealand	45.8%	41.5%
Brazil	45.5%	42.1%
India	41.2%	41.2%
U.S.	40.3%	36.0%
China	39.5%	39.5%
Australia	36.0%	35.5%
Denmark	35.2%	33.2%

IMPACT OF INCOME ON RISK

One characteristic Ms. Son and her colleagues did not consider was income, which, similar to education level, is a non-medical factor that influences health outcomes, also known as a social determinant of health. (For example, people with low income are often disadvantaged by reduced access to healthy foods and neighbourhoods that facilitate walking.)

Dr. Jones' team, on the other hand, did include such an analysis, stratifying participants into five groups by household income, from less than $20,000 per year to greater than $150,000 annually (at the time of study enrolment, between 2011 and 2015).

The results were striking.

> *"As income level goes down, most risk factors increase.*

In fact, when categorized by weighted PAF, the 12 risk factors accounted for 58.7% of dementia cases in the lowest income group, but only 31.8% in the highest group, the paper stated.

"I hope this highlights the systematic issues that can contribute to increased risk of dementia," Dr. Jones said. Income is "relevant to gender since we know that overall, women across their lifetimes earn less than men," he added. (Dr. Jones is also involved in research looking at environmental risk factors for dementia, such as sleep disturbances related to occupations involving shift work and chronic noise in work environments and neighbourhoods.)

PROTECTIVE STRATEGIES CALENDAR

To help inspire people to adopt lifestyle changes to reduce dementia risk, Ms. Son's team created a calendar that highlights the 12 protective strategies included in her study. You can find a QR code to request a copy here: www.clsa-elcv.ca/12-ways-to-reduce-your-dementia-risk/

PRIORITIZING PREVENTIVE STRATEGIES

On a policy-making level, the research of both teams can help governments prioritize which risk factors to target with prevention strategies.

On an individual level, the takeaway from the two studies is that "we can reduce our risk of dementia if we get physical activity regularly; protect our hearing from an early age and get it checked regularly; get our blood pressure checked regularly," and work on maintaining healthy weight, said Ms. Son. She added this also applies to people with a family history of the disease.

> *"Tackling these key risk factors not only helps women prevent or delay dementia but also provides more years of healthy life and well-being.*

Ms. Son continued, "Considering that 61.8% of Canadians living with dementia in 2020 were women, and this is expected to increase to over one million women in 2050, the potential benefits are substantial."

POPULATION ATTRIBUTABLE RISK

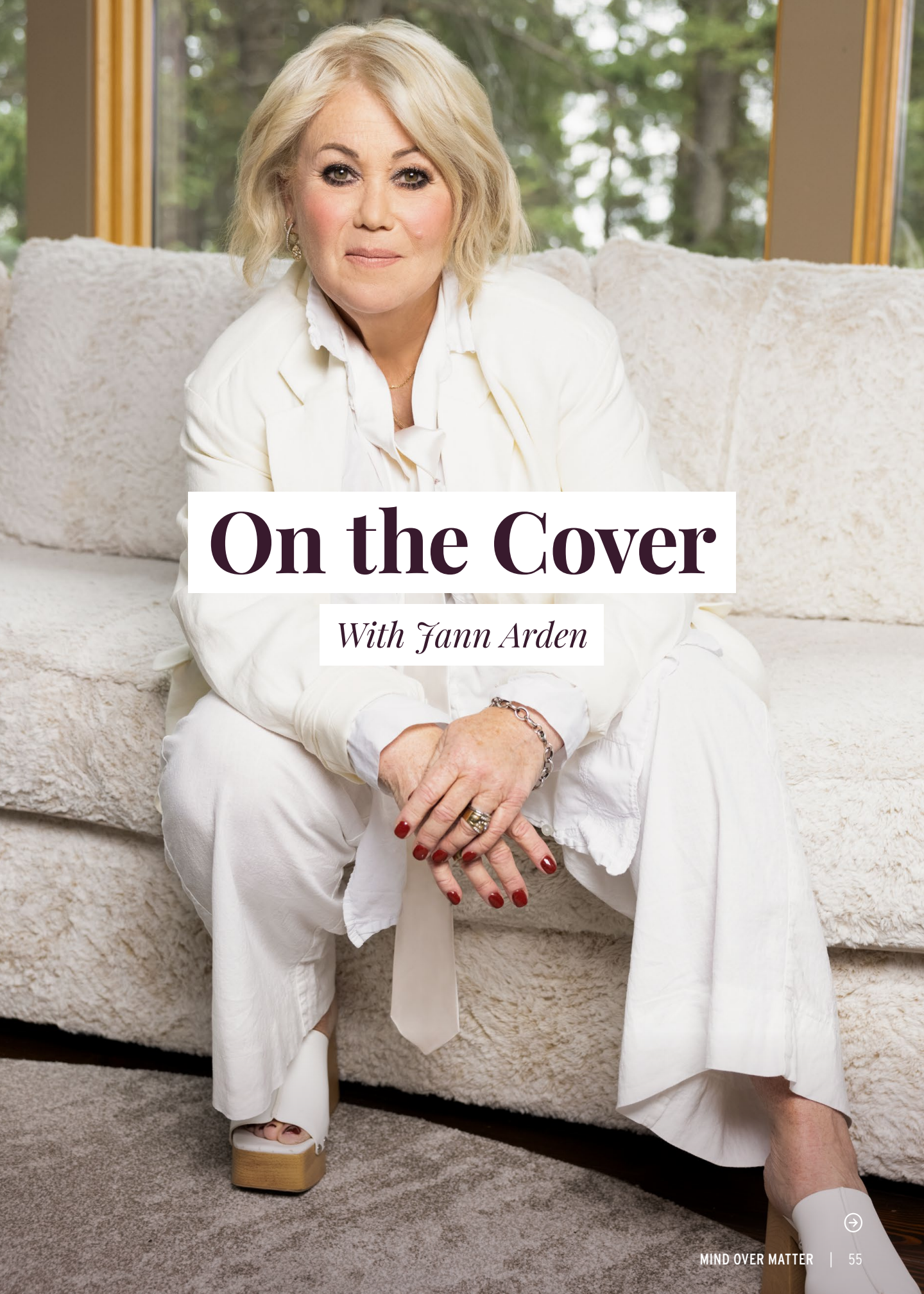
	LANCET COMMISSION 2020	SON ET AL.
EARLY LIFE		
Less Education (Less than high school grad.)	7%	3.2%
MID-LIFE (AGE 45 TO 64)		
Hearing Loss	8%	6.5%
Traumatic Brain Injury	3%	4.4%
Hypertension	2%	6.2%
Excessive Alcohol	1%	0.9%
Obesity	1%	6.4%
LATER LIFE (65+ YEARS)		
Smoking	5%	1.5%
Depression	4%	4.0%
Social Isolation	4%	0.4%
Physical Inactivity	2%	10.2%
Air Pollution	2%	N/A
Diabetes	1%	2.5%
Sleep Disturbances	N/A	3.0%
COMBINED PAF	**40%**	**49.2%**

(A breakdown from the study led by Dr. Jones isn't included here because it didn't categorize risks by life stage.)

	SON ET AL.		JONES ET AL.	
	MEN	WOMEN	MEN	WOMEN
Less Education	2.8%	2.8%	4.2%	4.4%
Hearing Loss	9.6%	8.7%	3.7%	3.0%
Traumatic Brain Injury	4.8%	3.1%	5.7%	3.9%
Hypertension	7.3%	7.2%	6.3%	5.7%
Excessive Alcohol	1.3%	0.5%	0.4%	0.3%
Obesity	6.0%	6.3%	5.7%	5.6%
Smoking	2.3%	2.5%	2.1%	2.1%
Depression	3.7%	6.5%	6.4%	8.8%
Social Isolation	0.5%	0.2%	5.4%	4.1%
Physical Inactivity	8.7%	10.0%	11.1%	11.9%
Diabetes	1.8%	1.4%	3.9%	3.2%
Sleep Disturbances	1.8%	1.4%	3.9%	3.2%
Air Pollution	N/A	N/A	0.8%	0.8%

The two research teams used somewhat different methodology, which is one reason the figures differ across the two studies. In some cases, they also used different definitions for the same risk factor.

For instance, in one study, social isolation was based on self-reports of engaging in a range of social activities less than once a week, while in the other, it was defined as having less than one social contact within a month with family, friends, or neighbours.



On the Cover

With Jann Arden

Even when Alzheimer's disease (AD) robbed Jann Arden's mother of the ability to understand the function of a toothbrush or remember the names of people close to her, one thing endured: music.

Joan Richards knew thousands and thousands of songs, and they persisted in her memory, despite the profound damage that dementia was doing to her brain.

"She knew music, she could sing the words, and it always absolutely baffled me," said her daughter.

It was not only because Joan's daughter is one of Canada's most celebrated musicians. There is much anecdotal evidence and scientific research documenting the ability of music to reach people coping with dementia.

There are also brain health benefits, as noted in a 2023 literature review published in *Brain, Behavior, & Immunity – Health*: "Music profoundly impacts emotional states, offering therapeutic benefits in alleviating stress, anxiety, and depression."

"There's got to be something there in how those memories are able to reach back into the brain and pull colour and light and emotion forward," Jann told Mind Over Matter® in an interview from Calgary.

"It is quite frankly nothing short of miraculous what music does."

Jann had a close-up view, having been a care partner to both her mother and her father, Derrel Richards (who also had AD), in the final years of their lives. She built a cottage for them on her property in southern Alberta. Derrel died in 2015, followed by Joan in 2018.

Along the way, Jann learned hard lessons about the challenges of being a care partner, challenges that she speaks about frankly and publicly.

> ***"It changes you in ways you probably don't even understand until time has passed. Obviously, it's very traumatizing, really stressful, frustrating. There's a lot of anxiety when someone you love starts having problems with short-term memory.***

She said her mother would become belligerent and angry with her and did not believe she needed help. At times, Joan would suggest Jann had allowed people into the house who were stealing from her. In the beginning, Jann would show anger in response, but through hard experience, she found a better way.

"I learned more about myself in the journey with my mom than I did with any other single task or any other thing, any other relationship, job, career that I've undertaken in my life. I've learned more about myself – and became a better version

of myself – because of the experience of going through Alzheimer's with my folks."

She learned to set aside the anger, to be patient, to accept that Joan would ask the same question repeatedly. She stopped challenging her mother's statements, however untethered to reality they became.

"IT ALSO REALLY MAKES YOU UNDERSTAND YOUR OWN ABILITY TO BE EMPATHETIC AND TO ACTUALLY CARE ABOUT SOMEBODY ELSE, EVEN THOUGH THERE DOESN'T SEEM TO BE RECIPROCITY.

Jann kept a journal, which she developed into a book, *Feeding My Mother: Comfort and Laughter in The Kitchen as a Daughter Lives with her Mom's Memory Loss*. Acclaimed as both funny and heartbreaking, it became a bestseller.

She recognizes that she had resources that most others do not. She was able to bring in professional, live-in care partners to help support her parents, a substantial expenditure that is out of reach for most people. She said the pandemic exposed cracks in the long-term care system, which will only worsen with an aging population and rising rates of dementia.

"People are already very overworked. It's going to be a crushing overload of the system."

Jann has become a strong supporter of the mission of Women's Brain Health Initiative (WBHI), having spoken at a previous WBHI event, participating in the upcoming Harmony in Care event, and appearing on the cover of Mind Over Matter®.

"It's probably one of the most important missions that anybody is on. It is a huge, huge foreboding issue. The research that they're doing is unlocking those doors that we need to look behind," Jann said of WBHI's work to protect the brain health of women, care partners, and their families. "We need to find out why music is important. Why are they remembering songs? Why do they know words to the songs? How does that play into this? The research just has to be done."

Having lost both parents to AD, she is doing everything she can to support her own brain health.

She exercises, watches her diet, gave up drinking while caring for her parents, reads voraciously, and is obviously a creative person.

Asked if her experience as a care partner influenced her music, Jann's answer is, "Your guess is as good as mine."

Her latest project is *MIXTAPE*, her 16th studio album, a selection of some of her favourite songs from the 1990s. It was a decade in which she released her first albums, including *Living Under June*, and saw some of her biggest hits, such as *Insensitive*.

"The '90s was my decade, and I thought that there was just so much great music," she said.

Jann admits that with such a wealth of choices, it was hard to pick a short list of songs for *MIXTAPE*. She settled on a collection that includes music from Sia, Seal, TLC, Don Henley, and Chris Isaak, along with her new single, Des'ree's *You Gotta Be*.

"I just recorded songs that were stuck in my mind that I love to sing, and oddly, songs that I thought I knew, but when I went to record them, I found I didn't really know them at all, which was very interesting."

In May, Jann launches a cross-country *MIXTAPE* tour, not long after the publication of the 20th edition of Mind Over Matter® magazine, with her on the cover. One of Canada's best-known faces, making a statement about a disease that touches so many.

"If it helps lift the veil of shame and guilt and kind of secrecy off this disease and makes it more normalized, that's an important thing."

Sleep on It

Poor Sleep is Not Inevitable for Dementia Care Partners

Poor sleep is a common challenge for many, but it is particularly prevalent among those who provide unpaid care for individuals with dementia.

An alarming 67% of informal dementia care partners report struggling with sleep disturbances – a stark contrast to the 50% seen in the general population.

A 2019 review and meta-analysis of 35 studies involving more than 3,200 dementia care partners – by Dr. Chenlu Gao and colleagues – found that both sleep *quantity* and sleep *quality* were significantly worse among the care partners compared to the non-caregiving controls. Care partners slept 2.42 to 3.5 hours less per week, because of troubles falling asleep and staying asleep. These findings were published in *JAMA Network Open*.

WHY DO DEMENTIA CARE PARTNERS STRUGGLE WITH SLEEP?

Dementia care partners face sleep challenges partly due to the same factors that disrupt sleep for half of the general population. Sleep challenges become more common with increasing age whether you're a care partner or not because of changing hormones, less physical activity, pain, increased awakenings to go to the washroom, grief, illness, etc.

But dementia care partners experience unique, additional contributors to poor sleep.

01 THE DIRECT IMPACT OF DEMENTIA PATIENTS' SLEEP PATTERNS.

Care partners' sleep is often disrupted by the nighttime behaviours of the people with dementia they care for, e.g., irregular sleep timing, insomnia, nighttime awakenings (sometimes involving agitation or wandering), and nightmares. Care partners may find themselves feeling hyper-vigilant and sleeping lightly in anticipation of the potential needs of the person with dementia throughout the night.

02 THE BROADER IMPACT OF CHRONIC STRESS ON SLEEP.

Dementia caregiving is a demanding, time-consuming responsibility. It is like working an almost full-time job, with family members and other unpaid care partners estimated to spend an average of nearly 31 hours each week caring for someone with dementia, according to the Alzheimer's Association. All of this emotionally- and cognitively-demanding responsibility means that many dementia care partners experience chronic stress, which can negatively impact sleep.

03 THE MENTAL HEALTH TOLL OF DEMENTIA CAREGIVING & ITS IMPACT ON SLEEP.

Dementia caregiving can negatively affect care partners' mental health – for example, contributing to feelings of distress, hopelessness, and frustration, along with symptoms of depression – which can in turn negatively affect care partner sleep. The relationship between mood disorders (like depression) and sleep disturbances are bidirectional, e.g., depression contributes to poor sleep, but then that poor sleep contributes to symptoms of depression, creating a cyclical challenge.

IMPACTS OF POOR CARE PARTNER SLEEP

Sufficient, good-quality sleep is critical for health, well-being, and quality of life. It's so important that Women's Brain Health Initiative has included sleep as one of the Six Pillars of Brain Health.

Poor sleep has been linked with negative impacts on *mental* health (e.g., negative mindset, depression, anxiety), as well as on *cognitive* performance (e.g., sleep quality can influence memory, learning, decision-making, and judgement).

Poor sleep has also been associated with many negative *physical* effects. For example, poor sleep among dementia care partners has been linked with increased inflammation, which is known to increase the risk of cardiovascular and other chronic diseases, as well as mortality.

"Chronic poor sleep over months and years has been linked with some concerning negative impacts specifically on the brain, including quicker cortical thinning and lower

Sleep compression involves slowly decreasing time spent in bed, to reduce the time awake in bed at night.

Relaxation techniques that might be taught as part of Cognitive Behaviour Therapy for Insomnia (CBT-I) include deep breathing and mindfulness.

clearance of amyloid-beta and tau, which are hallmarks of Alzheimer's disease," explained Dr. Gao, lead author of the *JAMA Network Open* research paper mentioned previously and a research fellow at Massachusetts General Hospital in Boston.

> ***As a result, poor sleep among caregivers may be linked with increased risk for them to develop Alzheimer's disease or another type of dementia.***

WHAT'S A DEMENTIA CARE PARTNER TO DO?

Sleep is absolutely essential. But given all the unique challenges dementia care partners face that can contribute to poor sleep, is poor sleep inevitable for them? No, it's not. Dr. Gao's 2019 research found that "sleep problems in caregivers are not immutable."

"Our meta-analysis showed that dementia caregivers who participated in a sleep intervention experienced better sleep post-intervention, compared to dementia caregivers in a control group," explained Dr. Michael Scullin, corresponding author of the research paper and an associate professor at Baylor University in Waco, Texas.

> ***In particular, we found that post-intervention sleep quality was better after behavioural interventions such as sleep hygiene education, stimulus control, and light chronotherapy.***

Research is underway into an innovative behavioural sleep intervention program that targets both people with Alzheimer's disease (AD) *and* their care partners, **Care2Sleep.**

Care2Sleep originated from the Nighttime Insomnia Treatment and Education in Alzheimer's Disease (NITE-AD) program, which was designed specifically to address the needs of individuals with dementia.

NITE-AD involves working with care partners to improve the sleep of the person with dementia through a combination of strategies, including:

- personalized sleep hygiene education (e.g., consistent bedtime and rising time, reducing daytime napping, avoiding caffeine and alcohol in the evening);
- training in how to address behavioural and psychological symptoms of dementia, especially nighttime wandering;
- daily walking; and
- increased light exposure.

The NITE-AD program was chosen as the starting point for Care2Sleep because it had been found to significantly improve sleep and reduce depression in the participants with AD.

The Care2Sleep program is a *dyadic* sleep intervention, i.e., one that works with pairs of care partners and people with AD. The intervention's content and approach were developed by Dr. Yeonsu Song and colleagues in a small initial study in 2019 with five dyads.

The researchers then conducted a pilot study with a larger group of care partner-patient dyads to evaluate the effectiveness of their newly developed program.

Sleep hygiene refers to lifestyle habits, behaviours, and sleep environment factors that support good sleep. Examples include: following a consistent sleep schedule, keeping your bedroom cool and dark, avoiding activities that are stimulating before bed (like TV and other screen time), and avoiding alcohol and caffeine in the evening.

Stimulus control is a type of therapy that aims to train your mind and body to associate your bed with sleeping. It might involve waiting until you're actually tired before getting into bed, only using your bed for sleep (i.e., not working or watching TV in bed), and/or getting up and doing something else if you're unable to fall asleep either at the beginning of the night or after awakening during the night, for example.

Light chronotherapy uses timed light exposure to affect the circadian pattern of the sleep-wake cycle.

> *Care2Sleep takes a multi-pronged approach, incorporating key components of Cognitive Behavioural Therapy for Insomnia (such as sleep hygiene, stimulus control, sleep compression, and relaxation techniques), daily walking, and natural light exposure, as well as problem-solving for managing nocturnal dementia-related behaviours*

"The program is delivered by trained sleep educators over five weekly one-hour sessions." continued Dr. Song, an associate professor of nursing at UCLA in Los Angeles.

For the pilot, 30 dyads were randomly assigned to either a five-session Care2Sleep intervention or an information-only control group. In the end, 13 dyads completed all five Care2Sleep sessions and 14 dyads completed the control condition.

"Our pilot study revealed that, compared to the control group, dyads who received the Care2Sleep intervention showed patterns of sleep improvement at the three-month follow-up, although the improvements were not statistically significant, primarily due to the small sample size resulting from the COVID-19 pandemic," said Dr. Song.

> *In addition, the caregivers in the Care2Sleep group reported more positive aspects of caregiving immediately post-treatment as well as three months later, compared to the controls.*

"Overall, this study demonstrated the feasibility of improving sleep in dementia care dyads with an intervention using behavioural strategies that target both the person with dementia and the caregiver," continued Dr. Song.

> *Even though our findings did not reach the threshold of statistical significance, the overall pattern of results suggested some improvements in both sleep and caregiving-related experiences.*

Dr. Song added: "Further research is needed with a much larger number of participants to fully evaluate the potential of the Care2Sleep program beyond these initial promising findings." These results were published in 2024 in *Journal of the American Geriatrics Society*.

Thanks to a more than US$3.75-million grant from the National Institutes of Health, Dr. Song's research continues. They are currently two years into the five-year project, A Dyadic Approach to Improve Sleep and Well-Being Among Persons with Alzheimer's Disease and Their Caregivers. The research is taking place at multiple sites, as well as virtually, in California. They are still seeking participants for this research, so if you're interested and are a resident of California, visit **alzheimers.gov/clinical-trials/sleep-education-people-dementia-and-their-caregivers** for more information.

CALL TO ACTION FOR CARE PARTNERS

"Research clearly shows that sleep is critical for health, and caregivers are no exception," said Dr. Song.

> **SINCE SLEEP DEBT ACCUMULATES OVER TIME WITH COMPOUNDING NEGATIVE EFFECTS, IT'S IMPORTANT FOR CAREGIVERS TO ADDRESS ANY SLEEP CHALLENGES AS SOON AS POSSIBLE.**

"That might mean sitting outside in sunny weather or going out for daily walks (with or without the person with dementia). It might mean establishing a regular sleep schedule with good sleep hygiene on their own. Or, it might mean working with a healthcare professional to help them and their loved one with dementia to sleep better," continued Dr. Song.

"It may not be easy, but caregivers must make self-care – including good sleep – a priority, for the sake of their own health."

Ovarian Removal at Mid-life

How Does it Affect Your Brain?

For years, scientists have been investigating the relationship between ovarian removal and brain health. Now, a growing body of research suggests that women who undergo this surgery before natural menopause may experience mild short-term cognitive issues, as well as increased risk of impairment and dementia later in life.

Experts emphasize that this information is essential for women considering the surgery for medical reasons, such as reducing their cancer risk.

WHILE MANY WOMEN WILL LIKELY STILL DECIDE TO UNDERGO THE PROCEDURE, UNDERSTANDING THE POTENTIAL IMPACTS CAN HELP THEM PREPARE FOR SIDE EFFECTS, EXPLORE POTENTIAL TREATMENTS, OR PLAN ON HAVING CLOSER MONITORING FOR EARLY SIGNS OF DEMENTIA.

"They might still choose the surgery, but at least they won't be surprised afterwards – which many women tell us they are," said Dr. Gillian Einstein, professor of psychology at the University of Toronto, and the Wilfred and Joyce Posluns Research Chair in Women's Brain Health and Aging.

HORMONES & THE BRAIN

Scientists have long suspected there was a link between the hormonal shift of menopause and cognitive decline. Dr. Einstein wondered if the hormone estradiol, a form of estrogen released during a woman's reproductive years, played a role in these changes.

To learn more, she began studying women with BRCA gene mutations who had undergone ovarian removal in their 30s and 40s. By focusing on this group, she was able to study the effects of hormonal changes alone, without other potential factors that contribute to memory loss, like natural aging and age-related health conditions.

"These women were having their ovaries removed early in life while they were young and healthy," Dr. Einstein explained.

Dr. Einstein's group has conducted studies including neurological testing, brain imaging, blood tests, and qualitative research and interviews. She and other researchers found that ovarian removal at mid-life or earlier was linked to both short- and long-term cognitive side effects.

"THERE'S A LOT OF EVIDENCE NOW THAT OOPHORECTOMY, A SURGICAL PROCEDURE WHERE ONE OR BOTH OF YOUR OVARIES ARE REMOVED, BEFORE THE AGE OF NATURAL MENOPAUSE IS A RISK FACTOR FOR COGNITIVE DECLINE AS WELL AS OTHER PROBLEMS.

One study by Dr. Einstein's team found that women with early ovarian removal had increased difficulty with associative memory, or the ability to connect different memories, such as matching a face with a name. Another study by her group found an increased risk of sleep disorders like insomnia and sleep apnea.

Long term, undergoing ovarian removal prior to the age of natural menopause is associated with an increased risk of Alzheimer's disease (AD) and dementia in late life, she noted.

STUDYING THE IMPACTS OF EARLY MENOPAUSE

Menopause at any age triggers a drop in estrogen, as well as other hormones, like progesterone. When the ovaries are removed before the age of natural menopause, this hormonal change occurs earlier in a woman's life than it would otherwise. These changes can affect the brain.

In animals, estrogen is known to affect the physiological process involved in memory formation called long-term potentiation, said neurologist Dr. Victor Henderson, Director of the Stanford Alzheimer's Disease Research Center. Studies have also suggested it plays a role in neuronal survival or the development of neurological processes, and in modifying the synapses of nerve cells.

"All of these, one would think, could have an effect on cognition in humans," he said.

But researchers are still working to understand the mechanisms that lead to changes in the brain, said Dr. Michelle Mielke, Chair of Epidemiology and Prevention at Wake Forest University School of Medicine.

She noted that there are many different pathologies in the brain that can cause dementia in older adults, including vascular dementia, or changes to the blood vessels; sticky proteins called amyloids that play a role in AD; and other neurodegenerative disorders.

Her team of scientists wanted to know if they could figure out which of these processes were involved in the type of cognitive decline associated with ovarian removal.

After finding no signs of abnormal amyloid buildup, the researchers then focused on studying changes to white matter, a kind of insulation in the brain that helps brain cells transmit information efficiently.

THEY FOUND THAT WOMEN WHO HAD UNDERGONE MID-LIFE OOPHORECTOMY, PARTICULARLY BEFORE AGE 40, HAD REDUCED WHITE MATTER INTEGRITY ACROSS MULTIPLE REGIONS OF THE BRAIN.

Dr. Mielke explained that these changes are a marker of vascular pathology in dementia.

"This would suggest, then, that it's potentially working through a vascular mechanism," she said.

REDUCING THE IMPACT OF COGNITIVE SIDE EFFECTS

Even with these potential side effects, experts agreed that for women considering oophorectomy for medical reasons, the benefits still likely outweigh potential risks.

Numerous studies have shown that the procedure is effective in reducing cancer risk for women with BRCA mutations. For women who have previously been treated for BRCA-associated cancers, it can reduce risk of recurrence.

"WE ARE NOT SUGGESTING THAT YOU SHOULDN'T HAVE YOUR OVARIES REMOVED.

But by understanding potential side effects, women can make better decisions about their health, Dr. Mielke said. That might include undergoing closer monitoring for memory problems or early signs of dementia.

Or, knowing that there may be ties to vascular dementia, women with pre-existing cardiovascular risk factors might take extra precautions in managing those conditions, she said.

In addition, there's value in knowing what to expect, Dr. Einstein noted. Women who experience cognitive changes may want to seek extra support, such as using memory aids, or learn compensating strategies to help them remember things throughout the day, she said.

WHAT ABOUT HRT?

While more research is needed, there is some evidence that hormone replacement therapy (HRT) may be beneficial for women who undergo ovarian removal before natural menopause, particularly before age 40.

"In terms of hormone replacement therapy, specifically estrogen, we don't necessarily know whether that can be protective or not," Dr. Mielke said.

"IN GENERAL, UNLESS YOU'RE AT HIGH RISK FOR CANCER, THERE IS A STRONG SUGGESTION THAT YOU TRY AND TAKE HORMONE REPLACEMENT THERAPY, BECAUSE AT LEAST SOME OF THE SIDE EFFECTS OF MENOPAUSE MAY BE ALLEVIATED A BIT.

In one recent study, Dr. Einstein's team found that estradiol therapy helped mitigate changes in spatial working memory – the type of memory that helps you remember where you parked your car. Notably, however, it didn't improve verbal episodic memory (which involves things like remembering details in stories).

"We like to say that estradiol is important but not a silver bullet," she said. Beyond hormones, "anything that's good for your heart is generally also good for your brain," Dr. Einstein explained.

Exercise has proven heart and brain benefits for women in menopause.

Eating a heart healthy diet, staying mentally and socially engaged, and getting adequate, high-quality sleep can also benefit brain health, she said.

INSPIRED BY WOMEN'S LIVES

Dr. Einstein will continue to study how women can reduce the cognitive impacts of oophorectomy. Future research includes a study investigating the role of inflammation in this process and whether NSAIDs can reduce risk.

Her lab is also launching a study backed by Women's Brain Health Initiative that will look at whether giving women piano lessons can help improve memory and cognition.

A third project will test women's cognitive function before and after ovarian removal. It's the first time this type of prospective study, the gold standard in scientific research, has been conducted in this population.

Dr. Einstein said that when she began working with women undergoing ovarian removal in their 30s and 40s, she was struck by the circumstances of their lives. The women in this group were actively working, raising children, maintaining marriages, and often caring for aging parents when they were suddenly faced with undergoing a life-changing surgery.

"They are very busy women, and this is a very big decision," she said. Those women now inspire her to continue her research, she explained.

"All of this has continued to fuel my desire to conduct research and produce good data, so that women considering this procedure can go into it with fully informed consent.

Too Young to Forget

Childhood Dementia

As a bench scientist, Dr. Alexey V. Pshezhetsky does not treat patients, but his office walls bear photos of several children who were born with a very rare genetic disease that progressively robs them of their abilities and skills, eventually causing dementia-like symptoms, and finally, death.

Dr. Pshezhetsky, a professor in the departments of Pediatrics and Biochemistry at the University of Montreal, and Elisa Linton Research Chair in Lysosomal Diseases at the CHU Sainte-Justine Research Centre, has spent 20 years studying Sanfilippo syndrome (also known as mucopolysaccharidosis type III or MPS III), a heartbreaking disorder that causes deterioration of brain cells.

"The course of the disease is just terrible," said Dr. Pshezhetsky.

TYPICALLY, CHILDREN ARE DIAGNOSED AROUND THE AGE OF THREE, FIRST DEVELOPING HYPERACTIVITY AND AGITATION, AND EXTREMELY LIMITED SLEEP. OVER TIME, "THEY LOSE THEIR ABILITY TO SPEAK, THEY LOSE WEIGHT, THEY CAN NO LONGER WALK, AND BASICALLY, THEY ARE IN DEEP DEMENTIA.

"Usually these children die before the age of 20," Dr. Pshezhetsky said. One symptom that's particularly distressing for parents is unexplained screaming that sounds like an expression of agony, but there is no way of telling whether the child is in pain, and if so, how to ease it.

While MPS III affects only a small fraction of the population (approximately one in 70,000 newborns), according to a 2023 study published in the journal *Brain*, it is one of a long list of conditions that cause progressive cognitive decline in children.

The research was spearheaded by an Australia-based organization called the Childhood Dementia Initiative, founded by Megan Maack, the mother of two children with Sanfilippo syndrome.

"She saw there were a lot of other children with other similar conditions facing similar challenges," explained Dr. Kristina Elvidge, Head of Research at the Childhood Dementia Initiative. "She saw there was an opportunity to bring all of these conditions under one umbrella, to achieve a greater scale of change in research and the health system."

ESTABLISHING BURDEN OF ILLNESS

To make a case for doing so, and help bring attention to the issue, "we decided to do a burden of illness study," Dr. Elvidge explained. "Basically, we had a panel of clinicians who look after children with these types of disorders go through a list of conditions and decide which ones fit the definition of childhood dementia." ("Childhood dementia" is a disease classification that is not currently recognized by any diagnostic system.)

The authors of the paper describe childhood dementia as a global neurocognitive decline that emerges after a period of developmental progress. Its hallmark is the "enduring and progressive loss of previously acquired developmental skills," such as eating and walking.

In addition to difficulties with concentration, comprehension, learning, and communication, symptoms may include confusion, personality changes, and severe sleep disturbances.

Ultimately, the researchers "came up with a list of 145 conditions," Dr. Elvidge said. "It's not that dissimilar to adult-onset dementia, where there are at least 100 different types," she noted.

However, there is one important contrast between the two groups of conditions. While most types of adult dementia are likely caused by a combination of genetic susceptibilities and environmental factors, children with one of the 145 disorders named in the study are born with genetic changes "that make it 100% certain they will get childhood dementia," Dr. Elvidge said.

Examples include Gaucher disease types II and III, Niemann-Pick disease types A and C, four genetic subtypes of Sanfilippo syndrome, and ten childhood-onset subtypes of Batten disease.

NOT SO RARE

After compiling this list, "we worked with health economists to do some disease modelling based on the incidence and life expectancy of those disorders," Dr. Elvidge said.

"There was a lot of data missing because some of these conditions are really very rare, but using the data we could gather, we estimate that the incidence of those conditions that are currently untreatable is one in 2,900 births.

"That's on par with cystic fibrosis. I think this is one of the biggest health issues that nobody knows about. These families have a very high unmet need, and they need greater attention from both health systems and researchers."

The group also found that "half of these children die before they turn ten years of age, and 70% die before adulthood," noted Dr. Elvidge.

> ***"It is estimated that there are more than 2,000 children and young people living with childhood dementia in Canada, and around 105 die each year.***

"This is a similar number to deaths from childhood cancer aged 0-14 years, which is 135 per year," she added.

The study focuses on conditions caused by alterations in a single gene, approximately two-thirds of which are classified as inborn errors of metabolism (IEMs), with the largest subcategories within this group being disorders of one of two specific structures within cells – mitochondria (which

produce energy) or lysosomes (which are responsible for disposal and recycling of cellular content).

MPS III is an example of a lysosomal storage disorder. "In a way, the lysosome is a recycling plant of the cell," explained Dr. Pshezhetsky. Inside the lysosome, different enzymes break down large biological molecules (such as proteins and complex carbohydrates) into smaller component parts (such as amino acids and simple sugars). If one of those enzymes is absent, the substance it's responsible for digesting accumulates.

"In some cases, this (buildup) causes specific damage to the neurons that results in their dysfunction and death," said Dr. Pshezhetsky. Children with MPS III have a problem with the breakdown of a group of long-chain sugar molecules called mucopolysaccharides or glycosaminoglycans (GAGs). Consequently, one of these GAGs – heparan sulphate – builds up within cells.

"There are four subtypes of Sanfilippo or MPS III – A, B, C, and D," said Dr. Pshezhetsky, each of which affects a different enzyme involved in breaking down heparan sulphate. However, "there are other disorders with similar symptoms, such as Niemann-Pick disease and disorders in the Batten disease family."

Both groups of conditions result in the accumulation of waste products within cells – fats in the case of Niemann-Pick disease, and fats, proteins, and sugars in Batten disease (a.k.a. neuronal ceroid lipofuscinosis or NCL).

RAISING PUBLIC AWARENESS

The Childhood Dementia Initiative has been piloting the concept of grouping such diseases under one umbrella for several reasons. One is to attract more public attention, since arguably, the term immediately gets across the cruel toll these conditions take on affected families.

Since these disorders are so rare individually, "it's really challenging to create awareness and share potential research opportunities," noted Elisabeth Linton, CEO of the Sanfilippo Children's Research Foundation and a member of the Canadian MPS Society. (Mrs. Linton's daughter Elisa was diagnosed with MPS IIIB at the age of four and died at the age of 22.)

CHALLENGES IN RARE DISEASE RESEARCH

The Childhood Dementia Initiative is also "seeking funding to devise a blueprint for childhood dementia research globally," said Dr. Elvidge. Designing and running clinical trials for rare, fatal, or life-threatening childhood diseases presents numerous special challenges.

For instance, depending on the condition, "there may be only a few patients within Canada," noted Breanne Stewart, Network Director of RareKids-CAN, a new network aimed at establishing a robust platform in Canada to support rare disease clinical trials and enable access to treatment. One challenge this presents is that it's often not possible to conduct a study at a single institution without the need for patients and their families to travel.

Research methodology must also be very different than those used in ordinary clinical trials. "In conventional clinical trials, you have a treatment of reference, like medication A, or standard of care," which is compared to the new therapy, explained Dr. Thierry Lacaze-Masmonteil, Nominated Principal Investigator at RareKids-CAN. In the rare disease space, there are no such existing treatments. That, and the natural trajectory of the disease make it impossible to include a control group.

> **"YOU CANNOT ASK PATIENTS WITH A SERIOUS CONDITION THAT IS DETERIORATING TO WAIT OR BE IN A PLACEBO ARM.**

It's also much more challenging to obtain a regulatory approval from Health Canada to launch a clinical trial. For example, with the "explosion of novel therapies, whether it's gene therapy, or using a piece of RNA or DNA, or stem cells," there may be no historical data on safety for an entirely new, innovative experimental treatment, noted Dr. Lacaze-Masmonteil.

"We cannot expect these drugs to be safe at the same level," as say, a new blood pressure medication, he added. The regulatory process "needs to be adapted to this complex situation, where patients care less about safety, because they have no other choice."

Or, as Mrs. Linton put it, "Even if something goes awry, and (an experimental treatment) proves not to be effective or safe, it's not going to change the outcome for our children. The bottom line is that they are going to succumb to the disease if they don't have a treatment."

The immense cost of developing precision treatments such as gene therapy presents an additional hurdle. "What we want to do is streamline that process and have therapies for a lot of conditions being developed in parallel at the same time, rather than having one developed over here and another over there," said Dr. Elvidge. "Replicating everything makes it even more expensive to develop and produce those therapies."

Another rationale for co-ordinating research efforts is that a new discovery might lead to a therapy that would offer benefit for more than one disorder, since "there are disease mechanisms overlapping in some of these conditions," Dr. Elvidge said.

SIMILARITIES BETWEEN SANFILIPPO & ALZHEIMER'S

Research on these rare childhood conditions could potentially provide insights into adult-onset dementias, as well.

For example, some similar pathological processes occur in both Alzheimer's disease (AD) and MPS III. "Neuroinflammation is one, where there is an increased presence of immune cells in the brain," noted Dr. Pshezhetsky. In both conditions, microglia (brain immune cells) and astrocytes (cells that support nerve cells in the brain) are involved in promoting this inflammation, and astrocytes proliferate.

The two diseases also share an accumulation of abnormal forms of two proteins – amyloid and tau – in the brain.

Additionally, "in Sanfilippo and other neurological lysosomal disorders, you also see (a protein called) alpha-synuclein misfold and accumulate," Dr. Pshezhetsky said, which occurs in Lewy body dementia and AD.

Dr. Pshezhetsky's lab is working on a treatment for MPS III that is a combination of a bone marrow transplant with gene therapy, which might prevent damage if administered early in the disease. "We culture the stem blood cells, propagate them, and transduce them with a virus which incorporates a working copy of the defective gene," he explained. (The replacement gene contains instructions for producing high levels of the missing enzyme.)

"The stem cells are transplanted back into the patient, and when white blood cells – specifically macrophages – are produced from the transplant, they travel to the brain, produce the enzyme, and supply it to other brain cells," Dr. Pshezhetsky said. Currently, "we're testing this method on a mouse model, and we're obtaining results that are quite promising.

"In parallel, we're working on other approaches that use small molecules, which is something that could probably be used for other forms of childhood dementia," Dr. Pshezhetsky said.

"With these small molecules, we target the synapse, which is the site where neurons communicate. What we found is that there is a severe synaptic deficiency in all the Sanfilippo disorders that starts very early, before the nerve cells start dying," Dr. Pshezhetsky explained. Loss of these connections is a central feature of AD, and is closely linked to memory loss and cognitive decline.

MOVING TOWARD NEW TREATMENTS

"We're using a small molecule that can boost production of synaptic proteins and formation of new synapses," Dr. Pshezhetsky explained. "It doesn't go to the root of the problem – you still have the genetic defect and accumulation of metabolites. But we see that if we treat mice, we can mitigate the development of behavioural symptoms. Also, when we analyzed the brain of treated Sanfilippo mice, we found that the same molecule reduced neuroinflammation."

Even better, "we don't need to inject this molecule into the brain," Dr. Pshezhetsky added. "It can be given like a nasal spray."

In Australia, some labs that have traditionally focused on "Alzheimer's or adult dementia more broadly are now starting to work on childhood dementia alongside their adult dementia research," Dr. Elvidge said, adding Childhood Dementia Initiative hopes to attract more researchers to the field.

In Dr. Pshezhetsky's opinion, "getting more attention is key because these patients need to be heard and recognized," he said. "The clock is ticking for these children. Raising money for research is important because in Canada, as is everywhere, research is underfunded. But what is also important is to get the attention of politicians and government officials to provide specific benefits and aid to these families."

CHILDHOOD DEMENTIA RESOURCES

CANADIAN MPS SOCIETY FOR MUCOPOLYSACCHARIDE & RELATED DISEASES
mpssociety.ca

CHILDHOOD DEMENTIA INITIATIVE
childhooddementia.org

RAREKIDS-CAN
rarekidscan.com

THE SANFILIPPO CHILDREN'S RESEARCH FOUNDATION
alifeforelisa.org

Mind Your Morsels

Savour the Knowledge

Proper nutrition is essential for healthy aging and can play a key role in reducing the risk of dementia. But what exactly should we eat to nourish our brains?

Answering that question isn't simple. While the overall benefits of a healthy diet for brain health are well-established, pinpointing specific dietary components remains a challenge for researchers due to various complexities.

Nutrition research is inherently intricate, as it involves numerous factors – including the types of foods consumed, meal timing, food quality and sourcing, preparation methods, and portion sizes.

DIET'S IMPACT ON HEALTH IS OFTEN INFLUENCED BY OTHER VARIABLES, SUCH AS PHYSICAL ACTIVITY, GENETICS, AND EVEN THE SOCIAL INTERACTIONS THAT TAKE PLACE DURING MEALS.

This complexity hasn't deterred researchers, though. Many studies have looked at various aspects of nutrition in search of the ideal foods or specific nutrients for brain health. In this article, we look at highlights from some of the latest findings.

SPECIFIC NUTRIENTS

Extensive research has examined specific nutrients that may support cognitive function and reduce the risk of dementia.

A 2024 study by Dr. Christopher Zwilling and colleagues published in *npj Aging* took a novel approach to identifying nutrients that support cognitive health. Involving 100 neurologically healthy older adults, the research bypassed the limitations of self-reported food diaries and instead analyzed nutrient biomarkers – measurable nutrient levels in participants' blood – to provide a more precise assessment of diet's impact on brain health.

Brain scans of the participants revealed two distinct patterns of brain aging – some participants showed Accelerated brain aging, and others showed slower-than-expected (i.e., Delayed) brain aging.

Compared to those with Accelerated brain aging, participants with Delayed brain aging were found to have larger brain volumes, increased white matter integrity, increased functional connectivity, and other positive differences.

A variety of cognitive tests were also completed by the participants, including assessments of intelligence, executive function, and memory. Performance on these tests varied between the two brain aging groups, with participants in the Delayed brain aging group outperforming those in the Accelerated brain aging group on all the tests. In short, those with better physical brain health exhibited better cognitive function.

Nutritional Cognitive Neuroscience is an emerging field that focuses on identifying specific foods and nutrients that promote healthy brain aging.

Researchers then looked at the nutrient blood biomarkers in each of these two groups and discovered differences again.

Those in the Delayed brain aging group had higher levels of 13 key nutrients in their blood, including certain fatty acids, carotenoids, vitamin E, and choline.

To recap, the study identified particular nutrient patterns in the blood that were associated with better physical brain health, as well as better cognitive performance. The beneficial nutrients identified were ones found in the Mediterranean diet (which has been linked with healthy brain aging in previous research).

It's important to note that these findings demonstrate a correlation between blood-based levels of certain nutrients and cognitive performance, as well as brain structure, function, and metabolism. They do not show causation. Randomized control trials will be needed to test if it's possible to directly affect brain health and cognitive function by increasing intake of specific nutrients.

Other nutrients, for example, certain B vitamins, have been found in other studies to be neuroprotective as well.

Learning about specific nutrients that support brain health is fascinating, and research is ongoing to identify effective brain health nutraceuticals – isolated nutrients in supplement form that offer therapeutic benefits beyond those obtained through diet alone.

In the meantime, we already have a wealth of knowledge on how to support brain health through dietary choices.

Extensive research has linked certain eating patterns to significant cognitive benefits.

BENEFICIAL DIETARY PATTERNS

Three of the most heavily studied diets known to support brain health are the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. Each has been linked to various cognitive benefits and overall brain health.

MEDITERRANEAN DIET

The Mediterranean diet emphasizes traditional foods eaten in countries that surround the Mediterranean Sea, such as Greece and Spain. The diet is characterized by high consumption of fruits and vegetables, whole grains, olive oil, beans, nuts, legumes, seeds, herbs and spices; frequent consumption of fish and seafood; moderate amounts of poultry, eggs, cheese, and yogurt; and low consumption of red meat and sweets.

Extensive research has shown that closely following the Mediterranean diet is associated with a slower rate of cognitive decline, reduced risk of impairment, and a lower likelihood of developing dementia.

"The Mediterranean diet involves not just the pattern of foods eaten and minimized, but also socio-cultural aspects like the enjoyment of meals with friends and family," said Dr. Bahram Arjmandi, professor emeritus at Florida State University, who studied the effects of dietary patterns on Alzheimer's disease (AD) with colleagues and shared the findings in a 2023 paper in *Nutrients*.

"So, it's possible that some of the neuroprotective benefits of the Mediterranean diet are not just about the food alone, but also about the social connection associated with food preparation and consumption."

(Note that nutrition and social activity are two of the Six Pillars of Brain Health we promote at Women's Brain Health Initiative.)

SOURCES OF BRAIN-HEALTHY NUTRIENTS

Omega-3 is one of the most important fatty acids for brain health. Dietary sources include fatty fish such as mackerel, salmon, herring, and sardines; chia seeds, walnuts, and flax seeds.

Carotenoid-rich foods include leafy greens (spinach, kale, collards, etc.), bell peppers, carrots, broccoli, tomatoes, grapefruit, and watermelon. There are lots of others. The key is to "eat the rainbow," i.e., consume a wide variety of brightly-coloured vegetables and fruits.

Excellent sources of vitamin E include nuts, seeds, and vegetable oils. Significant amounts of vitamin E are also in green leafy vegetables.

Excellent sources of choline include animal-based proteins such as meat, fish, and eggs. Cruciferous vegetables (such as broccoli, Brussels sprouts, cabbage, and cauliflower), and some beans are also rich in choline.

DASH DIET

Since heart health is closely connected to brain health, it's no surprise that the Dietary Approaches to Stop Hypertension (DASH) diet – originally developed to manage blood pressure – also offers significant benefits for cognitive function and brain health.

The DASH diet is similar to the Mediterranean diet in that it involves high consumption of plant-based foods. However, the DASH diet also emphasizes limiting intake of sodium and sweetened beverages.

While the Mediterranean diet allows for some consumption of red wine, the DASH diet does not recommend alcohol.

"The DASH diet has been shown in research to reduce blood pressure and low-density lipoprotein (LDL) cholesterol, as well as to lower inflammation and body

weight – all factors which play a role in keeping the brain healthy," said Dr. Arjmandi.

"Long-term adherence to the DASH diet has been found to be associated with improved cognitive function, and reduced risk of dementia."

MIND DIET

As the name suggests, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is a combination of the Mediterranean diet and the DASH diet. It was developed by a team of U.S. researchers specifically to protect against neurodegeneration.

The MIND diet consists of 14 dietary components, including nine brain-healthy food groups to emphasize and five brain-unhealthy food groups to avoid or minimize.

The initial study of the MIND diet – conducted by Dr. Martha Clare Morris and colleagues – was an observational study involving 960 participants over an average 4.7-year period.

High adherence to the MIND diet was associated with a slower rate of cognitive decline, compared to low adherence.

The difference in rate of decline between the high- and low-adherence groups was estimated to be equivalent to being 7.5 years younger. (These findings were shared in 2015 in *Alzheimer's & Dementia*.)

Subsequent research has found that the MIND diet is associated with better cognition, reduced risk of cognitive impairment, and lower risk of developing AD.

DETRIMENTAL DIETARY PATTERN

Equally important as what you **do** eat is what you **don't** eat. We've already highlighted certain food groups that should be minimized or avoided for optimal brain health. In this section, we explore research on a dietary pattern that is particularly harmful to cognitive function – yet remains all too common – the western diet.

The western diet is characterized by a high intake of refined grains, sugar, unhealthy fats, and salt, while being notably low in vegetables and fruit. It also heavily features ultra-processed foods and beverages, which have been linked to negative effects on both physical and cognitive health.

THE MIND DIET DIETARY COMPONENTS

HEALTHY GROUPS	UNHEALTHY GROUPS
✓ berries	✕ red meats
✓ green leafy vegetables	✕ butter and stick margarine
✓ other vegetables	✕ cheese
✓ whole grains	✕ pastries and sweets
✓ nuts	✕ fried or fast food
✓ beans	
✓ fish	
✓ poultry	
✓ olive oil	

RESEARCH SHOWS THAT CONSUMING A WESTERN DIET HAS A CAUSAL RELATIONSHIP WITH BRAIN AGING, AND IT'S ASSOCIATED WITH POORER COGNITIVE FUNCTION, ESPECIALLY AMONG OLDER ADULTS.

"In addition, the western dietary pattern is associated with higher incidence of depression, obesity, cardiovascular disease, Type 2 diabetes, and other illnesses," added Dr. Arjmandi.

SUPPORT YOUR BRAIN THROUGH THE FOODS YOU CHOOSE

Dementia is thought to arise from a complex interplay of genetic, environmental, and lifestyle factors. While we can't alter our genetics and may have only limited influence over our environment, it's empowering to know that nutrition is one area where we can make a meaningful difference.

BY MAKING MINDFUL CHOICES ABOUT WHAT WE EAT – AND WHAT WE AVOID – WE CAN ACTIVELY SUPPORT OUR BRAIN HEALTH.

"When it comes to brain health, it's not just about what you eat, but also about when you commit to healthier dietary patterns," mentioned Dr. Ines Ellouze, assistant professor at Higher Institute of Biotechnology of Béja, University of Jendouba, in Tunisia, and one of the other authors of the 2023 paper in *Nutrients* with Dr. Arjmandi.

"Adopting a brain-friendly diet earlier in life can significantly impact your neurocognitive well-being. The sooner you reduce harmful food choices and prioritize nutrient-rich, wholesome options, the better equipped your brain will be to stay healthy."

SERVES 2

Parmigiano Reggiano & Smoked Salmon Tacos

Superfood Fact:

Smoked salmon is rich in omega-3 fatty acids, essential for brain health and cognitive function. Packed with nutrients and vitamins, it supports overall health while reducing the risk of cancer, heart disease, and cognitive decline. It is low in calories, but highly nutritious.

Farro Tuna Salad

This farro salad is great for any summer picnic. It's so satisfying and delicious, and if you've never had farro, it's a type of ancient grain that is super healthy, with a bit of a nutty flavour and slightly chewy texture.

INGREDIENTS

- 2 cups freshly grated Parmigiano Reggiano, 1/2 cup per taco shell
- Black pepper, QB*
- 1 cup plain yogurt
- 1 garlic clove, minced
- 1 lime, juiced
- Frisée lettuce, QB*
- 12 slices cold smoked salmon or lox
- 1/2 cucumber, sliced
- 1/3 cup capers, drained
- Fresh dill, QB*

INSTRUCTIONS

1. Preheat the oven to 400F. Line a baking sheet with parchment paper. Create small mounds of grated Parmigiano Reggiano on the baking sheet. Spread each one out evenly and add black pepper. Bake in the oven for 2-3 minutes until the cheese starts to slightly brown. Immediately remove from the sheet and place on a rolling pin to form taco shells. Let them sit for a couple minutes to firm up.

2. In a bowl, add yogurt, garlic, black pepper, lime juice, and mix together. Fill each shell with lettuce, salmon, yogurt sauce, cucumbers, capers, and fresh dill. Enjoy!

** QB means "quanto basta," which translates to "as much as you need."*

Superfood Fact:

Chicken is a rich source of lean protein and brain-boosting nutrients like choline, which supports memory, and vitamins B6 and B12, essential for brain development. Studies confirm that the essence of chicken can help enhance or maintain brain function in the elderly.

Chicken Cacciatore

SERVES 4-6

INGREDIENTS

- **3 tbsp extra-virgin olive oil**
- **2 garlic cloves, whole**
- **4 sprigs rosemary**
- **1 whole chicken, cut into pieces**
- **1 red chili, chopped**
- **Salt, QB***
- **1 tbsp tomato paste**
- **3/4 cup dry white wine**
- **1 cup canned plum tomatoes**
- **Fresh marjoram**
- **1 lemon, zested**
- **Optional: Italian bread**

INSTRUCTIONS

1. In a large pan, heat the olive oil and add garlic, rosemary, the chicken pieces, chili pepper, and salt. Sauté the chicken until brown, about 5 minutes per side. Then, add the tomato paste and stir. Add white wine. Add in the tomatoes and smash them to release the juices. Add some more salt. Then, bring the sauce to a simmer over medium-low heat. Cover with a lid and let it cook for about 30 minutes until the chicken is cooked.

2. Plate the chicken, spoon the sauce over the chicken, and top with fresh marjoram and lemon zest. Serve and enjoy!

For more brain-healthy recipes by David Rocco, scan here.

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This edition's recipes are courtesy of international celebrity chef, executive producer, and author of three internationally bestselling cookbooks, David Rocco.

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