$5.95

WBHI.ORG

Mind Over Matter®

VOLUME 17

HELPING YOU PROTECT YOUR BRAIN HEALTH

Trust Your Gut

Free Brain Health Resources

Women & Hypertension

Forever *Young*

Window to *the Brain*

Thumbs Up for *Women's Brain Health*

Women's Brain Health Initiative

25 Years of Putting Our Brains to Work For Yours.

This year, Brain Canada celebrates a quarter century of accelerating, amplifying, and funding critical brain research. Working with a community of caring partners and donors, we've invested over $290 million in next-generation investigators, capacity-building initiatives, innovative research teams, and unique collaborations to drive brain science forward.

With your support, we'll continue advancing the brain health of people in Canada for decades to come.

Financial contribution from
Avec le financement de
Health Canada Santé Canada

Fondation Brain Canada Foundation

Editor-in-Chief

The landscape of Alzheimer's treatments is evolving at an astonishing pace, offering newfound hope in our battle against this relentless adversary that disproportionately affects women. Yet, it is essential to recognize that these innovative therapies, while promising, come laden with complexities. The true beacon of promise shines on the horizon of proactive dementia prevention strategies.

Through the collaborative efforts of individuals and organizations deeply committed to women's brain health and mental well-being across generations, Women's Brain Health Initiative (WBHI) has created a wealth of free, invaluable resources to help you safeguard your cognitive vitality, including this publication, thanks to our partner, Brain Canada.

We are thrilled to announce the evolution of our Mind Over Matter® magazine, powered by the unwavering support of Brain Canada, expanding into the digital realm. Recognizing the growing demand for accessible knowledge, our BrainFit-Habit Tracker mobile app's Explore section encompasses a rich tapestry of Mind Over Matter® articles, empowering individuals to take charge of their journey toward better brain health.

Our progress is made possible by the generosity of countless donors who have enabled WBHI to translate scientific insights into tangible tools and programs tailored to fortify against dementia while preserving cognitive vitality. Our focus remains on addressing the distinct vulnerabilities women and their families face.

Your support is key to expanding our educational programs that touch lives, particularly those in marginalized communities often deprived of vital health education. Together, we can empower individuals to safeguard their cherished memories and the legacies of their loved ones.

In our collective pursuit, every individual's gray matter matters profoundly. With your belief in us and your support, we stand poised at the forefront of a solution that can potentially change lives, enriching our shared human experience.

In this 17th issue of Mind Over Matter®, I extend a warm invitation to explore the most up-to-date findings, guidance, and discussions in brain health.

We cover the brain benefits of vitamin K, magnesium, keeping your gut healthy, and being an active grandparent. We explore the brain health risks of kidney disease, certain metals, and hypertension.

We also provide you with the Stand Ahead® Challenge scheduled for December 2 in honour of Women's Brain Health Day, and thanks to presenting sponsor BMO, an in-person and livestream event will take place so we can celebrate together.

Additionally, we spotlight a selection of our complimentary resources designed to support you and your loved ones in maintaining mental sharpness and agility, including Memory Morsels®, a website filled with delicious brain-healthy recipes by leading chefs and tips to help keep your brain functioning the way you want. You'll find a few of our latest mouth-watering recipes in this edition of Mind Over Matter® thanks to Brain Health Kitchen's Annie Fenn that we invite you to try.

Wishing you and yours good health.

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

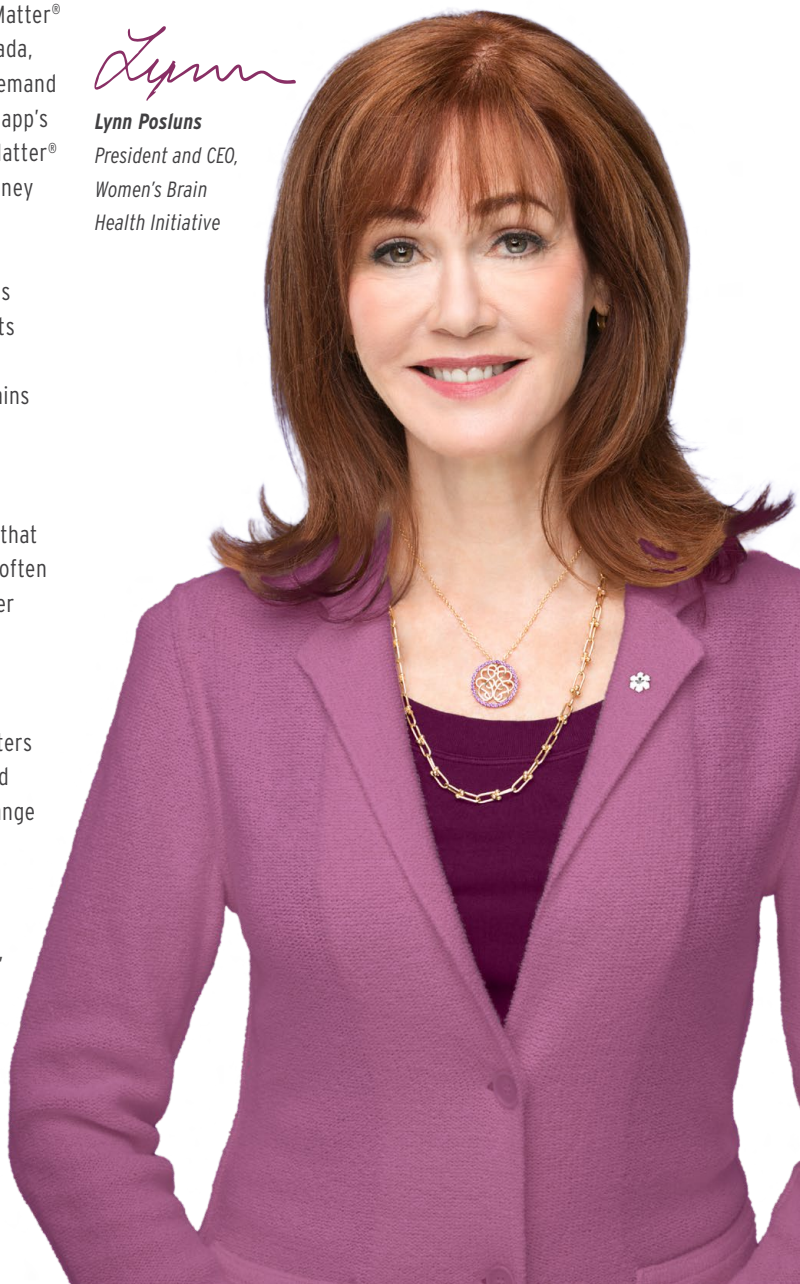


PHOTO: JAYLYN TODD

TABLE OF CONTENTS

LOOKING FOR MORE COPIES?

mom@womensbrainhealth.org

Contributors

ALEX MLYNEK // MANAGING EDITOR

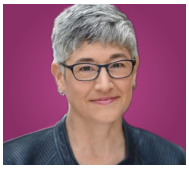
Alex Mlynek is a Toronto-based journalist who has worked as an editor for *Today's Parent* and *Canadian Business* magazines. Her writing has appeared in a number of publications, including *Reader's Digest*, *Broadview*, *Chatelaine*, *Best Health*, *The Walrus* and *Report on Business*. She loves telling 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.

SUSANNE GAGE // WRITER

Susanne is a marketing/communications agency and events professional, with a solid appreciation for smart thinking. A believer in life balance and healthy body and mind, Susanne is also a passionate advocate for giving back. "As a business woman, wife, mother, daughter, and friend, I am inspired by the impact of WBHI and the collaborative opportunities to make a real difference."

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 a new granddaughter, 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.



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.

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

Over the past decade, Vitina has lent her branding and design expertise to support WBHI's mission. Her passion for mindful living aligns seamlessly with the organization's mission to safeguard the mental and brain health of women, caregivers, and their families.

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.

COVER PHOTO: JAYLYN TODD

TAZIM NASSER & FARAH NASSER // ON THE COVER

Tazim Nasser only started to learn about the mission of Women's Brain Health Initiative (WBHI) when she was invited to appear on the cover of Mind Over Matter® with her daughter, Global News anchor, Farah Nasser. But she quickly became a dedicated supporter, inviting WBHI President and CEO Lynn Posluns to speak to the Ismaili Woman's Network-West GTAA volunteer groups she chairs. Tazim admitted that she didn't have much time to think about health matters as a young woman because she was fully occupied with making her way in a new country as a teenage immigrant. She credits Farah with teaching her about the value of healthy eating and exercise. For her part, Farah thanks her mom for life lessons about resilience. "She taught me nothing was impossible; no dream was too big."

WE ARE TRULY GRATEFUL TO:

Fondation Brain Canada Foundation

Financial contribution from
Avec le financement de

Health Canada Santé Canada

AND ALL THOSE WHO GENEROUSLY SUPPORTED THIS PUBLICATION:

Beverley Andrews
Pamela Austin
BMO Financial Group
Lorna Caldwell
CIBC
Marg Clarke
Crowe Soberman LLP
Jade Crystal
Djavad Mowafaghlan Foundation
Lynn Glazer
Kitty & George Grossman
Margaret Hagerman
Susan Hodkinson
HomeEquity Bank
JoAnne Korten
Nancy Laughton
Monica McIntosh
Margaret Nightingale
Diane Novick
Felicia Posluns
Joyce Posluns
Lynn Posluns
Wendy Posluns
RBC Foundation
RBC Wealth Management
Lionel & Helaine Robins
Melissa Rush
Gloria Salomon-Levy
Scotia Trust
Gary & Nanci Segal
Sylvia Soyka
TELUS
The Benevity Community Impact Fund
The Caroline Wight Trust
Myrna Weinstein
WeirFoulds LLP
Cathy & Peter Williamson

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.

Trust Your Gut

DO YOU HAVE THE GUTS TO KEEP YOUR BRAIN HEALTHY?

A few months into the COVID pandemic, Katharine Gorjup's life was in jeopardy from a completely different type of infection. Following a round of IV antibiotics to treat a dental infection, the Toronto woman, then 59, subsequently suffered through six months of recurrent C-difficile infections that failed to respond to one antibiotic after another.

A type of bacteria that typically doesn't cause problems in healthy individuals, C difficile can sometimes multiply out of control in the large intestine, leading to severe, potentially life-threatening diarrhea.

By the time Gorjup's doctors had exhausted the antibiotic arsenal, "I'd been living on the toilet for six months. I couldn't keep food down – I went down to 90 pounds. I looked like I was dying of cancer," Gorjup said.

What happened to Gorjup is perhaps the most obvious and dramatic example of what can happen when the community of microbes that normally live in our digestive tract – commonly known as the gut microbiome – is thrown out of balance. In Gorjup's case, antibiotics had likely decimated beneficial bowel bacteria that had previously kept C difficile in check, thereby allowing it to multiply exponentially.

Keeping the gut microbiome healthy can impact more than your body's ability to fight infection.

It can also be a key component of brain health. This article explores why this is and how to keep your gut healthy.

THE BRAIN HEALTH–GUT MICROBIOME CONNECTION

The gut microbiome is an ecosystem with a population roughly equivalent to the number of cells in our body.

It consists of a diverse mix of microorganisms, including bacteria, viruses, fungi, and bacteriophages, which carry out numerous essential functions, such as aiding digestion, synthesizing vitamins, metabolizing medications, and producing neurotransmitters similar to the brain. (Molecules that carry nerve signals throughout the body, neurotransmitters regulate mood and play key roles in cognitive functions such as learning and memory.)

The metropolis of gut microbes also affects the functioning of the immune system, and forms part of a two-way communications network between the gut and central nervous system, commonly known as the gut-brain axis.

Microbiota: The entire community of microorganisms living in or on a specific part of the body, such as the vagina, underarm, urinary tract, or colon. The most heavily populated microbiome in the human body is located in the gastrointestinal tract, and is commonly referred to as the gut microbiome.

Microbiome: This encompasses all of the microbes inhabiting a specific environment, plus their genes, and the substances they produce.

THE MICROBIOME CAN EXERT WIDE-RANGING EFFECTS THAT MAY INFLUENCE OUR SUSCEPTIBILITY TO CONDITIONS THAT AFFECT BRAIN HEALTH VIA THE GUT-BRAIN AXIS.

Dr. Siobhain O'Mahony, a principal investigator and senior lecturer at APC Microbiome Ireland, University College Cork, Ireland, explained how these systems interact. "The products the microbiota produce can directly and indirectly affect the peripheral nervous system as well as the central nervous system."

She continued, "They can also influence the brain via the vagus nerve, which connects the bowel to the brain. As well, they can produce cytokines that are anti-inflammatory or pro-inflammatory, to impact the immune system directly."

SEX DIFFERENCES IN THE GUT MICROBIOME

Sex hormones seem to affect the makeup of the gut microbiome, and conversely, the gut microbiota can influence levels of these hormones in the blood. Generally speaking, before menopause, women appear to have greater diversity in their gut microbiota than men, and the composition differs, too, with the abundance of certain bacteria differing between the sexes.

"There are actually receptors for gonadal hormones – so estrogen, progesterone and testosterone – on bacteria," in the gut, Dr. O'Mahony said. "So that gives us an idea that there's an interaction between them".

As well, "there are huge changes in the gut microbiome during pregnancy, puberty, and menopause." There is also some evidence that the gut microbiome in women and men can respond differently to an identical intervention.

In people with obesity, and post-menopausal women, differences between the sexes shrink substantially. →

THE GUT MICROBIOME COMPOSITION MAY ALSO PLAY A MORE SIGNIFICANT ROLE IN OBESITY FOR WOMEN THAN MEN.

It could potentially contribute to increased blood pressure – linked with a higher risk of developing cognitive impairment and dementia – particularly before menopause.

However, more research is needed to unravel the complex interactions between sex hormones, the gut microbiota, and the immune system and how they might influence women's brain health.

THE LEAKY GUT EFFECT

Differences in the composition and function of the microbiome have been linked to a host of diseases, including such neurological disorders as Alzheimer's disease (AD), as well as conditions that are associated with an increased risk of cognitive decline and dementia, including cardiovascular disease, Type 2 diabetes, and frailty.

Ongoing low-grade immune system overactivity appears to be a common contributor to these problems. One thing that can lead to this misplaced immune activation is the gut lining changing from its normal tightly sealed structure to a barrier that's easier for microbiota to get through.

Roughly 70% of the immune cells in the body can be found in the intestines.

These immune cells are primarily situated behind a delicate barrier of closely joined cells known as the epithelium. This barrier is usually coated with a dense layer of mucus that acts as a shield, preventing the microbiota from entering.

When this double-layered defensive line becomes impaired in some way, "parts of bacteria, or bacteria themselves, can leak out into the systemic blood system," Dr. O'Mahony said, which in turn "creates an immune response."

Research by Dr. O'Mahony and others has established that stress hormones, such as cortisol, "can increase bowel permeability and can change the gut microbiome," she said.

DURING PREGNANCY, WHEN THERE IS STRESS, ANXIETY, AND DEPRESSION, EVEN AT SUBCLINICAL LEVELS, WE'VE FOUND CHANGES TO CIRCULATING FACTORS IN THE MOTHER'S BLOOD THAT INDICATE HER BOWEL IS MORE PERMEABLE.

According to an April 2022 review article published in the journal *Frontiers in Nutrition,* "the leakage of the intestinal barrier and the disruption of the gut microbiome are increasingly recognized as key factors in different pathophysiological conditions," including cardiovascular diseases, obesity, and Type 2 diabetes.

Similarly, these factors may play a role in the progression of AD. According to a review published in the *Journal of Neurogastroenterology and Motility* in January 2019, "alterations in the gut microbiota composition induce increased permeability of the gut barrier and immune activation, leading to systemic inflammation, which may, in turn, impair the blood-brain barrier and promote neuroinflammation, neural injury, and ultimately neurodegeneration."

HOW GUT HEALTH IMPACTS FRAILTY

There also appears to be links between the richness of diversity in the gut microbiome and susceptibility to age-related conditions, like frailty, that are risk factors for cognitive impairment and inflammation.

"It is very clear that people living in care homes generally tend to have less diverse microbiomes" and higher levels of frailty "than older people living in the community," said Dr. Emma Allen-Vercoe, professor and Canada Research Chair in the Department of Molecular and Cellular Biology at the University of Guelph.

And some research, such as a study that used data from 143,215 participants in the UK Biobank, has shown that, "individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounding factors." This article was published in *The Lancet: Healthy Longevity* in November 2020.

Other evidence points to a connection between higher levels of inflammation and frailty. Take, for example, the research results published in *Frontiers in Psychology*. In the 2022 systematic review, which spanned 22 studies (comprising a total of 17,373 mostly community-dwelling participants), 95% showed significant links between inflammation (and in particular, high levels of inflammatory markers C-reactive protein and interleukin-6) and frailty status.

Admittedly, due to the observational nature of studies such as those examining the relationship between gut microbiome composition and frailty, "it's hard to know whether the situation the individuals are living in led to the lack of diversity, or the lack of diversity led to frailty," noted Dr. Allen-Vercoe.

"But we do have a few clues. Some of those are the wealth of data we now have that shows exposures to medicines, such as antibiotics, poor foods, and living an isolated lifestyle tends to reduce the diversity of your microbes," she added.

CAN YOU BOOST YOUR GUT MICROBIOME?

With all the research that's been done to date, "we don't know what a healthy microbiome looks like," said Dr. Natasha Haskey, a registered dietician and post-doctoral fellow in the Irving K. Barber Faculty of Science's Department of Biology at the University of British Columbia's Okanagan campus in Kelowna.

"You and I might both be healthy, healthy being the absence of disease, but our microbiome fingerprints might be quite different," she said. Consequently, it's impossible to predict the effect of a specific intervention to manipulate the microbiome on a given individual.

SOME LIFESTYLE MEASURES, THOUGH, PROMOTE INCREASED DIVERSITY IN THE GUT MICROBIOME WHILE DAMPENING DAMAGING INFLAMMATION.

"One way we can change the microbiome is through what we eat," Dr. Haskey said. "If people start consuming a healthier diet, we can see changes in the microbiome within a week, which stay relatively stable as long as they stay on the particular diet." In fact, according to Dr. Haskey, diet and antibiotic use are the two modifiable factors with the strongest influence on gut microbiome health.

The eating pattern Dr. Haskey recommends is a Mediterranean-style diet since, according to existing research, it helps achieve what she called "a sort of balanced inflammation. I personally don't like the word anti-inflammatory since we do need some inflammation in our body to stay healthy."

"It doesn't have to be vegetarian or vegan, but it is plant-forward," she said.

> *"You can eat a variety of healthy foods, but one of the key components is colourful fruits and vegetables, rich in polyphenols.*

These compounds promote a healthy balance of gut microbiota. Vegetables, fruits, and other plant foods such as beans, legumes, and whole grains, are also abundant in dietary fibre.

Dietary fibre is broken down by certain species of gut microbiota through fermentation, to produce short chain fatty acids (SCFAs), which, among many other functions, play important roles in regulating immune function and protecting the integrity of the intestinal barrier.

Rather than emphasizing low fat intake, the Mediterranean diet is "rich in monounsaturated fats," Dr. Haskey explained, found in such foods as olive oil, avocado, nuts, and seeds. Fish and seafood, which are sources of omega-3 fats, are recommended, too.

Dr. Haskey's dietary prescription "also includes dairy products," she said. "In some of my work, we've seen that milk fat has a protective effect on the intestinal barrier. We've found a metabolic benefit to dairy. It's not one fat on its own, it's a blend of fats unique about the Mediterranean diet."

At the same time, Dr. Haskey recommends limiting omega-6 fats from such oils as corn, safflower, and sunflower, all of which may hide on the labels of ultra-processed foods under the term "vegetable oil." She noted,"In our mechanistic studies, we saw [omega-6s] had a detrimental effect on inflammation."

ANOTHER REASON TO CURB CONSUMPTION OF ULTRA-PROCESSED FOODS IS TO MINIMIZE INTAKE OF SUCH ADDITIVES AS ARTIFICIAL SWEETENERS AND EMULSIFIERS, WHICH ARE USED TO IMPROVE TEXTURE AND EXTEND SHELF LIFE.

"We're just beginning to understand their impact on the microbiome," Dr. Haskey said, but there are indications some may be potentially harmful. She cited the example of research that has shown certain emulsifiers influence the mucus that lines the digestive tract, creating more of a thin layer.

It also may be worth increasing the intake of foods not always mentioned in the same breath as the Mediterranean diet. "There have been a few papers lately which showed benefits of fermented foods over and above just a high-fibre diet," noted Dr. Jeremy Burton, ⟶

Probiotics: According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), these are "live organisms that, when administered in adequate amounts, confer a health benefit on the host." Strictly speaking, this includes only strains with scientifically documented effects. The live microbes in traditional fermented foods and beverages such as kimchi, sauerkraut, and kefir, "typically do not meet the required evidence level" to qualify as probiotics. For a list of probiotic products that have been shown to be effective for treating specific conditions, visit probioticchart.ca

Prebiotics: These are substances that we can't digest, but which serve as food for microbes in our gut that perform beneficial functions. This includes many, but not all, types of dietary fibre, one being inulin, which is found in such plant foods as chicory root and onions.

who holds the Chair of Human Microbiome and Probiotics at the Lawson Health Research Institute and St. Joseph's Health Care London, and is an associate professor at Western University's Schulich School of Medicine and Dentistry in London, Ont.

For example, in one study published online in August 2021 in *Cell*, 36 healthy adults were randomly assigned to increase their intake of either high-fibre or fermented foods, such as yogurt, kefir, cottage cheese, kombucha, fermented vegetables such as kimchi, and vegetable brine drinks.

After ten weeks, those in the fermented food group saw an increase in gut microbiota diversity and a drop in levels of 19 inflammatory proteins, including one associated with such conditions as Type 2 diabetes.

It's not yet clear whether it is the microorganisms responsible for fermentation, or compounds in the fermented foods, that bring about these beneficial changes

Perhaps the greatest medical advance to come out of gut microbiome research to date is treating recurrent C-difficile infection by re-seeding the patient's bowel with a sample population of microbiota. This is typically done by directly introducing stool from a healthy donor (fecal transplant) by enema or oral capsules.

The approach has become standard at such centres as St. Joseph's Health Care London, where Katharine Gorjup received this treatment, seeing her condition return to near normal within days.

Research like this should lead to much less crude, more targeted therapies for preventing diseases like dementia. For example, Dr. Allen-Vercoe predicts that irritable bowel syndrome, which is linked with heightened dementia risk, will one day be managed with ongoing supplementation to replace the microbial metabolites missing in people with the disease.

In the meantime, however, the strategy with the most evidence behind it is paying closer attention to what you put on your plate. As Dr. Burton put it, "what you eat is what you are with regards to your microbiome."

Special K

A CRITICAL VITAMIN FROM COAGULATION TO COGNITION

Vitamin K was named by a Danish scientist Henrik Dam in the 1930s for its essential role in blood clotting ("Koagulation" in Danish). Vitamin K is so crucial for clotting that the World Health Organization recommends that all newborn babies (who naturally have very little vitamin K stored up) get a prophylactic dose to prevent rare but lethal outcomes from vitamin K deficiency bleeding.

But over the last few decades, we've learned that vitamin K does much more than regulate our blood.

WE NEED VITAMIN K TO FORM A PROTEIN "BUILDING BLOCK" CALLED GAMMA-CARBOXYGLUTAMATE, OR GLA, WHICH BINDS TO CALCIUM.

Gla proteins have been identified in different molecular structures throughout the body and serve a range of metabolic functions like building bones, preventing bone breakdown, preventing calcium blockages in blood vessels, eliminating unwanted or damaged cells, glucose metabolism, and even communicating between nerve cells. A 2019 review of clinical studies by Dr. Simes and colleagues →

published in *International Journal of Molecular Sciences* shows that vitamin K may even play a protective role in inflammation and oxidative stress independent of the Gla proteins. Vitamin K is a truly multi-functional vitamin.

TYPES AND SOURCES OF VITAMIN K

Vitamin K is present in a variety of foods, but the richest sources are from plants. All leafy green vegetables have vitamin K in the form of phylloquinone, or vitamin K1. Good sources of vitamin K1 include collards, spinach, cruciferous vegetables (e.g., broccoli and brussels sprouts), and herbs (e.g., cilantro and parsley).

AN EASY RULE OF THUMB IS THAT DARKER GREENS HAVE MORE VITAMIN K1.

It's also available in smaller quantities from spices (e.g., paprika, chili powder, and cloves) and some plant oils like soybean and canola, as well as nuts. Vitamin K1 functions similarly to its namesake by participating in blood coagulation.

A secondary form of vitamin K called menaquinones, or K2, is available in different structures named for their repeating molecular chains (e.g., MK-4, MK-7, MK-9). Unlike phylloquinones that only come from food, there are three ways that we get K2.

The primary way is through diet. Foods made with bacterial cultures like yogurt and cheese, or foods that are fermented like natto (from soy), sauerkraut (from cabbage), and pickles (from cucumbers) have the largest amounts of K2. Considerably smaller amounts are present in animal products like butter, meat, and eggs.

Secondly, there are bacteria in the human gut that can synthesize small amounts of K2 (MK-5 to MK-15). Thirdly, our bodies can convert plant-based phylloquinones to MK-4 using a unique conversion process.

EVEN THOUGH OUR BODIES CAN CREATE VITAMIN K2 IN TWO DIFFERENT WAYS, WE DON'T MAKE ENOUGH, SO WE MUST EAT FOODS WITH VITAMIN K. VITAMIN K2 HELPS FORM GLA PROTEINS NEEDED FOR BONE, CARDIOVASCULAR, AND BRAIN HEALTH.

Vitamins are compounds that are essential to several body functions. We cannot synthesize vitamins in sufficient quantities on our own, so we must get them from foods or supplements. There are two types of vitamins: fat-soluble vitamins (A, D, E, and K) that can be stored in the body, and water-soluble vitamins (B complex and C) that are eliminated daily in urine and waste.

There is a third form, called menadione, or vitamin K3, which does not occur naturally in foods but has been synthesized as a supplement for livestock and pet feed, as some animals can convert this into K2 in their bodies. Vitamin K3 is not available for humans because of the risk of toxicity.

A LITTLE VITAMIN K GOES A LONG WAY

A very small amount of vitamin K is needed for optimal functioning. The European Food Safety Authority recommends an amount based on how much you weigh: 1 microgram (mcg) of vitamin K per kilogram of body weight per day. Health Canada's Dietary Reference Intake and the US Dietary Recommended Intake for vitamin K was previously 1 mcg/kg but shifted to a simpler approach that does not require individuals to know their weight.

The current daily vitamin K recommendation in Canada and the United States is 120 mcg for men and 90 mcg for women.

Dr. Guylaine Ferland, PhD, was a part of Health Canada's advisory panel that developed the Dietary Reference Intake for vitamin K. Dr. Ferland is a professor of nutrition at the Université de Montreal and a scientist at the Research Centre of the Montreal Heart Institute. She runs a research program dedicated to vitamin K metabolism and the role of nutrition in the aging process.

According to Dr. Ferland, vitamin K recommendations are based on the minimum amount needed for coagulation, where 1 mcg/kg is certainly sufficient. While the recommended vitamin K intake for a 60 kg (132 lb) woman is 60 mcg in Europe and 90 mcg in North America, practically speaking, she points out that the difference is so small that it is equivalent to eating an extra floret of broccoli!

Our low but critical requirements for vitamin K, explained Dr. Ferland, can be linked back to the evolution of humans.

> **THE REASON WHY VITAMIN K IS REQUIRED IN SUCH SMALL AMOUNTS IS BECAUSE IT IS REQUIRED FOR COAGULATION. YOU DON'T FOOL AROUND WITH COAGULATION: IF YOU HAVE TOO MUCH, YOU GET A STROKE; IF YOU HAVE TOO LITTLE, YOU GET A HEMORRHAGE.**

She remarked that humans would not have survived if we relied on large amounts of vitamin K from food, especially during times of famine in the course of history. Moreover, our bodies have evolved to recycle a large proportion of vitamin K, making the most of what we eat.

COMMON SOURCES OF VITAMIN K

The richest sources of vitamin K are vegetables, herbs, and fruit. Common sources and amounts from Health Canada's Canadian Nutrient File* are listed below.

FOOD	AMOUNT	VITAMIN K (MCG)
VEGETABLES AND HERBS		
Spinach, cooked	1/2 cup	469
Lettuce, raw	1 cup	154
Broccoli, cooked	1/2 cup	116
Parsley, fresh	4 grams	66
Asparagus, cooked	6 spears	46
Cilantro (coriander), fresh	4 grams	12
Chives, raw	4 grams	9
FRUIT		
Kiwifruit	1 medium	28
Blueberry, frozen	1/2 cup	22
Avocado	1/2 fruit	21
Pear	1 medium	8
ANIMAL PRODUCTS		
Cheddar cheese	50 grams	1.4
Butter, unsalted	10 grams	0.7
Plain yogurt	175 grams	0.4
Chicken egg	1 large	0.2
OILS		
Soybean oil	1 tablespoon (15 millilitres)	25
Canola oil	1 tablespoon (15 millilitres)	10
Olive oil	1 tablespoon (15 millilitres)	8
PREPARED FOODS		
Sweet or sour pickles	30 grams	14
Sauerkraut	1/2 cup	10
Soy milk	1 cup	9

**database accessed July 2023*

Continue Reading ⟶

A microgram is one of the smallest units to measure mass and is equivalent to one millionth of a gram. Daily requirements for many other vitamins like vitamins B and C are measured in milligrams, which is one thousand times larger!

TO SUPPLEMENT OR NOT TO SUPPLEMENT?

With the availability of vitamin K through various foods plus our ability to store, produce, and recycle vitamin K, it is no surprise that most experts do not think taking vitamin K as a supplement is necessary.

"We have scientific evidence that vitamin K plays a role in various systems, but we are not at the stage of knowing whether a higher level of vitamin K than current recommendations would benefit brain health, vascular health, and so forth," said Dr. Ferland. Currently, we do not have solid evidence for a dose-response relationship where vitamin K supplements are needed. Food is the most important way to get vitamin K and the nutrition needed to manage diseases."

There are several dose-response clinical trials currently underway with different amounts and types of vitamin K supplements, different durations of study, and different biomarkers of vitamin K status, but for now there's no way around it. You must eat your greens.

ANOTHER FACTOR TO CONSIDER IS THAT THERE IS A LIMIT TO HOW MUCH VITAMIN K YOUR BODY CAN STORE AND USE.

It is simply not true that if some is good, more will be better. "There is a very strong ceiling effect in nutrition, and this is especially the case with vitamins. We see this with vitamin K, D, and even calcium," noted Dr. Ferland. After a certain point, consuming more vitamin K does not increase the amount in your tissues.

At the other end of the spectrum, it is rare but possible to be vitamin K deficient if you have very low intake of vegetables, if you suffer from a disease that affects nutrient absorption (e.g., bowel diseases like Crohn's, liver disease, alcoholism), or if you have been using antibiotics for a prolonged period (because antibiotics destroy invader bacteria but also helpful bacteria in the gut).

Other factors that may affect your vitamin K status are medications. The anti-coagulant called warfarin competes with the function of vitamin K in the body. When taking warfarin, patients are asked to keep their vitamin K intake constant so that it does not interfere with their blood-thinning medication. In any of these special circumstances, it is best to discuss your intake of vitamin K with your physician.

AIM FOR ADEQUATE INTAKE EVERY DAY

In a 2021 review of research on vitamin K published in *Nutrition Reviews,* Dr. Mladenka and colleagues explain that while current dose-response relationships for vitamin K are not clear enough to recommend higher intakes, too little intake of vitamin K and low levels of vitamin K in body tissues appear to be linked to health declines and disease. Accumulating research has explored the role of adequate vitamin K for the health of bones, brain, and the cardiovascular system.

BONE HEALTH

Vitamin K is required for the synthesis of several Gla proteins responsible for bone health, including osteocalcin.

Adequate dietary vitamin K appears to be protective of bone quality and a risk of fractures.

As an example, in a 2004 article by Dr. Booth and colleagues published in *The Journal of Clinical Endocrinology and Metabolism,* low plasma levels of phylloquinone, or vitamin K1, were linked to low bone mineral density at the hip for men, and at the spine for postmenopausal women not using estrogen replacement. No associations were seen for premenopausal or postmenopausal women with estrogen, suggesting an interplay between estrogen status and vitamin K status.

A meta-analysis of nearly 81,000 participants by Dr. Hao and colleagues published in the journal *Medicine* showed that those with the highest intake of dietary vitamin K had the lowest risk of fractures. This meta-analysis included peer-reviewed research from the United States, Denmark, Norway, and China between 1999 and 2012, and looked exclusively at phylloquinone intake among adults over age 30.

BRAIN HEALTH

Regarding brain health, scientists have identified vitamin-K-dependent proteins that have neuroprotective effects, regulate communication between nerve cells, and even regulate cell growth.

ACCUMULATING EVIDENCE SUGGESTS THAT ADEQUATE DIETARY VITAMIN K IS PROTECTIVE OF COGNITIVE FUNCTION AND HAS A ROLE IN PREVENTING DEMENTIA.

For instance, in a sample of 320 older adults free of cognitive impairment, Dr. Presse and colleagues showed that those with a high phylloquinone status showed better verbal episodic memory

performance (e.g., memory of events) compared to those with low phylloquinone status. This 2013 study used data from the Québec Longitudinal Study on Nutrition and Successful Aging and was published in *Neurobiology of Aging*.

More recently, a 2022 study by Dr. Booth and colleagues in the journal *Alzheimer's & Dementia* found that higher vitamin K2 concentrations (MK4) in the brain of 325 participants was associated with a 17-20% lower risk of dementia or mild cognitive impairment. Data were based on the Rush Memory and Aging Project (MAP), a longitudinal study in the Chicago area that examines genetic and environmental risk factors for Alzheimer's disease.

Higher concentrations in specific regions were linked to better cognitive function scores before death and slower rates of cognitive decline. Circulating phylloquinone was also associated with better cognitive function and slower rates of cognitive decline. Authors suggested that if well-designed follow-up studies could determine mechanisms for dietary vitamin K slowing cognitive decline, this could have a significant public health impact.

CARDIOVASCULAR HEALTH

There are vitamin-K-dependent proteins like matrix Gla protein that help inhibit blood vessel calcification. In this way, scientists have hypothesized that vitamin K has a role in preventing cardiovascular diseases.

A 2017 review of observational and clinical studies by Drs. van Ballegooijen and Beulens published in *Current Nutrition Reports* summarizes key evidence showing that low vitamin K status may increase risk factors for cardiovascular disease.

Though findings were mixed for healthy populations, low vitamin K status appeared to have the most detrimental effects for groups with comorbidities, like Type 2 diabetes, hypertension, and kidney disease, which are risk factors for cardiovascular disease.

A 2021 review in *Advances in Nutrition* by Dr. Shea and colleagues supports that rigorous and reproducible studies are still needed before we can conclude that vitamin K is cardioprotective and the amount needed for cardioprotection.

At the same time, because vitamin K is found primarily in leafy green vegetables and plant oils, adequate vitamin K intake usually reflects healthy diets and lifestyles, which are inherently cardioprotective. It may not be possible to eliminate these confounding effects fully.

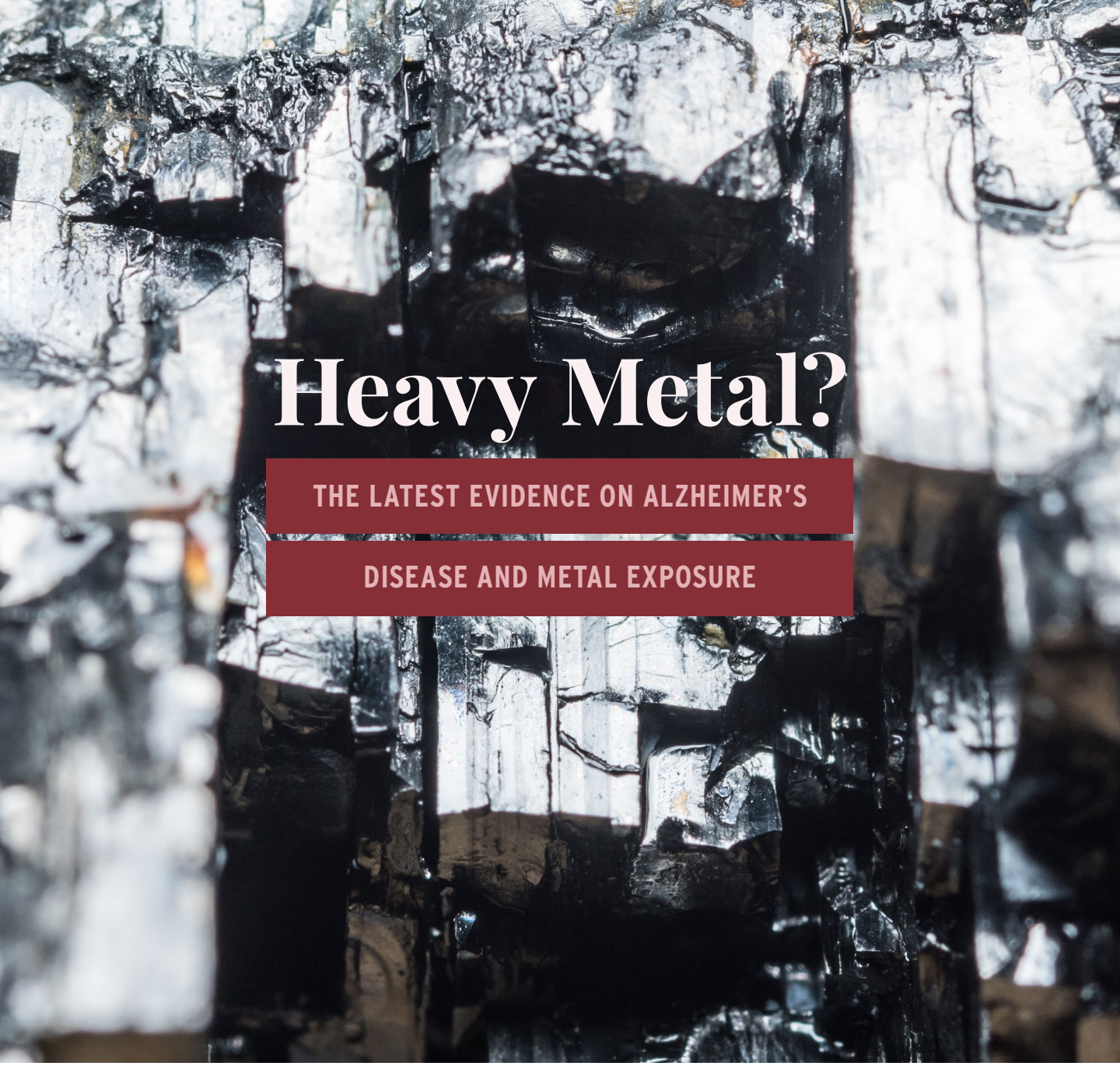
Overall, our bodies need vitamin K to function optimally throughout our lifespan.

Much of the research on the benefits of vitamin K points to the importance of adequate intake. While vitamin K deficiency has been seen to impair a range of metabolic systems, data are inconclusive about whether additional vitamin K intake beyond recommended amounts through diet will have clear benefits. What we do know is that foods rich in vitamin K are part of a healthy, balanced diet, so be sure to get enough every day.

PAVE THE WAY FOR VITAMIN K

Even though our bodies can produce and store limited quantities of vitamin K and even recycle it, we must eat foods with this essential vitamin every day. Here are some simple ways to meet your daily requirement:

- **If a raw salad just doesn't appeal to you, try cooking your greens and adding them to your favourite dishes. Unlike some other vitamins (e.g., vitamins C and E), cooking greens like spinach and cabbage does not break down vitamin K.**
- **Sprinkle fresh or dried herbs like parsley, thyme, or mint on your meal. Drying herbs concentrates vitamin K.**
- **Swap out the corn oil and cook with soybean, olive, or canola oil. Vitamin K is very resistant to heat, so when you cook with it, there is no vitamin loss.**
- **Reach for herb-infused oils like olive oil with basil to get a dose of vitamin K from two sources at once.**
- **Buy plant oils in dark bottles or cover with aluminum foil and place in a cupboard. Vitamin K breaks down when exposed to sunlight and fluorescent light.**



Heavy Metal?

THE LATEST EVIDENCE ON ALZHEIMER'S DISEASE AND METAL EXPOSURE

Recently, a study by Consumer Reports found lead and cadmium in several popular dark chocolate bars, leading many of us to give up our favourite treat. The study found that for 23 of 28 bars tested, consuming the very modest serving size of just one ounce daily would exceed levels considered harmful to health for at least one of these metals, according to limits established by the California Office of Environmental Health Hazard Assessment.

METALS ARE WIDESPREAD IN OUR ENVIRONMENT. ONCE INHALED, INGESTED, OR ABSORBED, THEY CAN REACH THE BRAIN AND MAY HARM BRAIN HEALTH, DEPENDING ON THE DEGREE OF EXPOSURE.

Mind Over Matter® rounded up the latest evidence and spoke to experts about common metals and their potential links to Alzheimer's disease (AD). This article summarizes what's known about lead, cadmium, aluminum, manganese, and iron relative to AD, plus some surprising facts about exposure risks.

We also discuss what to do if you suspect you have been exposed to dangerous levels of metals.

DESCRIBING METALS THAT AFFECT HUMAN HEALTH

Many articles and news stories about the health risks of metals equate "heavy" with toxicity, which isn't accurate. Technically, a heavy metal has a high atomic mass on the periodic table of

elements. But without a chemistry degree, it's tricky for the average individual to use the correct terminology.

"Grouping metals as essential versus non-essential is a more meaningful way to categorize metals affecting human health," said environmental health scientist Dr. Kelly Bakulski, associate professor of epidemiology at the University of Michigan School of Public Health.

"Non-essential metals, like lead and cadmium, are not required for bodily functions and are toxic at higher doses. By contrast, essential metals such as manganese and iron are needed by the body. Health problems result when essential metal levels are too high or too low."

NON-ESSENTIAL METALS

LEAD

Toxicity from lead exposure is a historic and modern health issue. Public health measures to remove lead from paint and gasoline were successful, but it remains in contaminated soil and dust.

If your home was built before 1970 and has paint containing lead, you may be inhaling lead in dust. Older plumbing may also contain lead, as seen in Flint, Michigan, in 2014 when corroded pipes leached dangerous amounts of lead into the drinking water. Lead is also still used in many industrial processes, such as the manufacturing of automobile batteries and electronic waste recycling.

Lead can be ingested, inhaled, or absorbed through the skin and then can enter the bloodstream.

"Lead has a similar size and charge as calcium, a key element for building bone. When lead circulates in our body, it can take calcium's place," explained Dr. Bakulski, lead author of a comprehensive review of exposure to lead, cadmium, and manganese and their relationships to AD and related dementias published in 2020 in *Journal of Alzheimer's Disease*.

"A large portion, 70 to 95%, of lead absorbed in early and middle years gets stored in bones. It can re-enter the bloodstream decades later during accelerated bone turnover that occurs with aging or osteoporosis and then travel to the brain."

Lead that crosses the blood-brain barrier can cause oxidative stress, altered signalling of essential metals, neuroinflammation, overstimulation of neurotransmitters, and the death of neurons.

Animal models of lead exposure in mice and monkeys have demonstrated elevated levels of hallmark signs of AD-related neurodegeneration, including precursors of amyloid-beta, and tau, as well as memory deficits.

Human population studies have found an association between lead exposure and neurodegeneration. While lead has been associated with cognitive impairment and cognitive decline over time, there is currently no prospective evidence linking lead exposure directly with AD risk, Dr. Bakulski said.

CADMIUM

Cadmium is a known cause of cancer, according to the World Health Organization's International Agency for Research on Cancer. The U.S. Centers for Disease Control and Prevention's Agency for Toxic Substances and Disease Registry (ATSDR) notes that breathing high levels can cause severe lung damage, consuming high amounts in food or drinking water can severely irritate the stomach, and long-term exposure increases the risk of kidney damage, osteoporosis, hypertension, decreased lung function, and diabetes.

Some cadmium is found in all soil and rocks.

DIET IS THE PRIMARY CADMIUM EXPOSURE SOURCE: ALL FOODS CONTAIN LOW LEVELS OF CADMIUM, WITH THE HIGHEST FOUND IN SHELLFISH, KIDNEY MEATS, AND LIVER.

Drinking water can be contaminated, and inhalation exposure can occur by breathing air in or near workplaces where cadmium is processed, such as mining and refining, waste disposal and incineration, and phosphate fertilizer manufacturing.

Cigarette smoke is another source of inhalation exposure of cadmium for smokers and non-smokers alike.

"Normally, only small amounts of cadmium can cross the blood-brain barrier in adults," explained Dr. Bakulski. "But when inhaled, it interacts directly with the olfactory bulb, bypassing the blood-brain barrier. Tobacco is one of the best plants at accumulating cadmium from soil and concentrating it in its leaves."

"Animal models have shown cadmium directly causes oxidative stress, neuroinflammation, and the death of brain cells. It may also induce toxicity by changing the permeability of the blood-brain barrier, leading to the production of amyloid beta and tau tangles," said Dr. Bakulski.

"There are emerging studies linking cadmium exposure in humans with AD. Aging studies have found it is associated with cognitive impairment and AD features, but more research is needed to understand how cadmium moves into and affects the human brain." →

ALUMINUM

In the 1960s and 1970s, many people worried about exposure to aluminum from pots and pans, beverage cans, and antacids after aluminum emerged as a potential risk factor for AD. Since then, studies have failed to confirm that aluminum causes AD, and few experts believe everyday sources of aluminum pose health risks, according to the Alzheimer's Association.

They state that age is by far the greatest risk factor for AD, and other factors, such as a family history of disease and head injury, can increase the odds.

Exposure to aluminum mainly occurs through processed food, water, and products containing aluminum, such as antacids, analgesics, and medications for treating diarrhea or ulcers, according to the ASTDR. People working in aircraft, car, and metal products manufacturing facilities may have a higher risk of exposure.

"Rats given aluminum chloride are used to model Alzheimer's disease in scientific studies and to evaluate potential treatments," said Dr. Allison Reiss, an associate professor at the NYU Grossman Long Island School of Medicine and a member of the Alzheimer's Foundation of America's Medical, Scientific & Memory Screening Advisory Board. "The aluminum chloride administration mimics impaired learning and memory and brings on the accumulation of amyloid plaques."

IN HUMANS, ALUMINUM IS POORLY ABSORBED THROUGH ORAL OR INHALATION EXPOSURE. IT BINDS TO VARIOUS RECEPTORS IN THE BLOOD AND CIRCULATES TO ALL AREAS OF THE BODY, WITH THE HIGHEST LEVELS FOUND IN THE LUNGS AND BONES.

Major deodorant brands offer aluminum-free formulations, although this may be a marketing gimmick as they do not make overt health claims about the lack of aluminum: Their websites say only that these products help you "start your day with confidence" or "freshen up" with a "gentle deodorant that delivers 48-hour protection and the care you deserve."

Still, the worry about potential links between aluminum and human neurodegenerative diseases persists. Researchers at the University of Toronto and Louisiana State University conducted the largest study of aluminum concentration in post-mortem brain tissue of individuals who had neurological and neurodegenerative diseases. Their paper was published in *Journal of Alzheimer's Disease & Parkinsonism* in 2019.

The investigators examined 511 brain samples from individuals affected by one of 18 different neurodegenerative diseases and two matched control groups. They found a statistically significant trend for increased aluminum in the brain tissue of people diagnosed with AD, Down syndrome, and dialysis dementia syndrome compared to age- and gender-matched control samples from the same brain areas.

They did not find an increase in the other disorders investigated, which included Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis.

"Many studies show an association between higher aluminum exposure and neurodegeneration, and chronic high levels of aluminum do result in neurotoxicity in the human brain," noted Dr. Reiss. "However, we don't have causal evidence showing it's a major player."

ESSENTIAL METALS

MANGANESE

Manganese is essential for several body functions, including bone growth, blood clotting, carbohydrate metabolism, immune response, and brain function. Most manganese in our bodies comes from eating whole grains, rice, nuts, and leafy vegetables.

Elevated levels of manganese in drinking water or air are neurotoxic, impairing cognitive function that may contribute to AD development.

Excessive workplace exposure to manganese can occur in mining, welding, and battery manufacturing. A large exposure to manganese can accumulate in the brain, causing an irreversible Parkinsonian syndrome called manganism.

Dietary manganese moves across the blood-brain barrier in a regulated fashion. However, when inhaled, it is absorbed through the olfactory bulb in the brain, bypassing the blood-brain barrier, said Dr. Bakulski.

"Animal models have demonstrated that excessive manganese levels cause oxidative stress and an accumulation of amyloid beta and tau tangles. In human epidemiologic studies, researchers have found manganese bound to amyloid beta and identified that elevated manganese levels found in occupational settings were associated with cognitive decline," noted Dr. Bakulski.

"However, a direct causal relationship between excessive manganese and AD has not yet been found and will require further studies."

IRON

Iron is one of the most critical essential metals in the body. We obtain it primarily from dietary sources, including meats, poultry, seafood, and fortified bread and cereal.

Almost half of the iron in our bodies is bound to hemoglobin, enabling blood to transport oxygen to our cells. In the brain, iron is involved in myelin sheath formation, neurotransmitter production, and antioxidant enzyme function. The blood-brain barrier regulates its entry and exit from the brain.

Dr. Julie Schneider is the Deborah R. and Edgar D. Jannotta Presidential Professor of Pathology (Neuropathology) and Neurological Sciences and the Associate Director and Neuropathology Core Leader of the Rush Alzheimer's Disease Center at the Rush University Medical Center in Chicago.

Together with colleagues from the University of Melbourne in Parkville, Australia, she studied the relationships between brain iron levels and AD's biological signs and clinical outcomes. They published their findings in *Molecular Psychiatry* in 2020.

They examined brain tissue generously donated by participants in the Rush Memory and Aging Project, an ongoing long-term study collecting nutrition habits and cognitive assessment and neurological exam results of individuals without dementia when they entered the study.

"We found iron accumulation was only weakly associated with amyloid and tau. However, it was strongly associated with the rate of cognitive decline, even when iron levels were normal," said Dr. Schneider.

> *Our findings suggested iron plays a role in AD cognitive decline that is independent of amyloid or tau accumulation.*

Dr. Schneider and her collaborators suspect iron leads to neurodegeneration when iron is stored by the protein ferritin, which provokes a cell death process called ferroptosis. According to their preliminary data, Dr. Schneider and colleagues further hypothesize that dietary fats elevate brain iron, and iron interacts with brain lipids to instigate this cell death process.

They are now conducting more studies to explore these hypotheses, including how these mechanisms may differ in the presence of misfolded proteins associated with AD, and by sex and APO4E status, the genetic marker associated with an increased risk of developing AD. A grant from the National Institutes of Health funds their work.

PROTECT YOUR BRAIN HEALTH

Limiting exposure to non-essential metals at home or in the workplace will help protect your brain health. For example, quitting smoking or reducing your exposure to second-hand smoke, testing your soil and paint for lead if you're living in a home that was built before 1970 , and testing your drinking water and using a filter or drinking bottled water if lead levels are high, are great ways to lower your risks.

> *Symptoms of severe metal poisoning include abdominal pain, dehydration, diarrhea, nausea or vomiting, and a scratchy throat.*

Severe symptoms include an abnormal heartbeat, anemia, brain damage, memory loss, kidney damage, liver damage, and miscarriage. Keep in mind that many other conditions can cause these symptoms, making metal poisoning challenging to diagnose.

If you have been exposed to elevated levels of non-essential metals, speak to your doctor about testing, which may include blood work, urine testing, X-ray imaging, and kidney and liver function tests. Treatment may involve taking medications or stomach pumping to remove the excess metal or hemodialysis to treat kidney failure.

So, is it safe to eat dark chocolate? Without access to an accredited food testing lab, it's hard to know whether your favourite bar has unsafe levels of lead or cadmium.

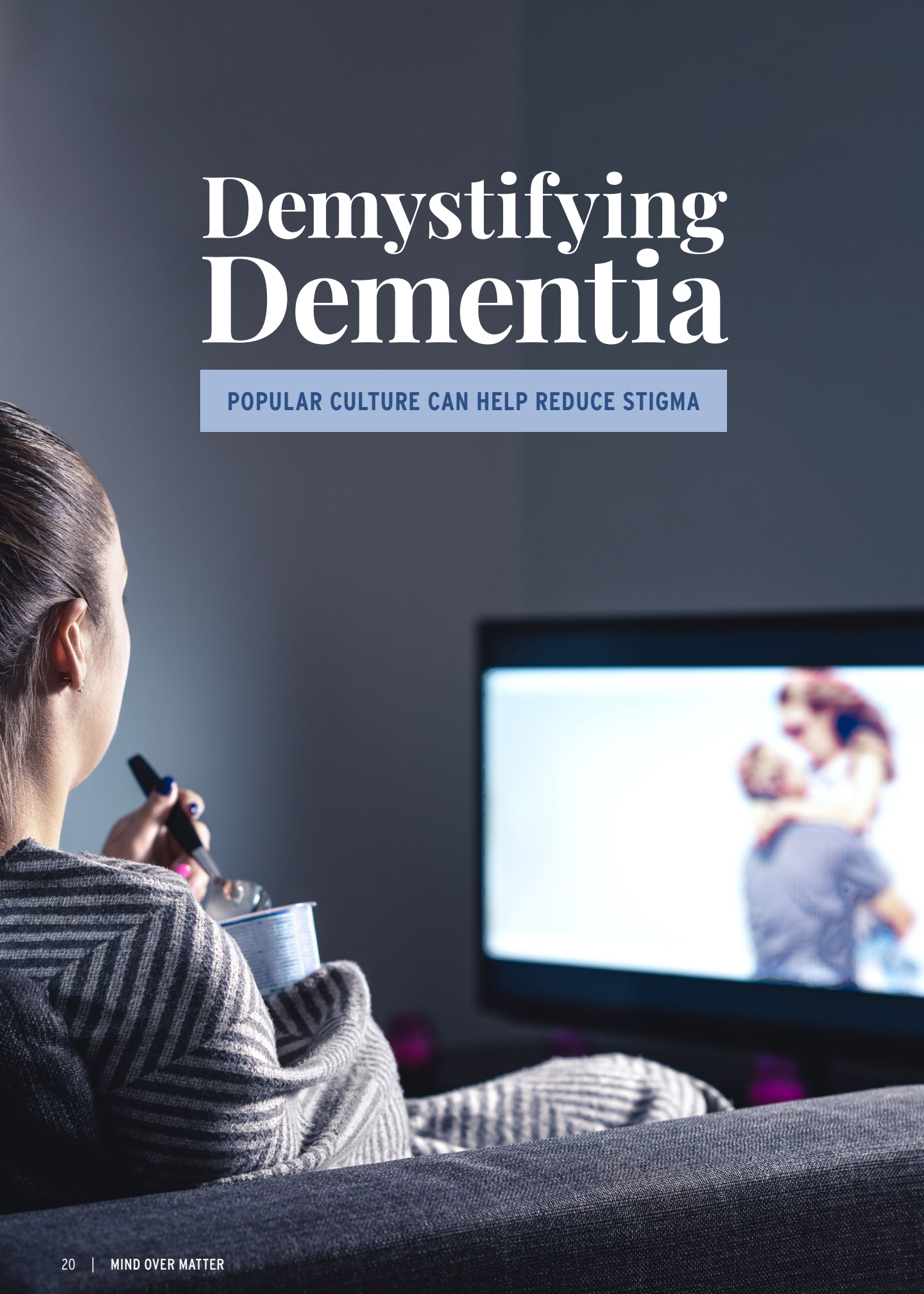
"The lead and cadmium levels found in the Consumer Reports study were concerning, especially since the serving size was quite modest," Dr. Bakulski said. "However, individuals should not bear the burden of deciding whether foods are safe. Public health authorities should better regulate industries, ensuring the right tests and steps are in place to reduce non-essential metals in food products, and then educate consumers about less dangerous choices. We already have national food safety standards for cadmium in rice, so we should be able to establish standards in other industries."

MORE INFORMATION ON TOXIC METALS

The U.S. Centers for Disease Control and Prevention's Agency for Toxic Substances and Disease Registry produces summaries of hazardous substances in a series called ASTDR ToxFAQs™. Learn more at https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx

Demystifying Dementia

POPULAR CULTURE CAN HELP REDUCE STIGMA



Literature, cinema, and the news media play a pivotal role in both mirroring and moulding societal perceptions of dementia, consequently influencing the stigma associated with it.

Examples like *The Notebook, Away from Her, The Father,* and *Still Alice* readily come to mind. Some of these works excel in authentically depicting the complexities and hardships of dementia, while others inadvertently reinforce prevalent stereotypes.

Those living with dementia have emerged as increasingly vocal advocates, boldly addressing the discrimination and the persistent dearth of knowledge and respect they encounter within the healthcare sector and the broader community.

Endeavouring to "see through the eyes" of someone living with the illness becomes the single most influential insight we can provide to care partners and the broader community, fostering a deeper understanding of their individual experiences and the need for change. Read on to learn about several people who've taught us more about dementia by sharing their stories.

GAVIN CRAWFORD

There is a fine line between tragedy and comedy, a line that Gavin Crawford has walked throughout his career as a comic. The host of CBC Radio's *Because News* and alumnus of *This Hour Has 22 Minutes* often infuses a twinge of sadness into his performances.

"The world is a sad and ridiculous place, and that's where I find a lot of comedy," he told Mind Over Matter®.

Crawford explored that boundary between tears and laughs in a deeply personal way when he embarked on a podcast about his mother Donna's experience with Alzheimer's disease (AD). In the seven episodes of *Let's Not Be Kidding*, he paints a loving, wry portrait of an endearingly quirky woman who was a tart-tongued, fierce protector of her gay son. He calls his mom his best friend and the inspiration for much of his comedy.

Crawford frankly describes her gradual loss of memory, while finding moments of hilarity, such as when she decided that his husband, Kyle, was the inventor of Christmas trees, or when they gave her marijuana as a possible treatment and saw her expertly inhaling a joint, even though she claimed she had never tried it before.

"A thing that happened was that I could talk about it in a funny way. I learned how to navigate the sadness, grief, and the humour," he said.

Crawford mixed in conversations with such other entertainers as Jann Arden and Scott Thompson who shared their experiences with parents with dementia. He said part of his motivation for creating the podcast was to give other people facing the same challenges a sense of what they could expect.

> **YOU DON'T REALIZE WHEN YOU'RE GOING THROUGH IT HOW LITTLE YOU TALK ABOUT IT WITH OTHER PEOPLE, EVEN IN YOUR OWN FAMILY. EVERYONE HAS A DIFFERENT EXPERIENCE, BUT WE DO HAVE SIMILARITIES THAT EVERYONE GOES THROUGH. I THOUGHT, THIS WOULD HAVE BEEN GOOD FOR ME TO KNOW, OR TO UNDERSTAND THAT YOU'RE NOT THE ONLY ONE.**

Perhaps the most heartbreaking moment was when he had to take his mother to a long-term care facility for her own safety, and Donna tearfully begged him not to leave her there. In the podcast, the guy who makes a living making people laugh broke down while recalling the memory.

"You're going to feel like the worst person in the world. But you have to do these really hard things for their safety. You really do feel like a villain out of [a] Roald Dahl [book]. It seems so harsh, but it's actually the least harsh thing you can do."

Artists have always drawn upon personal experiences for inspiration. With society speaking more frankly now about dementia, it is a theme that many are exploring.

TONY WANLESS & JUNE HUTTON

When journalist Tony Wanless discovered he had young-onset AD, he told his wife, June Hutton, a journalist and writer, that they should collaborate on a book about the experience.

"He really wanted to be able to reach out to people and teach them. He was very pro-medication after he was prescribed Aricept and found it made a difference for him. He wanted everyone to know it was a good thing and he would love to get on stage to talk about it," Hutton told Mind Over Matter® in an interview from her home in Vancouver.

"He had this whole plan, including the title, but he kept forgetting."

The title of their book, *Four Umbrellas, A Couple's Journey Into Young-Onset Alzheimer's*, came from an incident when Wanless packed four umbrellas for a trip, a metaphor for what the disease does to the brain. →

With his memory constantly eroding, Hutton became the principal narrator, with Wanless's observations inserted throughout. As the book progresses, the effects of the disease are evident, as he starts making an increasing number of errors in his copy, something that would have never happened before in a man who was a stickler for spelling and grammar.

"It was sometimes exciting, and other times heartbreaking because he was such a smart guy," said Hutton.

They frankly and honestly mined even the most challenging moments, aiming to give a true account of their experiences.

"When he would get angry with me, I'd say 'write that down … that's a perfect nugget.'"

Although they were telling a difficult and painful story, Hutton said writing a book together helped them get through it.

"It all helped when you're handed something as dreadful [as Alzheimer's]. We chose a creative response for us. It gave us a project during the pandemic in which we worked together. It was a bonding process."

Others who were going through a similar experience were hungry for knowledge about dementia.

Early this year, when she finally had to place Wanless in a care home, the staff bought several copies of the book and shared it with other families. In retrospect, Hutton believes that Wanless was showing early signs of AD as much as 20 years earlier, but they believed he was just an "absent-minded professor" type. Now she is angry that they had such difficulty getting his doctors to pay attention, a message she hopes readers will absorb.

"I'm hoping they come at their doctors hard. The doctors don't take it seriously. People should go in mad as hell, and it's usually women, because they're the caregivers."

JENNIFER DANCE

Jennifer Dance was also motivated to tell a story about the challenges faced by care partners. Her novel *Gone but Still Here* is infused with insights drawn from her time caring for her longtime partner Feroze.

"It was my personal experience of being a caregiver that drove me to it. I was having such a hard time and wanted to try and give other people a heads up. I tell people that if I had not put Feroze in long-term care three years ago, I think I would be dead now," Dance told Mind Over Matter®.

In the novel, the character of Mary struggles to finish a book about her late first husband, Keith, and their challenges as an interracial couple coping with bigotry in the 1970s, a story that mirrors Dance's real-life experiences. She was also married to a Black man named Keith who died young.

Mary's task is complicated by the progress of dementia. Jennifer Dance does not have AD but was diagnosed with mild cognitive impairment, a precursor to dementia.

"I related to Mary's struggles to get the story down, and that's why I wanted to tell the story of Keith. He was my first love, and for me to survive losing him the way that I did, I had to push his memory down. Keith needed to come back into my mind and my story."

Dance also feels deep gratitude for the people offering support programs through the Alzheimer Society of York Region and wanted to share her experiences to give back to those who helped her and Feroze in a time of deep need. She believes that it's helpful to see more stories about dementia in popular culture.

> **I THINK IT'S GREAT BECAUSE UP UNTIL FAIRLY RECENTLY, ALL MENTAL HEALTH ISSUES HAVE BEEN TABOO, BUT A WHOLE LOAD OF PEOPLE ARE GOING THROUGH THIS, AND I DON'T THINK THERE'S BEEN ENOUGH SUPPORT FOR THEM AND THE CAREGIVER. IT'S SUCH A STRUGGLE.**

Jennifer Dance, June Hutton, and Gavin Crawford all said that telling their stories was therapeutic. In Crawford's case, he finds that he cannot watch movies like *Still Alice* or *The Father* that tell fictional stories about dementia. He is always listening to people relating their real-life experiences. Since his podcast came out, many people have contacted him.

"It's become a much larger thing than I ever anticipated doing. I get feedback almost daily, with people writing, 'You don't know me, but this is what's happening with my loved one.' They share their stories with me, which is actually great because I know they really need to."

Reducing stigma is an important step in improving the well-being of people with dementia and helping to protect against social exclusion. By dismantling misconceptions and stereotypes surrounding dementia, we can create a more inclusive and compassionate society that supports those affected by this condition, ultimately enhancing their quality of life, and ensuring their rightful place in our communities.

Kidney Disease & Cognitive Impairment

AN UNDERRECOGNIZED CONNECTION

You probably don't give your kidneys much thought. But the bean-shaped, fist-sized organs below your rib cage on each side of your spine filter about 142 litres or 150 quarts of blood daily, removing toxins and extra fluid from your blood so you can excrete them in urine.

Your kidneys maintain a healthy balance of salts, minerals, and water in your blood and also make hormones that control blood pressure, make red blood cells, and keep your bones strong.

People with kidney disease have damaged kidneys that no longer filter blood properly. You may already know that rising waste products in the blood can cause serious health complications, including high blood pressure, cardiovascular disease, anemia, weak bones, nerve damage, and poor nutritional health. Left untreated, kidney disease →

can progress to kidney failure, requiring life-saving kidney replacement treatment with dialysis or kidney transplantation.

You may not realize there is a link between kidney disease and cognitive impairment and dementia.

In this article, we share the latest evidence on the connection between kidney disease and cognitive impairment, explain why it matters, and discuss promising new technology researchers are using to learn more about the nature of neurological deficits in patients requiring dialysis.

HOW UREMIC TOXINS AFFECT BRAIN HEALTH

In their 2019 literature review in *Brazilian Journal of Nephrology*, researchers identified the following relationships between uremic toxins and various cognitive domains:

- uric acid: poorer attention, visual processing speed, and working memory;
- indoxyl sulphate and p-cresyl sulphate: poorer cognitive function in early stages of chronic kidney disease;
- homocysteine: greater cognitive and motor impairment, especially regarding frontal-executive function, attention, verbal memory, fine motor speed, processing speed, episodic memory, and visual, spatial, language, and constructional ability;
- interleukin 1-beta: impairments in multiple domains;
- interleukin 6: poorer executive function, aging processes, degeneration of interneurons responsible for processing, encoding, and retrieving information, and problems with auditory recognition memory, attention memory, and working memory, but not general memory; and
- parathyroid hormone: increased brain circulating and neuronal calcium levels causing changes in brain function, reduced cerebral blood flow, and behavioural and motor abnormalities.

KIDNEY DISEASE AND DEMENTIA

According to a review paper by nephrologists at Tufts Medical Center in Boston, published in *American Journal of Kidney Disease* in 2019, as many as 40% of people with chronic kidney disease (CKD) have cognitive impairment, and people with CKD have a substantially higher risk for cognitive deficits than the general population.

The overall prevalence and magnitude of cognitive dysfunction in people with CKD have been controversial. Researchers at Queen's University and Kingston Health Sciences Centre (KHSC) in Kingston, Ontario, conducted a meta-analysis and systematic review of 148 published, peer-reviewed articles to shed light on the degree of cognitive decline in people with CKD.

Dr. Jessica Vanderlinden, then a PhD candidate, and her research supervisor Dr. Gord Boyd, an associate professor of neurology at Queen's University and a critical care doctor and neurologist at KHSC, published the results of their study in *Nephrology* in 2019.

Pre-dialysis and dialysis patients had significant deficits in global functioning, attention, and processing speed compared with people without kidney disease, according to scores on common cognitive assessments such as the Mini-Mental State Examination (MMSE).

However, the average MMSE score for these patients as a group was above the standard cut-off for identifying cognitive impairment, meaning the MMSE was not sensitive enough to identify cognitive deficits in many individuals.

"The MMSE is convenient and quick to administer, but it is heavily weighted toward attention, language, and memory and only includes one point for the perceptual-motor domain," said Dr. Boyd.

In his virtual Grand Rounds presentation for the Ottawa Hospital in April 2023, Dr. Boyd shared a compelling photo to underscore the importance of finding a better method for assessing cognitive dysfunction in patients with CKD.

The image showed a very banged up car parked in the hospital parking garage in the spot allocated for dialysis patients. The adjacent pillars were scratched and chipped, indicating many vehicles had hit them. "The photo illustrates that the degree of visual-spatial and executive function impairment experienced by dialysis patients is quite pronounced and interferes with their daily lives," Dr. Boyd said.

In their review paper, the nephrologists at Tufts Medical Center speculated that the higher rate of cerebrovascular disease in individuals with CKD is likely driving the association with dementia. They also said toxic substances that build up in the blood as kidney function declines, called uremic toxins, depression,

KIDNEY FUNCTION TESTS

Early kidney disease usually has no symptoms, and 40% of people with severely reduced kidney function who are not on dialysis are unaware they have chronic kidney disease (CKD), according to the Centers for Disease Control and Prevention.

The most common causes of CKD are diabetes and high blood pressure. The National Kidney Foundation advises that long-term, high-dose use of pain medicines, such as ibuprofen, naproxen, and higher dose aspirin, can cause CKD.

Kidney function testing is essential, especially if you have diabetes, high blood pressure, heart disease, or a family history of kidney failure. Ask your doctor if kidney function tests are included as part of your annual physical. Early diagnosis means faster access to treatment to help protect your kidneys from further damage.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), your doctor will use these tests to check how well your kidneys are functioning:

- A blood test to calculate your estimated glomerular filtration rate (GFR) based on the levels of creatine in your blood, a waste product of normal muscle breakdown in your body. A GFR of 60 or higher is considered in the normal range, while less than 60 may indicate you have kidney disease. A GFR of 15 or less indicates kidney failure. Most individuals with a GFR below 15 need dialysis or a kidney transplant.

- A urine test to measure the presence of albumin, a protein that indicates kidney damage. Healthy kidneys don't let albumin pass into urine, so less albumin in urine indicates better kidney health. The urine albumin-to-creatinine ratio estimates how much albumin passes in urine over 24 hours. A urine albumin-to-creatinine ratio of 30 mg/g or less is normal, while more than 30 mg/g may indicate kidney disease.

Keep in mind that a decline in kidney function is normal as you age and may not be a sign of kidney damage, according to the National Kidney Foundation. You're born with about a million nephrons in each kidney but lose some over time, and others may not function as well as when you were younger. Your doctor will provide guidance on your test results.

sleep disturbances, anemia, and taking multiple prescription medications may also be contributing factors.

Researchers from Brazil published a literature review in *Brazilian Journal of Nephrology* in 2019, that summarized the specific impact of uremic toxins on different cognitive domains. They wrote that the uremic toxins likely harm cognitive function in two ways: direct neurotoxicity and harm to the cerebral endothelium, the latter resulting in oxidative stress, disruption of the blood-brain barrier, and chronic inflammation.

DETECTING COGNITIVE IMPAIRMENT IN PATIENTS WITH END-STAGE KIDNEY DISEASE

Studies have shown that cognitive impairment is highest among individuals with kidney failure requiring dialysis. "There is a complex interplay between the brain and the kidneys. Hypertension, diabetes, elevated cholesterol, and smoking are shared risk factors between kidney disease and brain disease. CKD adds additional burdens on brain health in the forms of persistent inflammation, chronic uremia, and arterial stiffness," said Dr. Boyd.

> *Dialysis has further negative impacts on the brain, including recurring reduced blood flow, white matter damage, and a loss of nerve fibres that carry messages.*

Dr. Boyd has been testing whether a new technology called the Kinesiological Instrument for Normal and Altered Reaching Movement (KINARM) device can more accurately detect cognitive deficits in intensive care patients with CKD and acute kidney injury than a standard assessment. ⟶

KINARM combines robotics and brain injury assessment technology. The patient dons a virtual reality visor and uses hand-held controls to perform a series of ten tasks, such as reaching for a target, interacting with a ball, or tracing a trail through a sequence of targets. The KINARM device tracks and measures their movements, providing support and resistance as required, and takes about 45 to 60 minutes to complete.

Dr. Stephen Scott, a professor in the Department of Biomedical and Molecular Sciences at Queen's University, invented KINARM to study how different brain regions are involved in motor control and learning. The technology is based on the fact that upper limb movement provides robust information about brain function.

Over time, he developed tests for analyzing a broad range of brain functions, including motor skills, memory, decision-making, and perception. KINARM software compares participants' test results with those of healthy individuals to identify impairments in numerous domains, including perceptual-motor, complex attention, and executive function.

Dr. Boyd and Dr. Vanderlinden used KINARM to quantify neurocognitive impairment in 21 survivors of acute kidney injury, caused mainly by kidney disease, compared with 21 individuals with similar cardiovascular issues but without kidney disease.

While a standard pen and paper assessment called the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) detected impairment in only 5% of patients, KINARM testing revealed 48% of these patients had visuomotor impairments, 50% had attention problems, and 52% showed impaired executive function, compared to 10%, 10%, and 24%, respectively, for the control group. These study results, published in *Nephrology Dialysis Transplantation* in 2021, were the first to prospectively report on neurocognitive function after an episode of acute kidney injury.

CURRENTLY, THE KINARM DEVICE IS AVAILABLE ONLY FOR CLINICAL RESEARCH TO LEARN ABOUT BRAIN FUNCTION AND DYSFUNCTION IN DIFFERENT PATIENT POPULATIONS.

For example, Dr. Boyd and another one of his students, Tasha Jawa, in the MD-PhD program at Queen's University, are principal investigators of an observational clinical study in progress called the INCOGNITO-AKI study, which will use this tool.

The study aims to enroll 104 intensive care patients with acute kidney injury who initiate kidney replacement therapy. They are measuring patients' cerebral oxygen saturation with a sensor placed on the forehead to see if this assessment could be useful for predicting the risk for long-term neurocognitive impairment.

Study participants return for KINARM and RBANS testing and brain magnetic resonance imaging scans three months and 12 months after their discharge from the hospital. The investigators are also assessing driving safety, adverse events, and medication adherence at 12 months as further indicators of impairment.

An additional strength of using KINARM to assess cognitive impairment in patients with CKD is that the results are compared to age, sex, and handedness-matched controls.

GENERALLY SPEAKING, CKD AFFECTS MORE MEN THAN WOMEN, WHICH IS WHY IT'S IMPORTANT TO LOOK AT SEX DIFFERENCES.

Dr. Boyd explained, "In our initial study looking at KINARM data among CKD patients, being male was an independent risk factor for worse cognitive performance compared with women. The only other demographic factor associated with performance was level of education, which is pretty common in cognition studies."

Clinician scientists continue to investigate new approaches to dialysis to improve patient outcomes, as evidence builds showing older patients undergoing the procedure experience moderate to severe cognitive impairment that affects their quality of life. For example, Dr. Boyd's colleagues are studying whether cooled fluid used for dialysis or providing additional fluids may improve neurological outcomes in ICU patients.

While we await the results of these new developments and further research, the link between kidney and cognitive health is clear, so it's important to be kind to those bean-shaped organs. Your brain depends on it.

TAKING CARE OF YOUR KIDNEY HEALTH

Taking care of your kidney health is essential to your overall health and brain health. "Your brain is a bank," Dr. Boyd said. "The more you invest in healthy habits earlier in life, the more you have to withdraw later."

Incorporating Women's Brain Health Initiative's Six Pillars of Brain Health, including eating a healthy diet, getting sufficient exercise, managing stress levels to keep inflammation in check, and getting a good night's sleep, will help you maintain good kidney health. "If you have diabetes or high blood pressure, make sure they are well-controlled," Dr. Boyd said. "And keep doing your crossword puzzles."

Women & Hypertension

A CONVERSATION WITH NEPHROLOGIST DR. SOFIA AHMED

Nephrologist Dr. Sofia Ahmed is a professor and Chair of Sex and Gender Research in the Faculty of Medicine and Dentistry at the University of Alberta in Edmonton. She received Hypertension Canada's Senior Investigator Award in 2022 for her significant contributions to advancing research into sex-related differences in hypertension and blood pressure.

Dr. Ahmed recently presented at the Healthy Bodies, Healthy Minds event hosted by Women's Brain Health Initiative in Vancouver. We spoke with Dr. Ahmed to learn more about hypertension and how it affects women differently than men, important findings from her research, and where things stand regarding incorporating women into health research in general. →

HOW DOES HYPERTENSION HARM BRAIN HEALTH?

High blood pressure, also known as hypertension, is a leading cause of stroke and kidney disease, which can both lead to cognitive impairment.

THE RELATIONSHIP WITH KIDNEY DISEASE IS A BIT OF A CHICKEN AND EGG SITUATION, AS IT CAN ALSO CAUSE HYPERTENSION.

Uncontrolled hypertension is associated with an increased risk of cognitive decline and dementia, including Alzheimer's disease and vascular dementia, due to damage to blood vessels in the brain. People diagnosed with hypertension can lower their risk for cognitive decline and these dementias by taking their prescribed blood pressure medications.

HOW IS HYPERTENSION DIFFERENT IN WOMEN VERSUS MEN?

The prevalence of hypertension in the U.S. for adults over 20 was about 52% for men versus about 43% for women, according to a review of recent U.S. data published in *Current Hypertension Reports* in 2022.

DESPITE THE LOWER PREVALENCE FOR WOMEN, THE INVESTIGATORS ALSO IDENTIFIED THAT WOMEN EXPERIENCE A STEEPER INCLINE IN BLOOD PRESSURE STARTING IN THEIR 30s AND HAVE A GREATER RISK OF ADVERSE CARDIOVASCULAR EVENTS AT LOWER BLOOD PRESSURE LEVELS THAN MEN.

A Canadian study published in the *Canadian Journal of Cardiology* in 2020 by researchers at the University of Calgary and Hypertension Canada's Research and Evaluation Committee found sex-related differences in hypertension awareness, treatment, and control rates.

Using data from the Canadian Health Measures Survey from 2007 to 2017, the investigators identified almost 6 million people with hypertension, about 23% of all Canadian adults, which remained consistent over the decade.

Overall awareness, treatment, and control were estimated at 84%, 79%, and 65%, respectively, with no changes for men over ten years. However, women's awareness, treatment, and control rates dropped substantially during 2016 to 2017 to 72%, 65%, and 49%, respectively. These results underscore an urgent need for more research and collaborative efforts to address the increase in preventable risk of hypertension for women, especially since women have a higher lifetime risk of stroke and dying from stroke than men.

ARE TARGET BLOOD PRESSURE READINGS THE SAME FOR WOMEN AND MEN?

Yes, but new evidence suggests target readings should be revised to lower thresholds for women. Canadian, U.S., and international clinical practice guidelines have long considered a systolic blood pressure (SBP) of 120 mm Hg and higher as indicating elevated blood pressure, given the evidence of an increased risk of cardiovascular disease starting at that threshold.

Robust data show that blood pressure levels are typically lower in women than men.

For example, investigators at the Cedars-Sinai Medical Center in Los Angeles, California, evaluated sex differences in blood pressure associations with cardiovascular outcomes for more than 27,000 individuals, of which 54% were women.

They found an increased risk of heart attack and heart failure started at an SBP of 130 to 139 mm Hg in men but at a much lower level of 100 to 109 mm Hg in women. Their study was published in *Circulation* in 2021.

WHAT ARE SOME OF THE SEX- AND GENDER-SPECIFIC FACTORS THAT INFLUENCE HEALTH AND DISEASE IN WOMEN?

Many factors affect health and the risk of disease for women over their lifetimes, including the onset of menstruation, regularity of menstrual patterns, pregnancy and complications of pregnancy, hormonal contraception, menopause, menopausal hormone therapy, testosterone levels, and gender-affirming hormone therapy.

Gender-related factors also affect access to care, adherence to medication plans, and selection of treatment options. It's also important to consider gender diversity. Note that here I'm referring to "men" and "women," the common binary terms, because that's what research has reflected to date. But that's certainly not intended to discount gender diversity.

For example, together with my co-authors at the Cumming School of Medicine at the University of Calgary and the Alberta Kidney Disease Network, we studied the risk of hypertension in more than 112,000 Canadian women ages 45 and older taking different formats of estrogen therapy to treat symptoms of menopause.

WE FOUND THAT THE ORAL FORMAT OF ESTROGEN THERAPY WAS ASSOCIATED WITH A 14% HIGHER RISK OF HYPERTENSION THAN THE TRANSDERMAL FORMAT AND A 19% HIGHER RISK OF HYPERTENSION THAN VAGINAL CREAMS OR SUPPOSITORIES.

Nonoral estradiol, a specific form of estrogen, at the lowest dose for the shortest period, was associated with the least risk of developing high blood pressure. Compared to estradiol, conjugated equine estrogen was associated with an 8% increased risk of hypertension.

Our findings were published in *Hypertension* in June 2023. Note that this study examined the use of estrogen-only therapy, which is typically only prescribed for women who have had a hysterectomy. We are planning to conduct further studies to see if the more commonly prescribed combination estrogen and progestin therapy for treating menopausal symptoms has an impact on cardiovascular disease and kidney disease.

By 2025, there will be an estimated one billion menopausal individuals on the planet. Menopausal symptoms can have a huge impact on quality of life, productivity, and social relationships, as we know. But women and healthcare providers also need to be aware that the risk of hypertension varies for different formats of hormone therapy.

WHY IS IT ESSENTIAL TO INCLUDE WOMEN IN HEALTH RESEARCH?

Sex differences in cardiovascular risk due to high blood pressure is a perfect example of why we need more research affecting women's kidney, brain, and overall health. Outcomes and adverse events can vary by sex and gender.

> **THE WAY IN WHICH WOMEN ARE INCLUDED IN RESEARCH MATTERS, TOO. MANY STUDIES INCLUDING WOMEN PARTICIPANTS STILL REPORT OUTCOMES AND ADVERSE EVENTS AS AGGREGATE FIGURES, NOT STRATIFYING RESULTS BY SEX.**

That does a real disservice to everyone because it dilutes any potential benefits observed in one group and, at the same time, minimizes risks that occur in the other group. Further, reporting in the aggregate means that sex-specific evidence cannot be included in future systematic reviews and meta-analyses.

WHAT ARE SOME EXAMPLES OF THE NEGATIVE CONSEQUENCES OF A LACK OF REPRESENTATION OF WOMEN IN HEALTH RESEARCH?

Here is a great example from several years ago. Eight of ten drugs pulled off the market between 1997 and 2000 by the U.S. Food and Drug Administration had greater health risks for women versus men. Researchers had not included female models in basic research, and women were underrepresented in clinical trials, so nobody knew about the risks until after the products were on the market.

> **THINK HOW MANY WOMEN COULD HAVE AVOIDED INCREASED HEALTH RISKS IF RESEARCHERS HAD COLLECTED AND REPORTED SEX-SPECIFIC DATA BEFORE THOSE MEDICATIONS WERE APPROVED AND PRESCRIBED.**

Another example is medications known as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treating heart failure. Observational studies have shown that guideline-recommended target doses compared with lower doses of these medications are associated with improved survival in men but greater mortality in women.

WHERE DO THINGS STAND TODAY REGARDING INCORPORATING SEX AND GENDER INTO HEALTH RESEARCH?

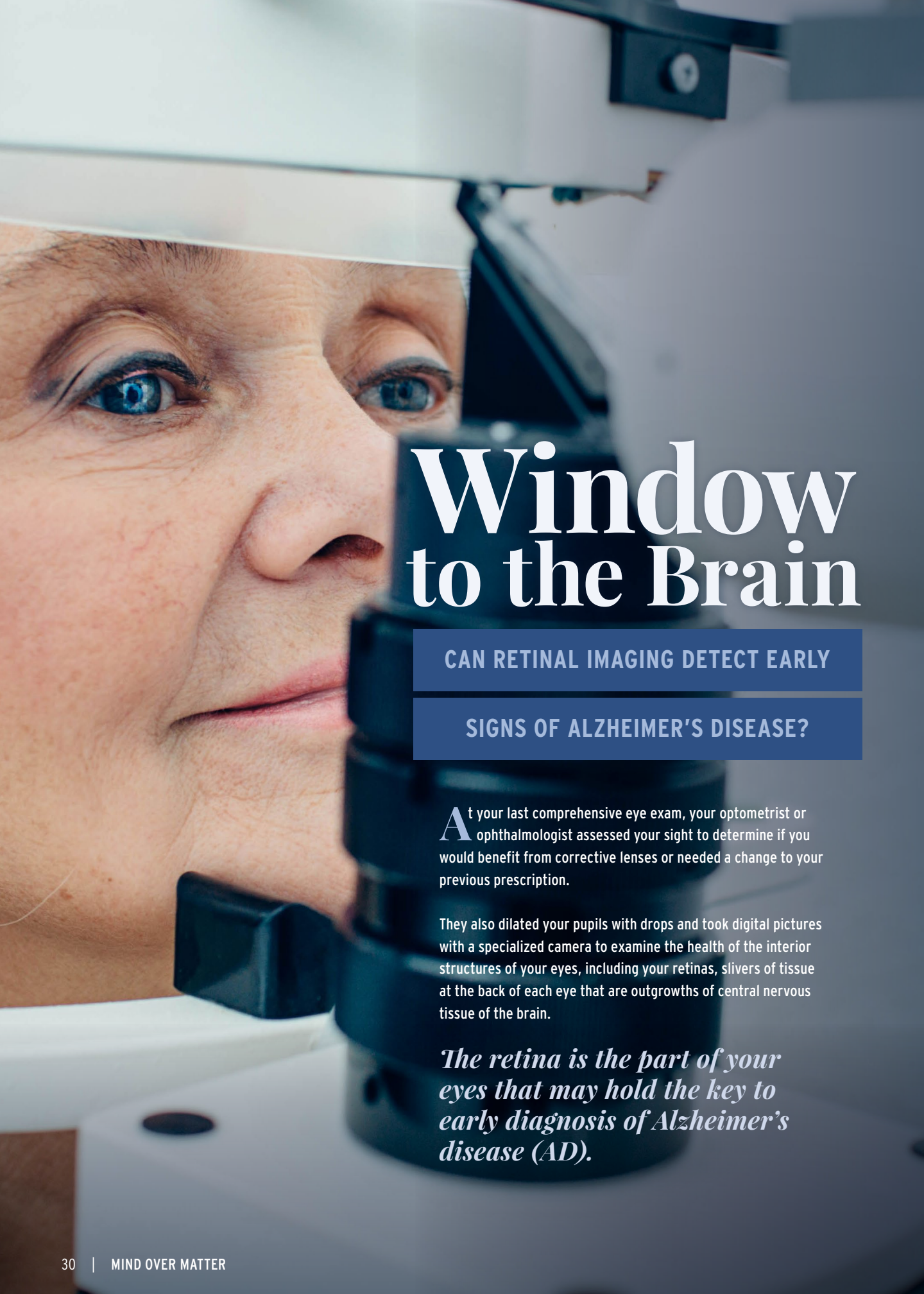
The importance of incorporating sex- and gender-related factors is increasingly recognized in health research in general. Many funding agencies now require scientists to demonstrate in their proposals how they are incorporating sex and gender. More journals are adopting the Sex and Gender Equity in Reporting guidelines in their editorial processes.

There is also a desire to include sex-specific recommendations in clinical guidelines, but that can only happen if evidence is available. I'm on the guidelines committee for Hypertension Canada; we are always scoping the current literature with a view to incorporating sex- and gender-related evidence when we can.

Cardiovascular trials and kidney trials are trending toward including more women, which is great news, but more progress needs to be made. I wrote an editorial published in *Nature Reviews Nephrology* this past April to raise some alarm bells about the dangers of caring for people living with or at risk of kidney disease using a "one size fits all" strategy.

Failure to consider the impact of sex- and gender-related factors on outcomes and adverse events at best limits our ability to treat patients appropriately. It can also lead to serious consequences, including death.

Overall, we need more sex- and gender-specific health research for more informed decision-making. As a clinician, what matters most to me is being able to tell patients, "The study looked at people very similar to you, and this is what they found. Let's talk about whether this treatment is right for you."



Window to the Brain

CAN RETINAL IMAGING DETECT EARLY SIGNS OF ALZHEIMER'S DISEASE?

At your last comprehensive eye exam, your optometrist or ophthalmologist assessed your sight to determine if you would benefit from corrective lenses or needed a change to your previous prescription.

They also dilated your pupils with drops and took digital pictures with a specialized camera to examine the health of the interior structures of your eyes, including your retinas, slivers of tissue at the back of each eye that are outgrowths of central nervous tissue of the brain.

The retina is the part of your eyes that may hold the key to early diagnosis of Alzheimer's disease (AD).

A fundus camera is a low-power microscope attached to a camera used to take images of the interior of your eye.

Neurologists typically diagnose AD through a full clinical workup, including patient history, blood work, and magnetic resonance imaging. They may also assess biomarkers of AD using positron emission tomography (PET) imaging or cerebrospinal fluid (CSF).

These tests are sensitive enough to detect early signs of amyloid accumulation in the brain decades before symptoms appear. However, they are typically expensive, difficult to access, and invasive: PET imaging involves an injection of a radioactive tracer into the blood, and CSF is collected through a needle placed between vertebrae in the spine in a procedure called a lumbar puncture.

Now, an innovative imaging technology called hyperspectral retinal imaging can detect accumulating amyloid in the retina long before symptoms of cognitive decline occur.

If clinical research continues to show positive results, individuals with memory concerns may soon be able to access a five-minute screening test for early signs of AD as part of a comprehensive eye exam at their local optometry clinic.

HYPERSPECTRAL RETINAL IMAGING

Drs. Robert Vince, Swati More, and James Beach, three researchers at the University of Minnesota's Center for Drug Design, needed a way to measure whether an AD drug they were developing in 2014 worked in preclinical mouse models. They created a specialized hyperspectral camera that attached to standard fundus imaging equipment.

"The drug didn't work out, but the hyperspectral imaging concept became the foundation for our retinal imaging technology," said Dr. Catherine Bornbaum, Chief Business Officer at RetiSpec, the Canadian company that licensed the technology and was the first worldwide to use it to test for the detection of early signs of AD in optometry clinics.

Hyperspectral imaging looks for a change in spectral light in regions of the eye. "When amyloid beta proteins begin to aggregate as toxic oligomers, they reflect light differently in a characteristic pattern called the Rayleigh scatter effect. These changes in the retina are not noticeable to the individual and cannot be detected with a standard fundus camera," said Dr. Bornbaum.

RetiSpec is currently conducting clinical trials at multiple optometry clinics in Canada and the United States. At Victoria Village Optometry in Toronto, one of the clinical trial sites, optometrist Dr. Negar Sohbati asks patients over age 55 if they have memory concerns and, if so, offers them an opportunity to participate in the study.

"Patients fall into three categories: they have no memory issues personally and are happy to see this research is taking place; they have noticed memory issues and are interested in a screening test, especially if they have a family history of the disease; or they have noticed some memory lapses but are fearful about finding out their test results," said Dr. Sohbati.

"For the latter group, I tell them participation is voluntary, and there are new treatment options for delaying disease progression in people with early-stage symptoms. Some take time to consider their decision and return for a test at another appointment."

Different from a standard fundus camera that captures red, green, and blue colours, the hyperspectral camera captures more than 100 wavelengths of colour at a very high resolution. Patients see a brief flash of light, the same as any standard fundus camera, as the camera captures the data.

THE DATA IS ANALYZED USING RETISPEC'S ARTIFICIAL INTELLIGENCE ALGORITHMS THAT COMPARE AN INDIVIDUAL'S RESULTS WITH THOSE WHO WERE DIAGNOSED WITH AD USING PET IMAGING OR CSF.

When clinically available, individuals will learn about their test results from their primary care physician or a nurse practitioner. Those with concerning signs of retinal amyloid deposits are referred to a neurologist for memory testing. Dr. Sohbati noted that while many of her patients have indicated they'd like to know their imaging results on the spot, she doesn't have access. RetiSpec's proprietary artificial intelligence algorithms assess the data and generate patient reports.

PRELIMINARY RESEARCH RESULTS

Preliminary findings from clinical trials of RetiSpec presented at a conference in November 2021 included 108 patients with mild cognitive impairment or preclinical AD. Researchers compared the advanced retinal screening test results with PET and CSF results. RetiSpec correctly identified individuals with brain amyloid 86% of the time and correctly identified those without brain amyloid 80% of the time.

While these results were strong, RetiSpec is collecting more clinical trial evidence before applying to Health Canada and the U.S. Food and Drug Administration for approval. Dr. Bornbaum anticipates approvals for everyday use in optometry clinics in early 2025. →

VISION IMPAIRMENT AND DEMENTIA: A TWO-WAY STREET

Vision impairment is common as we age. For many of us, that means losing the ability to see things up close, having trouble distinguishing colours, like black from blue, or needing more time to adjust to changing light levels. Eye diseases and conditions such as age-related macular degeneration, diabetic retinopathy, cataracts, and glaucoma may also reduce our ability to see well as we age.

Despite having healthy eyes, people with dementia may experience vision problems if dementia affects the part of their brain that handles processing visual information, according to the U.K. Alzheimer's Society. For example, one of the characteristic symptoms of progressive supranuclear palsy, a rare neurodegenerative disorder that otherwise mimics Parkinson's disease, is an inability to focus the eyes.

Even though it may be challenging to separate the signs of sight loss from those of dementia because they can overlap, it's essential to ensure individuals with dementia have eye exams because trouble seeing may increase confusion, the U.K. Alzheimer's Society advises.

A person with dementia can have a sight test, despite the common belief to the contrary.

The test can be adapted for people with dementia by allowing more time, asking questions that only have a yes or no answer or don't require a subjective response, and having a care partner accompany them.

It's easy to see how dementias damaging neurons in the brain can cause vision impairment, but the relationship works in the other direction, too. Vision impairment is a risk factor for dementia and accelerating cognitive decline, according to a systematic review and meta-analysis led by researchers at the University of Hamburg, Hamburg, Germany, published in *Journal of Alzheimer's Disease* in 2021.

After pooling evidence from 30 studies, their analysis found a 38% increased risk for all-cause dementia in people with visual impairment. The investigators also identified that diabetic retinopathy and cataract were associated with a 34% and 17% increased risk of dementia, respectively. They did not find an association between glaucoma or age-related macular degeneration and the risk of dementia.

A retrospective study published in the journal *Ophthalmology* in 2021 explored the relationship between vision impairment and dementia in adults over age 65. Researchers analyzed data for more than 10,000 participants in the U.S. National Health and Aging Trends Study collected from 2011 to 2018.

The investigators found that self-reported vision impairment was associated with a 2.3 times greater likelihood of dementia, and dementia was associated with a 2.5 times greater chance of vision impairment over time. They concluded these associations are likely multifactorial, bidirectional, and may trace to common risk factors for both eye and brain diseases.

Given the two-way relationship between vision impairment and dementia, taking good care of your eye health and brain health is wise.

EARLY DETECTION MATTERS

Diagnosing early signs of AD is essential for making lifestyle changes for slowing cognitive decline and speeding access to the latest treatment options. Moreover, newly approved disease-modifying drugs such as lecanemab (Leqembi®), which was approved by the U.S. Food and Drug Administration in July 2023, are indicated only for individuals with early-stage Alzheimer's disease or mild cognitive impairment.

Current wait times to see a neurologist can be long. One study published in *Alzheimer's & Dementia* in 2021 estimated a 50-month wait time for a referral to see a neurologist based on a brief cognitive test, but when accompanied by a confirmatory biomarker test, the wait time would shorten to 12 months. According to Dr. Sohbati,

> **SCREENING FOR AD AT OPTOMETRY CLINICS USING HYPERSPECTRAL RETINAL IMAGING COULD HELP STREAMLINE PATIENTS REFERRED TO NEUROLOGISTS ON FASTER TIMELINES AND POTENTIALLY ELIMINATE UNNECESSARY REFERRALS.**

"In future clinical research, hyperspectral retinal imaging could also be used as a faster, more accessible, and less invasive way to measure responses to new AD treatments, potentially speeding the time to approval compared to using standard PET and CSF tests," said Dr. Bornbaum.

STAY TUNED

Optina Diagnostics, in Montreal, and NeuroVision Imaging, Inc., in Sacramento, California, are two other companies currently conducting clinical research into hyperspectral retinal imaging for early AD detection.

"While there is still work ahead for validation and approval purposes, the science behind hyperspectral imaging is very strong," said Dr. Bornbaum. "We were in this space before any of the new disease-modifying drugs were available, and we're in good company with others that took the leap to build a new future with more accessible, less invasive, and less expensive testing for detecting early signs of Alzheimer's disease."

COMPREHENSIVE EYE EXAMS CAN DETECT SIGNS OF:

- cardiovascular diseases
- diabetes
- hypertension
- some cancers
- brain injuries
- neurological conditions

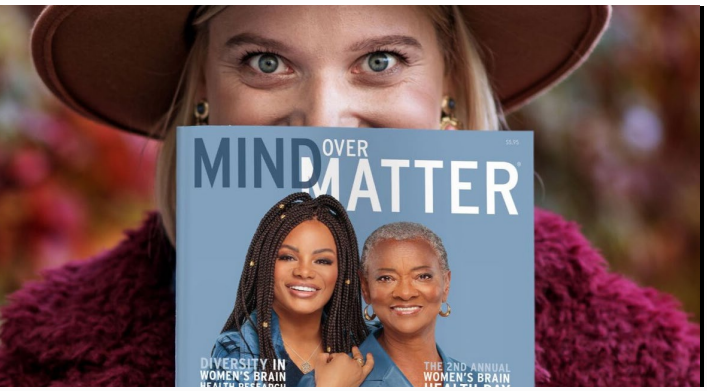
COMMON EYE PROBLEMS IN AGING ADULTS

- Presbyopia: loss of the ability to focus on close objects that happens over time as we age. It can cause blurry vision, headaches, sore eyes, and the need for more light.
- Cataracts: the lens becomes cloudy over time, causing blurry or distorted vision. Treatment includes surgical removal or getting an updated lens prescription.
- Diabetic retinopathy: signs of bleeding or the growth of abnormal blood vessels in the retina and retinal swelling due to uncontrolled blood sugar levels. Your eye specialist will refer you to your general practitioner for a blood test.
- Age-related macular degeneration: degeneration of the macula, the part of the eye that enables sharp central vision, leads to a loss of central vision, making it difficult to recognize faces, read, or drive. It is the leading cause of vision loss in older adults.
- Glaucoma: damage to the optic nerve at the back of the eye increases pressure, leading to vision loss and blindness.

BIOMARKERS BEYOND RETINAL AMYLOID

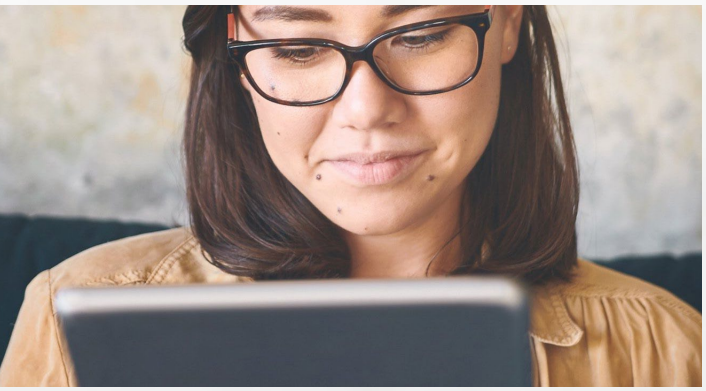
RetiSpec plans to add additional biomarkers to their screening algorithm in the future, including tau tangles and neurofilament light, other proteins known to aggregate abnormally in AD and other neurodegenerative diseases.

"Alzheimer's is our core focus for now, but we are also exploring biomarkers for Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy," Dr. Bornbaum said. "Ultimately, we'd like to build a tool that screens for different proteins associated with various neurodegenerative diseases and provide results in one report."



MIND OVER MATTER® MAGAZINE

Science-informed, easy-to-understand articles for maintaining healthy minds in a high-quality semi-annual publication, available in English and French.



MIND OVER MATTER® VIDEOS

Compelling evidence on the best ways to prolong your cognitive vitality in an effective and highly entertaining format, available in English and French.

MIND OVER MATTER® PODCASTS

Engaging and enlightening interview-style conversations with experts in the field of brain health and related areas, available in English and French.

Safegua
Brain

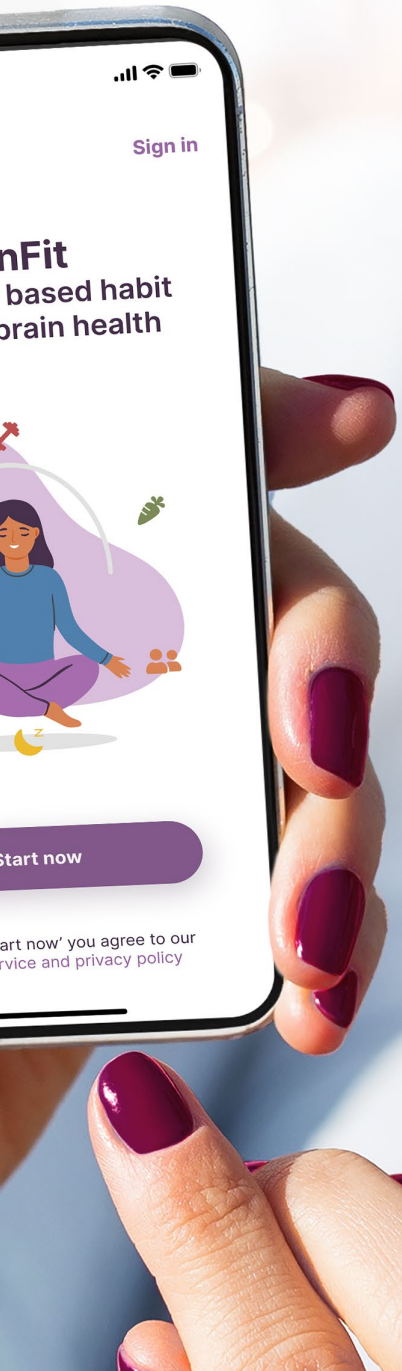
FREE TOOLS TO BOLST

Thanks to the support of many generous donors and partners, Women's Brain Health Initiative has created and produced several free resources to help support mental wellness and protect brain health.

If you are a care partner, first responder, or veteran, have mild cognitive impairment, interested in delaying or preventing dementia, or want to get and stay brain fit, we encourage you to help yourself!

rd Your Health

TER MENTAL WELLNESS



BRAINFIT – HABIT TRACKER

A mobile app that focuses on optimizing brain health, with an emphasis on each of the Six Pillars of Brain Health, available in English and French.

TO FIND OUT MORE ABOUT THESE FREE BRAIN HEALTH RESOURCES, PLEASE VISIT WBHI.ORG.

MEMORY MORSELS

Delicious, brain-healthy recipes, superfoods, brain health tips (our morsels), and great information to help keep your brain functioning the way you want.

BRAINABLE™

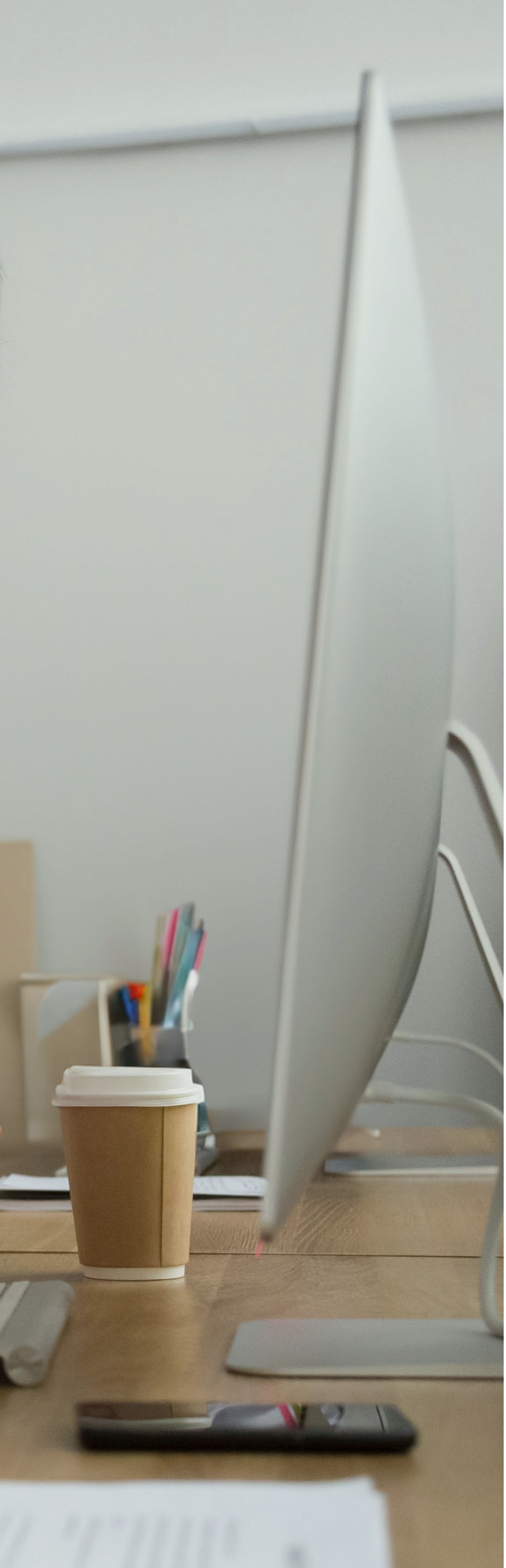
A student education program on the best ways to protect their brain health that supplements the middle school health and science curriculum, available in English and French.

BRAIN BUZZ

Impactful and entertaining one-to-two-minute 40-episode video series about how you can best protect your brain health.

Forever Young

THE IMPACT OF AGEISM ON YOUR HEALTH



From phrases like "senior moment" and "you look great for your age," to ads for products that are purported to help skin maintain a youthful glow, we're constantly surrounded by messages that imply "that it's sad to be old … that wrinkles are embarrassing, and old people are useless," writes Ashton Applewhite, a journalist and author of *This Chair Rocks: A Manifesto Against Ageism*.

In other words, the examples mentioned all express ageism against older people, a phenomenon that, according to a growing body of research, can damage our physical, mental, and cognitive health.

AGEISM REFERS TO THE STEREOTYPES, PREJUDICE, AND DISCRIMINATION DIRECTED TOWARD OTHERS OR ONESELF BASED ON AGE.

According to the World Health Organization's (WHO's) 2021 *Global Report On Ageism,* ageism is prevalent, ubiquitous, and insidious because it goes largely unrecognized and unchallenged.

As for its impact, a review conducted for the report, which included 422 studies from 45 countries, found that in 405 of the studies (96%), ageism was associated with worse outcomes for all health domains they looked at.

The vast majority of older adults experience ageism. In a cross-sectional study of 2,035 U.S. adults aged 50 to 80 published in *JAMA Network Open* in June 2022, 93.4% of respondents reported regularly experiencing one or more forms of "everyday ageism."

But ageism isn't felt equally. Women tend to encounter ageism at an earlier age compared to men. It can also interact with sexism, a combination called "gendered ageism," that results in a heavier burden for older women.

For instance, according to research by Dr. Jenny Godley, a sociologist, demographer, and associate professor at the University of Calgary, Canadian women face 1.5 times more age discrimination than men.

There is evidence that, as individuals, we do have the power to counteract some of ageism's most pernicious potential effects on our brain health.

Read on to learn about how ageism affects our lives (particularly the lives of women) and how we can stop this. ⟶

TYPES OF AGEISM

Ageism can be applied at different points across our lifespan. Characterizing all millennials as lazy or entitled is one example. Ageism can also take many forms, including:

Benevolent ageism: Benevolent or paternalistic ageism has a seemingly warm or caring tone, but the underlying implication is that the target is not competent or capable. For instance, "Here, let me do that for you."

Elderspeak: Addressing an older person as "dear" or "sweetie," adopting a sing-song tone, and using simplified language fall into this category.

Implicit ageism: Individuals engage in this type of ageism without awareness or intention, based on unconscious beliefs, assumptions, or stereotypes.

Institutional ageism: Sometimes called structural ageism, this "refers to laws, rules, norms, policies and practices of institutions – and the ideologies fostered to justify them – that unfairly restrict opportunities and systematically disadvantage individuals based on age," according to the World Health Organization.

Self-directed ageism: Based on the biases and stereotypes an individual has absorbed from their culture and turned against themselves, this is also known as internalized ageism.

HOW SYSTEMS REINFORCE AGEISM

Older people can be exposed to ageism through such institutions as the workplace, the media, health care, and health research.

In film and TV shows, for example, roles for older adults are scarce, and of those that do exist, many depict derogatory stereotypes.

> **UNCONSCIOUS AGEIST ATTITUDES CAN ALSO BE REFLECTED IN NEWS COVERAGE, PORTRAYING ALL OLDER PEOPLE AS WEAK OR DEPENDENT.**

For example, when the Federal/Provincial/Territorial Ministers Responsible for Seniors Forum analyzed 110 documents that included media articles and federal, provincial, and territorial communications related to older adults and the COVID-19 pandemic, "between 50 to 88% portrayed older people as victims," said Dr. Gail Low, a post-doctoral Quality of Life Fellow and associate professor in the Faculty of Nursing at the University of Alberta in Edmonton.

Other research indicates that ageism can also affect access to health care. For example, even though depression is less prevalent in later life, some studies have found that when older individuals seek help from mental health professionals, they are less likely to be treated adequately.

These professionals widely believe that depression is a normal part of aging, according to leading ageism researcher Dr. Becca Levy in her book, *Breaking the Age Code: How Your Beliefs About Aging Determine How Long and Well You Live*.

This has implications for brain health since some research suggests depression is associated with an increased risk of dementia in older age.

Another healthcare area that can be impacted by ageism is hearing loss. "We know hearing is important to your cognitive, social, and mental health," said Dr. Alison Chasteen, a professor in the Department of Psychology at the University of Toronto. Chasteen noted that "it's been challenging to try and get older people to acknowledge when they might be experiencing hearing loss," partly due to ageist stigma.

> **WHILE UNTREATED HEARING LOSS HAS BEEN LINKED WITH AN INCREASED LIKELIHOOD OF DEMENTIA, NEW RESEARCH SUGGESTS THAT USING HEARING AIDS CUTS THE RISK OF COGNITIVE DECLINE IN AT-RISK INDIVIDUALS BY NEARLY HALF OVER THREE YEARS.**

And lack of access to hearing aids is one space where sexism and ageism intersect.

Due to societal factors, women tend to find themselves at an economic disadvantage by the time they reach traditional retirement age. For example, due to the gender wage gap and time out of the workforce for child rearing and/or caregiving, "women end up with a lower pension than men," if in fact, they receive a pension at all, noted Dr. Paula Rochon, a geriatrician and Founding Director of the Women's Age Lab at Women's College Research Institute.

Consequently, retirement income is 18% lower for Canadian women age 65 and older than men the same age.

That means women are less likely to be able to afford things that can protect health and cognitive function, "like, for example, hearing aids," Rochon said.

Ageism is an issue in health research, as well. "It wasn't until just a couple of years ago that older people needed to be included in federally funded clinical trials in the United States," explained Rochon. This meant that studies on medications to treat more prevalent conditions among older people typically excluded this very population.

Since similar measures to include women in randomized controlled drug trials were not implemented until the 1990s, historically, sexism has compounded the impact of ageism in such research.

As a result, "you end up with people experiencing unnecessary side effects," she said. One such scenario involved zolpidem, a medication for insomnia. The drug had been on the market for years when it was finally discovered that the standard dose left women at high risk of short-term side effects (which include next-day drowsiness, cognitive impairment, and dizziness), and subsequently, the dose for women was cut in half. This is significant because some evidence suggests that extended use of this class of sleep medications may increase dementia risk.

THE IMPACT OF AGEIST STEREOTYPES

Research suggests exposure to the type of ageist stereotypes that permeate our culture – even subliminally – can immediately affect physical and mental performance. In a study conducted by Dr. Levy, older people were "primed" with a series of words associated with either positive or negative stereotypes of old age (such as "wise" or "senile") that were flashed onto a screen too quickly to be registered consciously, but slowly enough to be perceived.

Test scores tended to improve following positive priming and worsen after negative priming. Research teams have since replicated these results. Another study led by Dr. Levy found that priming exerts similar effects on walking speed – a measurement linked with physical health and function.

However, taking such negative age stereotypes to heart poses much greater threats. According to the WHO's systematic review, "the association between ageism and health outcomes was strongest for self-directed ageism." (We are so steeped in mental representations of aging that children as young as three express ageist attitudes.)

When "individuals accept negative age stereotypes about themselves, that has a significant impact on physical and mental health," noted Dr. Teresa Liu-Ambrose, Tier 1 Canada Research Chair in Healthy Aging, Co-director of the Centre for Aging SMART at Vancouver Coastal Health, and Director of the University of British Columbia's Aging, Mobility, and Cognitive Neuroscience Laboratory.

MEDIA REPRESENTATION OF OLDER PEOPLE

BETWEEN 2010 AND 2020:

People 50+ comprised:

- less than 25% of characters in top-grossing domestic movies and most popular TV programs.

Women 50+ made up:

- 1 out of 5 characters in film;
- 2 out of 5 characters in broadcast television; and
- 1 out of 3 in streaming television.

Source: Women Over 50: The Right to Be Seen on Screen, Geena Davis Institute on Gender in Media

> *People who have a less negative self-perspective about aging do better in terms of cognition, and they're less likely to develop dementia.*

Dr. Levy's research has linked positive views of aging with lower rates of depression and anxiety, cardiovascular events (including strokes and heart attacks), and a slower decline in the size of the hippocampus, a brain structure that plays a vital role in memory.

In one landmark study that connected mortality data from the U.S. National Death Index to questionnaire responses collected from 433 people aged 50 and older between 1977 and 1993, participants with the most positive self-perceptions of aging lived, on average, 7.5 years longer than those with the most negative views – even after accounting for factors like socioeconomic status and loneliness.

Another equally striking finding from Dr. Levy's research: in a 2018 study published in the journal *PLOS ONE* that used data from the U.S. Health and Retirement Survey, participants who carried the APOE4 gene variant – which increases dementia risk – who also held positive age beliefs were no more likely to develop the disease than people without that genetic risk factor.

HOW CHANGING ATTITUDES CAN HELP

In light of all of the evidence that our beliefs about aging can influence the trajectory of our brain health, the question is how we can cultivate a more positive mindset. ⟶

In *The Revera Report on Ageism*, which looked at responses from an online survey conducted in 2012 of 1,501 Canadians aged 18+, 34% of respondents aged 66 and older reported experiencing age discrimination perpetrated by the healthcare system or healthcare professionals. Of these, nearly 80% said a healthcare professional had dismissed their complaints as an inevitable sign of aging.

Studies that have examined the impact of interventions on ageist attitudes in general, though not specifically on internalized ageism, point to them as one promising approach. In a meta-analysis conducted for the WHO report, "we found they were effective," said Dr. David Burnes, Canada Research Chair in Older Adult Mistreatment Prevention, and a professor in the Factor-Inwentash Faculty of Social Work at the University of Toronto. "We still need to do some more rigorous randomized controlled trials, but based on the research that has been done, it's very promising."

The most successful interventions incorporated two main elements: young people engaged in some sort of meaningful activity with older adults, and "an educational component around demystifying some of the stereotypes about older adults that younger people often have," Dr. Burnes explained. Another promising theme that emerged: "Communities can create and implement these programs quite feasibly, for low cost," Dr. Burnes said.

Research into strategies for combating self-directed ageism is scant. However, some evidence suggests that participating in volunteer activities may help. For instance, in one analysis of reports from a sample of older adults who had participated in the 2008/10 and 2012/14 waves of the U.S. Health and Retirement Study, volunteering for 100 hours or more in the study's first phase was linked with more positive and less negative self-perceptions of aging in the second.

DR. LEVY RECOMMENDS A SET OF TOOLS CALLED THE ABC METHOD TO LOOSEN THE GRIP OF INTERNALIZED AGEISM: INCREASING AWARENESS, PLACING BLAME WHERE APPROPRIATE, AND CHALLENGING NEGATIVE AGE BELIEFS.

Some of the awareness exercises she suggests including recording both the negative and positive images of aging you encounter in the media over one week (including an absence of older characters in TV programs), and creating a portfolio of positive older role models, then listing a trait you admire about each one that you'd like to work on strengthening personally.

Examples of blame-shifting exercises include asking yourself who benefits from an ageist stereotype you encounter, taking a step back when you're tempted to attribute an incident to age, and considering alternative causes. For example, forgetfulness might be due to rushing or stress.

The first step Dr. Levy suggested in challenging internalized ageist beliefs is to seek out accurate information on aging to debunk negative age stereotypes. For example, "I've done a lot of research on how much healthier older adults are in this generation than any other – we have more lifespan, but our health span is also longer," noted Dr. Esme Thomson Fuller, professor and Director of the Institute for Life Course and Aging at the University of Toronto. As well, "levels of serious cognitive impairment dropped like a stone between 2008 and 2017," she added.

Dr. Levy cited research that contradicts several other stereotypes, including studies demonstrating that the brain continues to grow new neurons in response to challenges throughout life and that certain kinds of cognition, such as semantic memory, improve in later life.

Age may bring greater resilience to life stress, too.

"There's some evidence to suggest older people were faring better in terms of their overall mental health and well-being during COVID," said the University of Alberta's Dr. Low.

Regardless of its impact on your health and longevity, rejecting internalized ageist stereotypes can help ensure you stay mentally and socially engaged and become the best version of yourself. Consider the example of Olive Bryanton, profiled in the 2019 CBC POV documentary *Never Too Old* as she completed her PhD at age 81. As she says near the film's end, "there's no age limit on potential."

AGEISM RESOURCES

oldschool.info
reframingaging.org
thischairrocks.com
womensresearch.ca/womens-age-lab
yoisthisageist.com

The Role of Senescence in Alzheimer's Disease

A NEW FRONTIER IN THE SEARCH FOR A CURE

In the season finale cliffhanger of the television show *Grey's Anatomy*, the fictional character Dr. Meredith Grey proclaimed, "We have to question everything we know about Alzheimer's if we're going to cure it." Fiction often borrows issues from real life to spark interest in characters and storylines, so it's no wonder the screenwriters zeroed in on curing Alzheimer's disease (AD) as a timely topic.

"Dr." Grey may have been referring to the amyloid cascade hypothesis, which has been the central focus of AD therapeutic research for more than two decades.

THE AMYLOID HYPOTHESIS POSITS THAT ACCUMULATING AMYLOID BETA PROTEIN IN THE BRAIN TRIGGERS A CASCADE OF EVENTS THAT KILLS NEURONS, LEADING TO MEMORY LOSS AND DEMENTIA.

Those events include the development of abnormal tau proteins that build into threads and eventually form tangles inside neurons.

After many years of research into amyloid as a target, the first two treatments that remove amyloid beta from the brain, called anti-amyloid antibodies, were approved by the U.S. Food and Drug Administration (FDA). (See sidebar on page 44 for more details.)

In general, these drugs known as aducanumab (Aduhelm®) and lecanemab (Leqembi®) demonstrated a 30% reduction in the rate of cognitive decline in people with early-stage AD in clinical trials. While confirming amyloid plays a role in AD, these modest results indicate a large portion of the AD puzzle remains unsolved.

Since aging is the most significant risk factor for developing AD, researchers are investigating biological processes associated with aging as potential new treatment targets for altering AD progression.

The process in which cells stop dividing and do not die, called senescence, has emerged as a hot frontier of inquiry. →

Mind Over Matter® spoke with two researchers at the cutting edge of research into senescence in AD. Both agree that rather than representing an alternative to the amyloid hypothesis, senescence may be a central character in the cascade of events that occurs as AD develops and progresses.

Their translational work in the lab, insights from the first human clinical trials of a drug therapy for clearing senescent cells in patients with early signs of AD, and a new concept for a smart drug delivery system for combination therapies may lead to more effective ways to halt AD progression or prevent AD from developing in the future.

SENESCENCE: A PIVOTAL CHARACTER

Originally discovered by scientists in 1961, cellular senescence is not all bad: it's beneficial during normal early development, for maintaining tissues and repairing wounds, and limiting tumour progression. However, as we age, senescent cells can build up in various body tissues, including the brain.

Some people call senescent cells "zombie cells" because they remain partially active and can release harmful substances that damage nearby cells or even turn them into senescent cells, too.

Scientists have found senescent neurons, astrocytes, microglia, and endothelial cells in postmortem brain tissue of patients with AD and in animal models of the disease.

Dr. Julie Andersen, a scientist and professor at the Buck Institute for Research on Aging in Novato, California, studies the age-related processes driving neurodegenerative diseases, including AD and Parkinson's. She and the members of her lab use 3D human central nervous system cell cultures they developed to investigate the role of senescent cells and the toxic substances they secrete.

Dr. Chaska Walton, a research scientist working in Dr. Andersen's lab, spearheaded a review paper the group published in *Frontiers in Cellular Neuroscience* in 2020. They hypothesized that while some scientists have proposed senescence as an alternative treatment target for addressing AD, it may instead constitute an essential component of the cascade of brain damage that occurs as amyloid proteins accumulate.

"The accumulation of amyloid beta can also induce senescence. Once senescence is present, the damage may reach a point where senescence becomes the main problem, more so than the accumulation of amyloid," said Dr. Andersen. "At that point, removing amyloid plaques with anti-amyloid immunotherapies may have little impact."

Your brain has its own immune system, kept separate from the rest of your body by the blood–brain barrier.

"We know that senescent microglia, a type of immune cell resident in the brain, contribute to the development of Alzheimer's and that senescence initially spreads in the brain without being removed effectively due to the blood-brain barrier," explained Dr. Andersen.

"As the blood-brain barrier becomes increasingly leaky with aging and a fair number of senescent cells have accumulated in the brain, immune cells from the body can enter the brain, causing even more neuroinflammation and damage."

THE RATIONALE FOR SENOLYTIC THERAPY

Dr. Miranda Orr and her lab at the Sam and Ann Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio, Texas, were the first to demonstrate that drugs called senolytics selectively destroyed and cleared senescent cells without harming healthy cells in AD mouse models.

They used dasatinib, an approved drug for treating chronic myeloid leukemia and acute lymphoblastic leukemia, together with quercetin, a plant-based flavonoid with anti-inflammatory and antioxidant properties.

Their groundbreaking findings, published in the journal *Aging Cell* in 2018, showed that these senolytics effectively removed senescent cells and improved brain structure and function in rodent models at risk of developing AD and with advanced tau tangles, a hallmark of AD.

"Another lab validated our findings in the same year, and then a third group found similar findings in a different AD mouse model," said Dr. Orr. "We've been very excited about our progress, moving quickly from preclinical findings in mice to human clinical trials."

THE FIRST CLINICAL TRIAL OF SENOLYTICS FOR AD

Now an associate professor of gerontology and geriatric medicine and scientist at the Wake Forest University School of Medicine in Winston-Salem, N.C., Dr. Orr is a primary investigator

of the first clinical trial of dasatinib plus quercetin for people with early-stage symptoms of AD.

The study is called the Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD) trial and it is supported by funding from the Alzheimer's Drug Discovery Foundation.

In the phase 1 part of the study, five patients with early AD symptoms received oral dasatinib plus quercetin over two consecutive days, followed by two weeks of no drugs, and then repeated this pattern for six more cycles.

Investigators collected cerebrospinal fluid (CSF) and blood samples to see whether the medicines penetrated the central nervous system. They also looked for biomarkers of senescence in CSF and evaluated patients' cognition and brain images before treatment and after 12 weeks.

THE RESULTS SHOWED THAT THE SENOLYTIC THERAPY WAS SAFE, FEASIBLE, AND WELL TOLERATED BY PATIENTS.

Dr. Orr and colleagues found evidence of dasatinib in CSF but did not detect quercetin. "We expected to find quercetin in CSF. We're not sure if that was because we looked at the wrong time or because it has a lower bioavailability than we thought," said Dr. Orr. "We may conduct a phase 1b trial of dasatinib with different doses of quercetin to answer the question in the future."

The CSF analyses showed some promising signs of activity. The investigators noted a trend toward higher levels of amyloid beta-42, a main component of amyloid plaques and a positive indication that the senolytic therapy was clearing some amyloid.

They also observed lowered levels of several toxic substances associated with senescence, called cytokines and chemokines. However, levels of biomarkers called interleukin-6 (IL-6) and glial fibrillary acidic protein (GFAP) rose after treatment, indicating a trend toward increased inflammation.

"More research is needed to determine whether increases in these biomarkers indicated a brief inflammatory response to the treatment or merely the presence of debris from cleared senescent cells that produce those markers," Dr. Orr said.

Keep in mind that these CSF results provided directional learning only. It's not possible to say the medications caused these effects given the small number of patients, and as an open-label study, there was no placebo group for comparison. Cognitive performance and brain imaging results did not change much over the short 12-week time frame. The paper was published in *Nature Medicine* in September 2023.

Now, phase 2 of the SToMP-AD trial is recruiting patients, with results anticipated in late 2025.

The study is offered at Wake Forest Health University Sciences, the University of Texas Health Science Center at San Antonio, and will soon expand to additional sites in Europe. Patients with early-stage AD will receive either oral dasatinib plus quercetin or a placebo and undergo blood and cognitive testing over one year.

Dr. Orr and colleagues will evaluate the safety and efficacy of the treatment, as well as changes in cognitive impairment, including memory, orientation, judgement, problem-solving, and daily life activities. They will also assess tau levels in the brain using positron emission tomography (PET).

"At the end of trial, patients can opt in to have a lumbar puncture, and several have volunteered," said Dr. Orr. "CSF analysis will hopefully shed light on whether the rise in inflammation we saw previously is transient, falls over time, or is something we need to be concerned about."

COMING SOON: TREATING MULTIPLE TARGETS

In the meantime, Dr. Orr said there is a need to design new studies that research a combination of amyloid-lowering antibodies and senolytics since an accumulation of amyloid plaques and senescent cells are both involved in AD processes. "As amyloid-lowering drugs are now approved, we will likely have patients who are being treated with them who also want to enroll in our senolytic study," she said.

Dr. Andersen agreed a combination strategy is where the science is going next. "Ideally, anti-amyloid immunotherapies and senolytics would both be administered in early-stage AD for the best outcomes before the cascade of damage goes too far," she said. "Senescent neurons are still somewhat metabolically active, so removing too many of them at later disease stages with senolytics may prove fatal since damaged neurons can't regenerate." ⟶

ANTI-AMYLOID ANTIBODIES

The U.S. Food and Drug Administration (FDA) recently approved the first two disease-modifying therapies for AD. The anti-amyloid antibodies aducanumab (Aduhelm®) and lecanemab (Leqembi®) were approved for patients with mild cognitive impairment or mild dementia due to AD with increased levels of amyloid in the brain as confirmed by positron emission tomography (PET) scan or cerebrospinal fluid.

Administered by intravenous infusion, these medications slow cognitive decline associated with AD by reducing amyloid plaques. However, they are associated with a risk of swelling and microbleeds in the brain.

In an opinion article published in the journal *Drugs* in May 2023, Dr. Jeffrey Cummings, Director of the Chambers-Grundy Center for Transformative Neuroscience at the University of Nevada, Las Vegas, wrote that these drugs are transformative and support the amyloid hypothesis and amyloid as a treatment target. He also noted that it will be challenging for patients and care partners to decide whether a 30% reduction in disease progression is worth accepting the inconvenience and potential harm associated with these new therapies.

FAST FACTS ON ANTI-AMYLOID ANTIBODY APPROVALS*

Aducanumab (Aduhelm®):

- FDA granted accelerated approval in June 2021 with a view to meeting a significant unmet need;
- the approval was controversial: one of two phase 3 clinical trials showed a statistically significant reduction in cognitive decline compared to placebo, while the other study was inconclusive; and
- Health Canada and the European Medicines Agency (EMA) did not approve the drug.

Lecanemab (Leqembi®):

- FDA granted accelerated approval in January 2023 and traditional approval in July 2023;
- the approval was based on phase 3 clinical trial results that showed a reduction in amyloid plaques and slowed disease progression compared to placebo; and
- Health Canada and the EMA accepted the manufacturer's application for approval with decisions pending.

Donanemab:

- in the phase 3 study, many patients were able to stop treatment earlier than anticipated after reaching a predefined level of amyloid plaque clearance;
- phase 3 trial results reported in July 2023 showed the drug significantly slowed disease progression at 76 weeks in patients with early AD symptoms and amyloid and tau pathology compared with the placebo group; and
- the manufacturer expects the FDA's decision on their application for full approval by the end of 2023.

*As of Aug. 8, 2023

It's expensive for drug companies to conduct combination clinical trials. To address this issue, Drs. Andersen and Walton are co-principal investigators working on designing a novel smart-cell drug delivery platform for delivering therapies directly to brain cells. Their cutting-edge project is funded by a High-Risk, High-Reward grant from the U.S. National Institutes of Health.

> **"THE IDEA IS THAT THE SMART DELIVERY SYSTEM WOULD GO DIRECTLY TO AFFECTED BRAIN CELLS, SENSE WHAT'S REQUIRED, RELEASE AN ANTI-AMYLOID ANTIBODY, A SENOLYTIC, OR AN ANTI-INFLAMMATORY DRUG AS NEEDED, AND THEN TURN OFF," SAID DR. ANDERSEN.**

They are looking at intravenous and intranasal formats and conducting tests in lab models of AD to screen the most promising candidates for later research in human clinical trials.

Much work is ahead as scientists continue to explore senescence as a promising target in Alzheimer's disease.

Time will tell if the new season of *Grey's Anatomy* pulls from actual scientific advances and reveals senescence as the new insight in their storyline about solving AD. In the meantime, real scientists are working hard on this promising new frontier of AD research to discover new therapeutic approaches that may prevent or slow AD progression in the future.

Without a Clue

ANOSOGNOSIA – A DEFICIT IN AWARENESS

Anosognosia is a medical term for when someone has a lack of awareness or difficulties perceiving the nature of their injury, neurological deficit, or psychiatric condition where there is evidence of a disorder, disease, or condition or injury that affects the brain.

It is generally accompanied by a lesion (damaged tissue) in parts of the brain responsible for self-reflection. It may result from neurodegenerative disease or trauma but is also noted in psychiatric conditions with impaired neural activation, like schizophrenia.

To learn more about this condition, Mind Over Matter® interviewed Dr. Alfonso Fasano, a professor in the Division of Neurology at the University of Toronto and a clinician investigator at the Krembil Research Institute at Toronto Western Hospital.

"As interesting as it is difficult to explain," said Dr. Fasano, "Anosognosia is not fully understood." Anosognosia is a generic term loosely applied to various situations where patients have a deficit in their awareness, shared Dr. Fasano. It was coined by a neurologist named Joseph Babinski in 1914 and was initially used to describe a patient unaware of their paralysis after a right brain stroke.

Anosognosia is derived from the Greek meaning for not knowing a disease.

It is often used interchangeably with the terms "impaired insight," "subjective cognitive impairment," or "lack of awareness of deficits," emphasizing that **anosognosia is a neuropsychological impairment rather than a choice to ignore or deny health conditions.** →

Over the last hundred years, anosognosia has been associated with a range of diseases. Three "textbook" examples are right hemisphere stroke causing left body paralysis (the situation that led Babinski to coin the term), cortical blindness (Anton's syndrome), and fluent aphasia, but cases have also been documented for schizophrenia, bipolar disorder, involuntary movements in Parkinson's disease, moderate-to-severe traumatic brain injury, mild cognitive impairment, and dementias like Alzheimer's disease.

WHAT CAUSES ANOSOGNOSIA?

> **IN CERTAIN CONDITIONS, BECAUSE OF THE WAY THE BRAIN WORKS, THERE IS SOMETIMES TWO DEFICITS: A DEFICIT OF THE BRAIN AND A DEFICIT OF THE MECHANISM THAT HELPS YOU TO REALIZE THAT THERE IS A DEFICIT.**

Anosognosia is complex and can result from various mechanisms, but typically, the temporal parietal junction of the right brain is involved. Some parts of the brain have localized functions, like the occipital lobe that is involved in vision. Then, other parts without distinct functions are in between different zones and can be thought of as connecting functional zones and associating with other functions, explained Dr. Fasano.

"The temporal parietal junction is part of what we call the associative cortex, and plays a role in how we navigate space, our awareness of emotions, and our sense of agency. For example, I do something and recognize that the behaviour is mine. When the temporal parietal junction is impaired, we may lack insight into our behaviours."

DIAGNOSING THE HIDDEN CONDITION

There is a poor understanding of the prevalence rates for anosognosia with its associated illnesses. Dr. Fasano explained that despite differences in how and why anosognosia manifests, **"the biggest issue is that anosognosia is rarely recognized or addressed."**

> **DOCTORS GENERALLY ACT ON WHAT THE PATIENT IS REPORTING, BUT WHEN SOMEONE HAS ANOSOGNOSIA, THEY CAN'T REPORT WHAT THEY ARE UNAWARE OF.**

There is also little attention to the problem of anosognosia in the neurological field, said Dr. Fasano, and there are limited high-quality diagnostic tools. "As an example, for stroke patients, we commonly use the NIH Stroke Scale, but it only has one item to infer whether someone has anosognosia or not. So unfortunately, anosognosia is something that we don't typically look for when we assess patients."

A few specialized self-report neuropsychological surveys have been developed to help diagnose anosognosia for different conditions, like the Anosognosia Questionnaire-Dementia (AQ-D), which is given separately to patients and their caregivers.

Both patient and caregiver ratings of intellectual functioning (cognitive aspects) and changes in interests and personality (behavioural aspects) are compared to identify discrepancies. Brain imaging (MRI, CT, and EEG) is another tool that may help to uncover an underlying disorder, disease, or condition or injury that impacts the brain that may be responsible for impaired self-awareness for cases with structural brain damage. This tool is not useful for patients with dementia or psychiatric disorders.

A 2022 review published in *The Clinical Neuropsychologist* by Drs. Steward and Kretzmer showed that while there are no universal markers for anosognosia, three common approaches for diagnosing this condition have emerged:

1. comparing self-reports of deficits to clinician or caregiver reports;
2. structured clinical interviews; and,
3. comparing self-reports of performance to objective neuro-psychological testing of performance.

Given its reliance on self-report measures, anosognosia diagnoses may be influenced by overestimation errors, adding another layer of complexity to identifying this condition. Even healthy adults tend to provide overly positive self-representations and estimations of their physical abilities.

> **DOCTORS OFTEN NEED TO DETERMINE IF SOMEONE OVERESTIMATES THEIR PERFORMANCE OR IS UNAWARE OF THEIR DEFICIT.**

The quality of caregiver reports is another component to consider. In cases of suspected anosognosia, doctors will usually ask questions of the caregivers rather than the patient.

Though there may not be any underlying biological differences in how anosognosia manifests for men and women, in many

According to a 2018 report published by Drs. Mograbi and Morris in *Cortex*, the term anosognosia is used in different ways, including a lack of awareness for selected impairments, minimization of selected impairments, or a complete lack of awareness of all impairments.

cultures, women tend to serve caregiving roles more often than men, notice health changes, and be more willing to talk about health issues with doctors than men.

In this way, caregiver gender may influence the likelihood of diagnosis, where female caregivers may be more likely to share discrepancies between their assessments and patient self-assessments at appointments, inadvertently flagging the possibility of anosognosia for the doctor.

Indeed, in his clinical practice as a neurologist, Dr. Fasano usually sees more patients with female caregivers when compared to male caregivers and has noted more cases of anosognosia among men than women.

THE TROUBLE WITH NOT KNOWING

Because someone with anosognosia has trouble understanding the nature of their cognitive, behavioural, or functional changes, **this condition increases challenges for treatment and care, thereby accelerating illness progression or worsening impairments.**

Drs. Steward and Kretzmer's 2022 review in *The Clinical Neuropsychologist* presents a wide range of negative implications of anosognosia including increased resistance to treatment and support, poorer motivation to participate in rehabilitation programs, increased anger and frustration, and poorer quality of life.

For example, a patient who has suffered from a stroke and refuses to do rehabilitation exercises will have trouble to regain function in the affected areas. A patient with Parkinson's disease who overestimates their ability to walk is at an increased risk of falling and injury. Someone with schizophrenia who does not take their medications as prescribed will have psychotic episodes more often, which could affect their ability to maintain employment.

There are also safety implications for having anosognosia.

> **MISPERCEPTIONS OF ONE'S ILLNESS CAN CAUSE CONFLICTS WITH OTHERS, POOR JUDGEMENTS, OR LEAD TO RECKLESS BEHAVIOUR.**

A review by Dr. Barrett published in *Continuum* in 2021 suggests that many right-brain stroke patients continue to drive without awareness of their paralysis on one side, putting themselves and others at risk of an accident. It is understandably frustrating to listen to healthcare teams, caregivers, family, and friends talk about treatment options for ailments you are unaware of or discuss unnecessary behaviour restrictions.

The U.S.-based National Alliance on Mental Illness reports that people with anosognosia are more likely to get frustrated and angry and are subsequently at an increased risk of homelessness or arrest.

HELPING SOMEONE WITH ANOSOGNOSIA

There are a few experimental therapies for certain types of anosognosia, but they are limited in their applications and effectiveness. "Anosognosia is a neglected field, and there is such a long list of mechanisms that it is challenging to develop therapies," explained Dr. Fasano.

One approach for right-side stroke patients with anosognosia and lack of awareness for the surroundings on their left (the so-called *neglect*) is to use vestibular (inner ear) reflexes to increase their eyesight toward their affected side.

Other strategies currently being explored are non-invasive neuromodulation using technologies like transcranial stimulation or targeted visual cortex stimulation (TVCS) to address a patient's lack of awareness of their deficit.

"Sometimes the lack of awareness comes from the brain being too focused on something else. Every area of the brain works in competition with other areas. … In some cases, you might want to reduce activity in some areas to restore activity on the other side damaged by a stroke," said Dr. Fasano.

> **IN THE ABSENCE OF SPECIFIC THERAPIES, A FEW GENERAL APPROACHES MAY BE HELPFUL IF YOU KNOW SOMEONE WITH ANOSOGNOSIA.**

Continue to offer support and compassion to help the individual feel more in control of the situation and hopeful about their life. Remember that someone with anosognosia is not in denial, not to blame for their behaviour, and not doing certain things on purpose with awareness.

Dr. Fasano's clinical experiences have taught him that once you explain behaviours within the context of a disease, family members and caregivers are more understanding, and the relationship between patients and their support network improves.

> **WHEN THE FAMILY MEMBERS KNOW THAT A LOVED ONE'S BEHAVIOUR IS PART OF THE CONDITION RESULTING FROM A BRAIN DISORDER, THEY UNDERSTAND THAT THEIR FAMILY MEMBER NEEDS HELP. THIS ALLEVIATES FRUSTRATION ON THE PART OF CAREGIVERS AND PATIENTS.**

Finally, it is important to note that anosognosia is underdiagnosed. If you notice consistent differences between what someone can and thinks they can do, ensure this information is shared with their healthcare team. Receiving a diagnosis of anosognosia may help an individual gain access to support that can improve their care and daily life.

Active Grandparent Hypothesis

GRANDPARENTS' BRAINS GET A BOOST LOOKING AFTER THEIR GRANDKIDS

Engaging with her seven grandchildren is one of the great joys of Margaret Coleman's life.

"They bring me new interests. They free up my spirit because they are free spirits."

At age 76, Coleman has been a grandmother for 20 years and knows she needs to stay fit to make the most of their time together. She took two teenaged grandsons to Europe last year and before that there was a trip with two granddaughters to Toronto and another jaunt to Niagara Falls with a granddaughter. While she is not an exercise fanatic, she makes a point of doing a 30-minute walk three times a week, keeping track of her steps – the better to keep up with her grandchildren.

"It's all part of valuing yourself. If you lead a sedentary life, you're likely not inspired to go out and do things," she told Mind Over Matter® in an interview from her home in Waterloo, Ontario.

Physical activity has long been known to boost brain health, as does socialization and spending time with grandchildren. More recently, though, an intriguing field of research has suggested that human beings actually evolved to stay healthy and active into old age, long after childbearing years.

The Active Grandparent Hypothesis is explored in a 2021 editorial in *Proceedings of the National Academy of Sciences*. "What this paper does is help people understand that this is actually part of the human condition. It's what we evolved for. There's an evolutionary explanation for why physical activity is so important," said Dr. Daniel Lieberman, Chair of the Department of Human Evolutionary Biology at Harvard University, and the lead author of the editorial.

He points out that humans are a rare species in that we tend to live for decades past the time when we typically have children. He traces it back to our distant history as hunter-gatherers, when healthy grandparents were important components to our survival, not only with child care but with their accumulated wisdom about life.

> **WE AS HUMANS HELP OUR CHILDREN AND GRANDCHILDREN, WHICH THEN IMPROVES OUR REPRODUCTIVE SUCCESS. WE'RE SELECTED TO LIVE LONGER. BUT THE MECHANISM BY WHICH WE DO THAT IS PHYSICAL ACTIVITY. PHYSICAL ACTIVITY IS WHAT ENABLES US. IN OTHER WORDS, WE LIVE LONG IN ORDER TO BE PHYSICALLY ACTIVE, BUT IN TURN THAT PHYSICAL ACTIVITY HELPS US LIVE LONG.**

Dr. Lieberman notes that chimpanzees rarely live long enough to be grandparents and compared even with sedentary humans, the primates are not very active. "They're couch potatoes. So, one question is, if you got a chimpanzee to exercise, which you can't, would it live longer? We don't know the answer to that question," he added, with a chuckle.

He says exercise turns on beneficial processes in our body, ones that repair and maintain our muscles, whereas inactivity fosters unhealthy processes that might cause us to become obese. "As we age, exercise is even more important," he explained.

There is also evidence that a moderate level of caregiving by grandparents supports brain health.

A 2020 study of more than 7,000 Chinese residents published in *International Journal of Environmental Research and Public Health* on the association between caring for grandchildren and cognitive

function in middle-aged and older adults found caregiving for grandchildren was related to better cognitive function, especially for the older-aged group.

But the magnitude depended largely on the frequency and intensity of care. A moderating effect of age on the association between grandchild caregiving and cognition was found, especially in the older-aged group who provided moderate care to one grandchild.

MODERATE, NOT REGULAR, GRANDPARENTING, OR CARING FOR ONE GRANDCHILD WAS MORE POSITIVELY ASSOCIATED WITH COGNITIVE FUNCTION.

However, intensive and regular grandchild care was significantly associated with cognition only in men. No moderating effects of age were found in women.

And in a 2017 study by Dr. Rodlescia S. Sneed and Dr. Richard Schulz published in the *Journal of Aging and Health* found "caregiving grandparents showed slower rates of decline than non-caregiving grandparents. Further, declines were smallest among caregivers who provided more hours of care."

The study authors noted there are limitations to their study, including that "it is possible that some other unmeasured markers of health may confound the associations we observe between grandparent caregiving and cognition. Future studies might use more robust methods to address these issues."

It is important to make the distinction between grandparents who help out from time to time and those who have full custody of their grandchildren, either because the parents have died or are unable for one reason or another to care for their kids.

GRANDPARENTS WHO ARE THE PRINCIPAL CAREGIVERS EXPERIENCE HIGHER LEVELS OF STRESS, THE AUTHORS FOUND AFTER REVIEWING STUDIES BY OTHER RESEARCHERS, WHICH CAN HAVE A DETRIMENTAL IMPACT ON THEIR HEALTH, WHEREAS OCCASIONAL CAREGIVING HAS A POSITIVE IMPACT.

Dr. Laura Wright of the University of Saskatchewan also explores grandparenthood, but from a different angle.

"Everybody says it takes a village to raise a child, and one of the key people in that village are the grandparents," she told Mind Over Matter®.

Dr. Wright, an associate professor in the Department of Sociology, published a 2017 paper in *Demography* on grandparents, which she co-authored with Dr. Rachel Margolis from Western University. They found that while many North Americans choose to have children later, they are living longer and having longer periods of time as grandparents. Crucially, they are also remaining in good health longer.

"Healthy grandparents are much more able to take an active part in helping to raise their grandkids, especially if they live close."

For these people, good health produces a virtuous circle. They are not only able to assist their children and grandchildren, but they are also more self-sufficient and not a burden. "It's sort of like a double whammy. They can provide support and they don't require support."

The many benefits include the value of help with child care for the generation in the middle. Dr. Wright said that the availability of flexible child care arrangements increases the participation of women in the labour force and leads to higher salaries for them.

Her research found differences between the sexes. Men tend to become grandparents at a later age than women, while women on average live longer, meaning they generally get to be grandmas longer than men get to be grandpas. They typically have also been the ones who help out more with the kids.

"But that may change," said Dr. Wright. "This generation of fathers is much more likely to be actively involved, so I wouldn't be surprised to see that change."

All of this research comes at a time when the ranks of grandparents are exploding.

STATISTICS CANADA REPORTS THAT IN 2017 THERE WERE 7.5 MILLION GRANDPARENTS OVER THE AGE OF 45 IN THIS COUNTRY, COMPARED TO 5.4 MILLION IN 1995.

The Economist magazine commissioned research that estimated that there are 1.5 billion grandparents in the world, up from 500 million in 1960. Their share of the global population has grown to 20% from 17%. The research projects that there will be 2.1 billion grandparents by 2050, making up 22% of the population.

While their numbers grow, so does the imperative to follow a lifestyle that preserves both brain health and general health. It is not only good for the grandparents, it is good for the children and grandchildren.

The Active Grandparent Hypothesis may suggest that exercise as we grow older is the result of evolution, but Margaret Coleman does not think in those terms. She just wants to be there for her grandchildren and to enjoy them as much as she can for as long as she can.

"They encourage me to take care of myself – there's a purpose to take care of myself. They make me feel youthful and that I have a purpose."

Seems grandparents' brains do get a boost when they look after their grandkids once a week … but not more!

On the Cover

WITH TAZIM NASSER & FARAH NASSER

Tazim Nasser admits that thinking about her general health and brain health in particular "wasn't really on the radar" in her younger years. Just getting by in a new country was the all-encompassing focus. In 1973, at age 19, she left her native Tanzania with her 13-year-old brother, escaping an unstable political environment in which her father's businesses were nationalized.

Fifty years later, a lot has changed in Tazim's life. She is now sharing the cover of a magazine devoted to promoting brain health with her daughter, Global News anchor Farah Nasser. And she is much more knowledgeable about how to take care of herself, thanks to Farah's influence.

"Farah is very good. She tells me to eat well and to exercise. She's been my teacher for good health and being active. She's really influenced me in that way. Whenever I buy food, she looks at the label and says, 'This is so much sugar, why did you buy that?' She's helped her dad and me learn how to eat right," Tazim told Mind Over Matter®.

Farah jumps in to say she learned important lessons from her mother, too, adding that Tazim was understating the challenges she overcame when coming to Canada, working two jobs while going to school and supporting her brother, who was also balancing education and work.

"It was a real struggle for them. My mom is extremely resourceful. She's kind and caring, and can see into your soul. People gravitate towards her. I think that's why people gave her jobs."

> *What I learned from her sacrifice was resilience. She taught me nothing was impossible, no dream was too big.*

Tazim and her brother first landed in Guelph, following an older sister who had come to Canada to study. Later, she moved to Mississauga, where she met and married Shiraz Nasser, a civil engineer.

Farah was born first, followed by her brother, Latif. Tazim went to school to upgrade her skills and worked for 25 years in human resources at what was then Mississauga Hospital while always getting up early to make meals for her family and finding time to volunteer in the community. She made a point of pushing back against traditional beliefs to encourage her young daughter to forge her own path.

> **MY MOM WAS ALWAYS THE COOL MOM. SHE SAID, 'EXPERIENCE LIFE! JUST BECAUSE YOU'RE A WOMAN DOESN'T MEAN YOU CAN'T HAVE AMAZING EXPERIENCES.**

Even with the demanding schedule of a high-profile TV journalist, Farah pays attention to healthy eating and exercise.

"As I get older, I've also been meditating and doing a lot of yoga. And another thing Mom taught me was therapy, taking care of my mental health."

Tazim says she went through a period of strong feelings of loneliness after both of her children moved out. A colleague at the hospital recommended she seek out therapy, where she found a need to also explore other issues in her life, including the death of her own mother when Tazim was only 16.

> ***It was very difficult. I'm so glad I had therapy. I'm in a much better place. I would be struggling if I hadn't sought that out.***

Although officially retired, Tazim maintains a busy schedule, instinctively following a core recommendation for brain health. She and a few friends founded a volunteer group, the Ismaili Woman's Network-West GTAA, which supports several shelters for women and youth and assists recently arrived immigrants.

She has chaired it since 2018. As she learned more about the mission of Women's Brain Health Initiative, she invited the charity's President and CEO, Lynn Posluns, to speak to her group about brain health.

"There's no question we have to support this organization," said Tazim.

Farah has also been learning more about the issue, noting that they have relatives on her father's side who had Alzheimer's.

"I didn't realize how much I didn't know. I was shocked to learn how little research had been going into women's brain health, given that women make up most of those living with Alzheimer's. And this is something not discussed in our community," she said.

Along with serious discussions about an important public health matter, mother and daughter also savoured the photo shoot experience for the cover. As a TV journalist, Farah gets the full makeup and hair treatment regularly. But it was a unique treat for her mother.

"Oh my God, it was amazing! Seeing my mom getting that treatment warmed my heart; it's something that she so deserved."

Open Wide

A STRONG CASE FOR SHARING ALZHEIMER'S DISCOVERIES

Research into Alzheimer's disease (AD) often requires taking the long view. AD is the most common form of dementia and can lurk within someone's brain for decades before symptoms appear. As a result, scientists need access to people willing to participate in studies for many years; people who are willing to commit to regular questionnaires and examinations. Gathering such data is not only time-consuming but often prohibitively expensive.

That is why the Canadian Alzheimer's Prevention Data Repository and Sharing Platform (CAP) is so important. Led by Dr. Sylvia Villeneuve, an associate professor at McGill University and Director of the Centre for Studies on Prevention of Alzheimer's Disease (StoP-AD) at the Research Centre of the Douglas Mental Health University Institute, it offers researchers a rich array of information from a dedicated group of volunteers who are followed over many years.

CAP will allow researchers to collect new data on these dedicated volunteers and make the data available to the entire scientific community at no cost. The only request of scientists who use CAP to collect data is to openly share the information after five years.

> *I'm absolutely convinced this is the right thing to do to accelerate science. It's to diminish the barriers, to make sure this data is used as much as possible.*

The PREVENT-Alzheimer Program at the Douglas Research Centre recruited the study participants. PREVENT-Alzheimer stands for "**PRe**-symptomatic **EV**aluation of **E**xperimental or **N**ovel **T**reatments for **A**lzheimer's **D**isease." Between 2011 and 2017, the team at Douglas recruited hundreds of volunteers, people who showed no signs of AD but who had a family history of the disease and were thus at a higher risk. There are still about 330 active participants in the PREVENT-AD cohort.

Now, thanks to a Platform Support Grant (PSG) from Brain Canada, Dr. Villeneuve's team can resume recruitment and expand their information sharing with scientists.

Together with Optina Diagnostics, the Fonds de recherche du Québec – Santé (FRQS), the J.-Louis Lévesque Foundation, the Douglas Foundation, and the National Institutes of Health (NIH), Brain Canada is awarding $2.34 million to support CAP, describing it as "the first Canadian open platform with the infrastructure to acquire, harmonize and share sensitive data on preclinical AD ... a platform for accelerating Alzheimer's disease research and treatment in Canada and beyond."

"Doing open science is extremely difficult and costly," said Dr. Villeneuve. "We're using this money to allow us to share our data and help other researchers. One particularity about our platform is that we do not filter the data sharing based on the research group or the proposed project. Anyone from anywhere in the world with a faculty affiliation can access the data at no cost."

> **RESEARCHERS UNDERSTANDABLY TEND TO GUARD DATA THEY HAVE COLLECTED BECAUSE THEY HAVE GONE TO ALL THE TIME, EFFORT, AND EXPENSE OF GATHERING IT.**

But increasingly, there is a recognition that sharing information is the right thing to do for humanity. Dr. Villeneuve said a mentor

influenced her: Dr. Michael Weiner of the California-based Alzheimer's Disease Neuroimaging Initiative (ADNI), a pioneer in the concept of sharing data.

"He told me not to be scared about sharing data," said Dr. Villeneuve. "If we want to find a cure for Alzheimer's disease we need to work together."

Scientists at the Douglas Research Centre recruited their volunteers to support studies into what she calls the "silent phase" of AD, the 20 years before symptoms appear. The goal was to focus on research on how to slow or reverse changes in the brain that lead to dementia.

"We need to understand these people, because it's better to stop the disease when they are asymptomatic."

The information drawn from the PREVENT-AD volunteers also benefits researchers exploring many different aspects of dementia. Even before the Brain Canada grant, her team at the Douglas Research Centre shared data with about 400 scientists across 13 countries, with tangible results.

The PREVENT-AD cohort is a rich resource. Extra questions can be added to the regular questionnaires to meet the needs of other studies. Because of the substantial size of the group, it was particularly helpful for scientists exploring sex differences in dementia, who need large numbers of participants to make proper comparisons between women and men.

It was crucial for Dr. Jennifer Rabin, a scientist at the Sunnybrook Research Institute in Toronto. She and her team were studying APOE2, a gene variant protective against Alzheimer's disease.

They had novel findings indicating that the gene variant only protected men, with no similar effects observed in women.

Their team wanted a large cohort of volunteers to verify their results, and the PREVENT-AD group was exactly what they needed.

"We wanted to see if we could replicate [the novel findings] in other datasets. Having a dataset readily available for replication is of immense value, as it substantially enhanced our confidence in the findings," Dr. Rabin told Mind Over Matter®.

She combined the PREVENT-AD cohort with three other American-based cohorts and confirmed their findings. Her team's study was published earlier this year *in Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.

"The PREVENT-AD data are exceptionally well organized, and we truly appreciate the effort and dedication that went into curating it. Dr. Villeneuve is establishing a remarkable precedent within the Canadian research community."

"Their data was so well organized and easy to use, and that's very much appreciated. I'm sure it takes more effort on their end. [Dr. Villeneuve] is doing an amazing job."

Dr. Nathan Spreng, the James McGill Professor of Neurology and Neurosurgery at the Montreal Neurological Institute-Hospital (The Neuro), credits access to the PREVENT-AD cohort in helping him obtain funding for two research projects, including one to investigate the impact of loneliness on brain aging and pre-symptomatic AD.

"Access to PREVENT-AD was critical to our justification to fund and carry out this work in Canada," said Dr. Spreng. "It's one of very few cohorts globally with such rich longitudinal data in an at-risk yet asymptomatic population of older adults."

The Brain Canada grant and the creation of CAP meant the resumption of recruitment. Also, they meant going back to all the people currently in the PREVENT-AD cohort to reconfirm their consent to share their data with researchers from around the world. Dr. Villeneuve's team carefully protects participants' privacy by removing any information elements that could identify any single individual. Despite the long-term commitment, she says volunteers willingly come forward, particularly those whose family has been touched by AD.

After a rigorous, independent peer review, her project was selected for the 2021 Brain Canada's Platform Support Grants program. According to the foundation's criteria, these substantive grants are awarded to "teams that are creating and/or enhancing centralized shared resources to increase access to equipment, expertise, data and protocols across research networks."

PLATFORMS AND OPEN SCIENCE GO HAND IN HAND WHEN IT COMES TO MAKING PROGRESS IN NEUROSCIENCE.

Brain Canada President and CEO Viviane Poupon, PhD, continued, "When we make data available through open access platforms, we make our efforts – and our investment – more valuable and help everyone benefit from these important long-term studies. We are excited to follow the impact of Dr. Villeneuve's research in the years to come."

When Johanna Trimble's mother-in-law began to show signs of dementia, she and her family started asking questions. It was 2004, and her mother-in-law, Fervid Trimble, lived in an independent living suite in a seniors complex. An episode of the flu and a sodium deficiency caused by diuretics sent her to the hospital overnight. Still feeling weak, upon discharge, she went to her residence's health centre for a few days of recovery, but instead, she began showing signs of serious cognitive decline.

"She received a diagnosis of dementia," said Johanna. "But the symptoms don't come on so suddenly. This was uncharacteristic and not understandable to the family."

Johanna and her family did their own research and began to wonder if drug interactions were the problem. After the family requested a medication review with the staff, Fervid was taken off the newly prescribed medications.

"We saw the benefits very quickly," said Johanna. "Within a month, she was back to normal cognitively."

Fervid Trimble died in 2008, but the incident stuck with Johanna. She wondered whether it was a rare experience. Then she read a book by Dr. John Sloan, a Vancouver family physician. It opened her eyes to an issue called polypharmacy, which is often defined as prescribing five or more medications for a person, sometimes with the harms outweighing the benefits.

"He spoke about many cases of people being overprescribed, and one of the things he did for frail elders was to get them off too many drugs and get them out of the hospital. That rang a very loud bell for me," she told Mind Over Matter® in an interview from her home on B.C.'s Sunshine Coast.

It turned her into an activist and an advocate for frail elderly people, mostly women. She became part of an international movement toward deprescribing.

THE INS AND OUTS OF DEPRESCRIBING

Dr. Barbara Farrell, a pharmacist and scientist at Bruyère Research Institute in Ottawa, is one of the leaders of this movement in Canada. She told Mind Over Matter® that while some researchers started writing about polypharmacy in the 1960s, the problem has expanded, partially because of the explosive growth of the pharmaceutical industry.

Medication Makeover

SHOULD OLDER ADULTS DITCH SOME DRUGS?

> **THERE'S A CULTURE AROUND PEOPLE WANTING A MEDICATION TO TREAT A PROBLEM, AND THERE'S ALSO A CHALLENGE IN EDUCATION FOR HEALTHCARE PROVIDERS.**

"Physicians may not be taught that much about the side effects of medication; in the U.S., there's a lot of advertising for medication that could oversell the benefits," Dr. Farrell continued.

The impacts can be numerous and at times, catastrophic. Dr. Farrell says the more medications people take, the greater the danger of harmful interactions. For older people, it can increase the risks of falls, with broken hips or head injuries.

> **OVERMEDICATING CAN CONTRIBUTE TO COGNITIVE IMPAIRMENT, LEADING TO A MISDIAGNOSIS OF DEMENTIA.**

People can suffer from nightmares or incontinence. Harmful drug interactions have been associated with spikes in emergency department visits.

Dr. Farrell noted concerns about the over-prescription of antipsychotics in long-term care homes, which are typically used to treat behavioural symptoms of dementia, but over the long term could increase cardiovascular problems.

The issue is more common among older people and affects women and men differently. A review published in *The Lancet Healthy Longevity* in May 2021, co-authored by Dr. Paula Rochon of the Women's College Research Institute in Toronto, found that because women tend to live longer and are in the majority at long-term care homes, they are more likely to be exposed to polypharmacy.

> **THE REVIEW FOUND THAT "WOMEN ARE MORE AT RISK FOR DRUG-RELATED ADVERSE EVENTS DUE TO SEX-RELATED AND GENDER-RELATED CONSIDERATIONS."**

Dr. Farrell pointed out that as people age, they handle drugs differently, adding that drug trials generally do not include older, frail people, let alone those with dementia, so it is hard to know the impact on them.

But attitudes are changing. She says that in the last decade, there has been much more research into the risks of polypharmacy and the practice of deprescribing.

"The awareness of the problem and potential solutions has grown exponentially. I think it's because that word, 'deprescribing,' gave us a name for a solution, which I describe as the planned and supervised process of reducing or stopping [over-prescription of drugs]."

Her research team has developed guidelines for clinicians to help them decide when and how to deprescribe. These are found on the team's website: deprescribing.org. She's also part of a Canadian network focused on providing advice for deprescribing, which you can find more information about at deprescribingnetwork.ca.

> **IT'S NOT SIMPLY A CASE OF A PATIENT JUST STOPPING A DRUG, THERE COULD BE WITHDRAWAL ISSUES. IT'S IMPORTANT TO LOOK AT THE PROS AND CONS AND THEN MONITOR THAT PROCESS FOR ANY SIDE EFFECTS."**

When done appropriately, the results can be life changing. About a year ago, Dr. Farrell saw a woman on five medications, including an antidepressant she had been taking for decades. The patient could not finish a sentence, and a cognitive test indicated she had dementia. Over several weeks, Dr. Farrell's team gradually reduced the dosages of the antidepressant.

"Her daughter called us and said, 'What did you do to our mother? She's cooking again and taking out her own garbage.' We redid the cognitive test, and it was normal."

The case is cited in a paper Dr. Farrell will soon be publishing.

HOW CARE PARTNERS CAN HELP

There is much more awareness of polypharmacy these days, but it is still a concern care partners need to keep in mind.

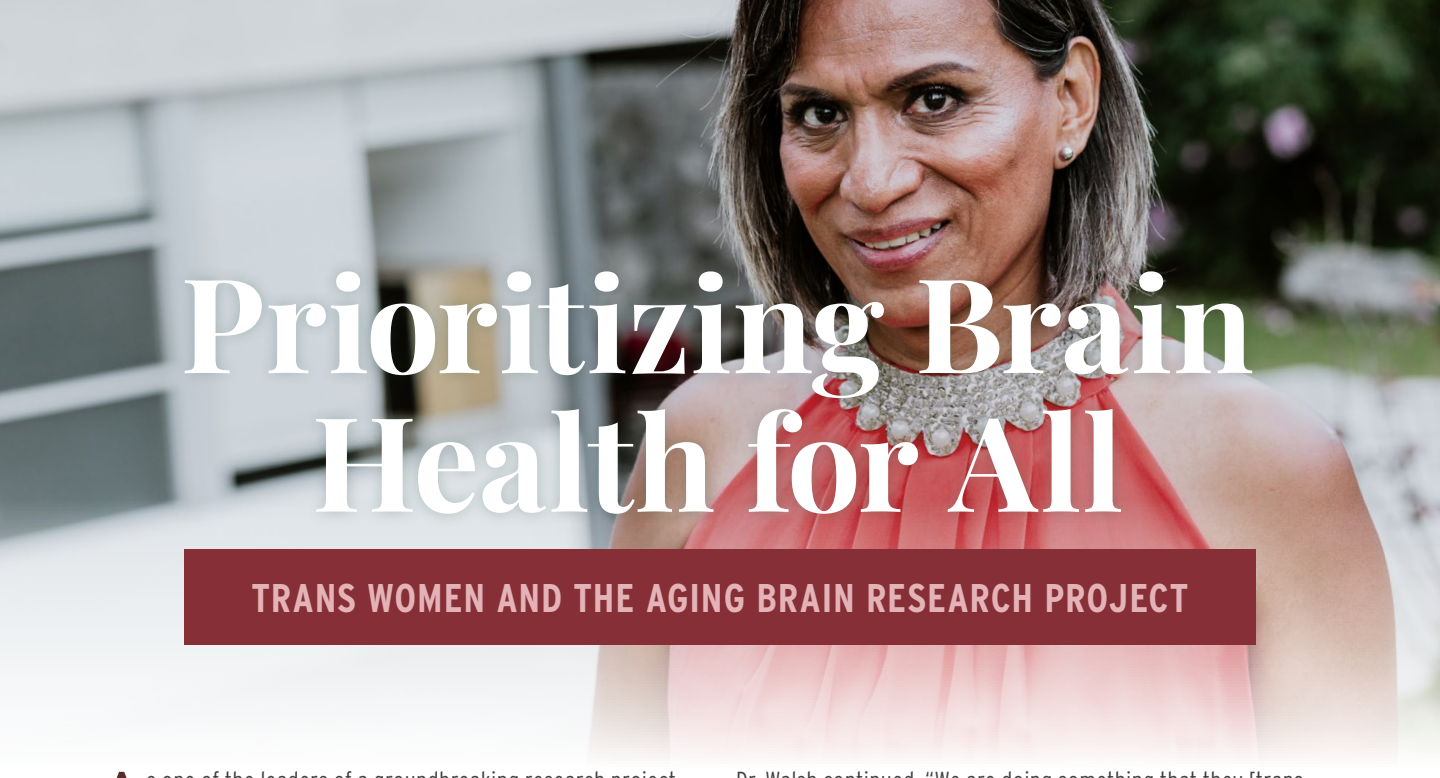
"Polypharmacy is still a pervasive issue. We're still identifying the overuse of medications," she noted.

> **TO HELP THEIR LOVED ONES, CARE PARTNERS SHOULD ASK QUESTIONS TO ENSURE THEY HAVE A CLEAR IDEA OF EACH PRESCRIBED MEDICATION'S DOSE, FREQUENCY, AND PURPOSE FOR A LOVED ONE.**

Johanna Trimble echoes that advice and agrees that progress has been made in raising awareness but believes much more work needs to be done with education for healthcare providers and in setting up systems.

To help with the former, she now co-teaches a yearly class for the pharmacy department at the University of British Columbia as a guest lecturer, giving the next generation of practitioners advice from the resident and family's point of view about prescribing in long-term care homes. When she does it, she thinks about her late mother-in-law.

"I'm sure she would have been happy to see me doing this. She was a teacher, and, in a way, she can go on teaching through her experience."



Prioritizing Brain Health for All

TRANS WOMEN AND THE AGING BRAIN RESEARCH PROJECT

As one of the leaders of a groundbreaking research project involving trans women, Dr. Reubs Walsh approaches the task with a deep sensitivity toward the community to be studied, a community of which they are a member.

"One of the big things to remember is that historically, trans people have not been treated well by medical personnel, and it still exists in some places," Dr. Walsh told Mind Over Matter®.

The subject of the study has obvious resonance for the community. The researchers are exploring the long-term cognitive effects of gender-affirming hormone/estradiol therapy (GAET) on older trans women, analyzing them in the context of stress and aging. To the team's knowledge, it is the first project of its kind ever undertaken.

Dr. Walsh, a post-doctoral fellow at the University of Toronto (U of T), is working with Dr. Gillian Einstein, who holds the Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging at the university. The project is supported by funding from Brain Canada Foundation (Brain Canada) and Women's Brain Health Initiative (WBHI), with post-doctoral salary for Dr. Walsh being supported by WBHI and the U of T Faculty of Arts and Science.

Dr. Walsh, a native of England who pursued doctoral studies in the Netherlands, has just received ethics approval and is now recruiting participants for the study.

> *We want to build a foundation of trust, and that's why we're going slowly.*

Dr. Walsh continued, "We are doing something that they [trans women] want to know, too, and we want to ensure that they trust us to be the ones to try to learn it."

The basic questions are the same that any person taking long-term treatments would have: What are the long-term impacts? Are the treatments beneficial or detrimental? Which cognitive domains and brain regions do they affect? How do the people who take these treatments feel about them? What is their experience?

"It's a research project that's long overdue," said Dr. Walsh. "I don't think I've met a trans person and told them what I'm doing without them having 50 questions. People want to know the answer about any side effects."

IN THEIR QUEST TO LEARN MORE, THE RESEARCHERS MUST ALSO NAVIGATE A CHALLENGING POLITICAL LANDSCAPE SURROUNDING TRANS ISSUES.

"This is a complicated study. We must get the information we need without upsetting or triggering people. A lot of trans people, especially older ones, have had some traumatic experiences, and we don't want to make it worse," Dr. Walsh added.

"We're not politically motivated. The biology itself isn't politically motivated," said Dr. Einstein.

"We do have to think about the politics because that is what every trans person, themselves, faces, but most importantly, this project is about the people who participate. They may be worried about what is found and how it may be used. We have to be sensitive to that," she added.

> *Biology is shaped by social conditions, including stigma. Ultimately, we want this research to help and inform.*

The research will go beyond studying the effect of hormones. The team is also interested in exploring the impact of the different kinds of stress, including trauma, endured by many trans people.

There are other potential risk factors for the cognition of trans people. Walsh points out that some isolate themselves socially as a form of protection, which elevates the risk of developing dementia.

"You don't know if you'll be safe or facing a threat. That's going to make you less likely to go out and be among people, and a kind of wear and tear takes place."

Dr. Einstein added: "One hypothesis might be that the stigma of being trans might outweigh any biological risks that gender-affirming hormone therapy might lead to."

There are questions beyond the impact on cognition. For example, there is evidence that trans women have an elevated risk of heart disease.

THE ASSUMPTION UP UNTIL NOW HAS BEEN THAT HORMONE THERAPY WAS RESPONSIBLE, BUT DR. EINSTEIN AND HER COLLEAGUES WONDER WHETHER STRESS MAY PLAY A CENTRAL ROLE.

They hope to start recruiting as many as 40 trans women in the new year, reaching out to various community groups from which to recruit participants. Dr. Walsh is hopeful that there will be great interest.

"Something about the trans community, as I've experienced it in Europe and here, is that it's very tight-knit, and sooner or later, everybody knows everybody. There's a good chance that once we've built good relationships with the first participants, it'll just snowball."

As a first step, participants will be asked to come in for a qualitative interview, during which they will be asked to speak about their experiences with hormone therapy and how it has affected their lived experiences.

The researchers will compare those stories with how participants score on certain tasks, such as the mental rotation test, in which people are asked to look at 3D images of objects from different angles and determine whether they are looking at the same object.

This particular test has typically shown a difference between the sexes. Cis men are thought to perform better on mental rotation tasks. However, researchers in Dr. Einstein's lab have challenged that belief, having found evidence that women tend to do just as well as men during their menstrual cycle when estradiol levels are lower. The researchers are interested in seeing how GAET might affect performance.

The funders of the research share their excitement about the project. "This research aligns with our goal to advance sex and gender brain science and remove systemic barriers and biases to ensure that all individuals have equal access to – and will benefit from – the results of bold brain research," says Brain Canada President and CEO Viviane Poupon, PhD.

"Reubs and Gillian are breaking new ground in an area that needs more exploration," said WBHI President and CEO Lynn Posluns. "We're proud to support them."

Dr. Einstein says this kind of research would be impossible without the assistance of funders like Brain Canada and WBHI, who aren't just interested in the next logical step and want to fund out-of-the-box, groundbreaking research.

They, as well as the Faculty of Arts and Science, who wanted to fund an outstanding young scholar in their next career step, understand that the results of the project could have profound meaning for trans people, providing them with information that everyone considering any treatment deserves and which allows for truly informed consent.

"THERE ARE RISKS AND BENEFITS TO EVERYTHING," SAID DR. EINSTEIN. "THE TRANS COMMUNITY NEEDS TO HEAR ABOUT BOTH SIDES, BUT IT IS DIFFICULT FOR SMALLER GROUPS TO GET THIS KIND OF HEALTH INFORMATION. WE ARE TRULY GRATEFUL TO OUR FUNDERS FOR SUPPORTING OUR PROJECT AND THE COMMUNITY.

As researchers increasingly recognize the importance of exploring sex differences, Dr. Walsh believes that their project will resonate beyond this one community, providing a deeper understanding of the implications of hormone therapy.

"This research program could have really positive consequences for medical care across gender lines," they said. "Everybody has a stake in this. Everybody will be better off."

Thumbs Up

THE LATEST CHALLENGE TO STAND AHEAD®

FOR WOMEN'S BRAIN HEALTH

For Karen Crooks, the mission of Women's Brain Health Initiative (WBHI) has a personal resonance. Her mother, Mary, is living with an advanced stage of Alzheimer's disease and Karen is the principal caregiver, with the support of her sister Lynn.

Over the past few years, Karen has joined dementia support groups, connected with the Alzheimer Society, and started following discussions about dementia issues on social media. That's where she came upon postings by WBHI and learned about the Stand Ahead® Challenge, the annual contest in which participants submit ideas for fun activities that support brain health.

"I said to my daughter Avery, who's a university student in concurrent education, let's come up with an idea for the challenge. It was just something fun for us to do together. Never thinking that it would turn out the way it did," Karen told Mind Over Matter®.

The way it turned out was that the mother-daughter collaboration won the contest, which comes with a gift certificate and gift basket that they will be sharing.

Searching for inspiration, they started by going to the website for the Stand Ahead® Challenge to check out the past four winners, which included a memory test with playing cards, writing your signature with your non-dominant hand, and the 2022 winner, the Conductor Challenge, which calls for you to draw an imaginary vertical line on a 1-2 count while simultaneously drawing an imaginary triangle on a 1-2-3 count. That one struck a chord with Avery.

"It reminded her of a game she played where you give a thumbs up with one hand and you point to it with your other hand and then you switch. And I was like, 'Oh my gosh, I love that!' Thumbs up for women's brain health!" said Karen.

> **I THOUGHT IT WAS SOMETHING ANYONE OF ANY AGE COULD TRY BUT WAS ALSO CHALLENGING.**

To add an extra element of brain-testing difficulty, the Thumbs Up Challenge asks you to do the switch between hands ten times in a row. It was one of three finalists in the contest.

The others were the Balance Challenge, submitted by Sarah Scott, which calls on you to stand in a one-legged prayer pose, close your eyes for ten seconds, then try the other leg; and the Say and Write Challenge, from Caron Nightingale, which asks you to recite a sentence and at the same time write a different sentence on a piece of paper.

PHOTO: JAYLYN TODD

WBHI supporters had the final say via online voting, and the Thumbs Up Challenge came out on top. Karen and Avery's victory has sparked a surge of people who are giving it a try, only to discover that it is trickier than it appears.

"It sounds really easy, but a lot of people have been contacting me saying 'Wow, this is a really tough thing to do,' and they're passing it along to family members to practice it," Karen said. "My son, who is quite physically able, told me that he thought it was easy, but he also struggled at first to do it."

Karen is a social worker with the Toronto Catholic District School Board and was already an admirer of WBHI's funding for brain health education programs and of research that studies why women get Alzheimer's more frequently than men.

"I'm thrilled to support it. I've been sharing WBHI postings with friends, and they're shocked to hear that the majority of people with Alzheimer's are women."

Winning the Stand Ahead® Challenge comes at a difficult time with Karen's mother. Mary was diagnosed with mild cognitive impairment ten years ago at age 70, which evolved into Alzheimer's. It has now progressed to the point when she can no longer safely stay in the retirement home where she has lived for the past two years.

"We're just waiting for a bed in a long-term care home. She's at a difficult stage in her memory loss and it has been very challenging for my sister Lynn and me, as well as Mary's five grandchildren and the whole family," said Karen.

> **I THINK MOST WOMEN ARE INTERESTED IN BRAIN HEALTH, BUT IT'S REALLY IMPORTANT FOR US BECAUSE OF OUR MOTHER'S SITUATION.**

She will surely be thinking of Mary on December 2, the annual Women's Brain Health Day. Karen is invited to attend a WBHI event to mark the day, where she may be called upon to demonstrate the Thumbs Up Challenge.

"I still can't do it consistently ten times in a row. It takes a lot of practice and a lot of focus to do it. I hope to have it down pat by December 2."

For more information about the 2023 Stand Ahead® Challenge and Women's Brain Health Day, please visit standahead.org

Magnesium & Brain Health

ARE YOU GETTING ENOUGH OF THIS VITAL MINERAL?

Magnesium is a mineral found in plants, animals, and humans. Most of the magnesium in humans is found in our bones; the remainder is in our muscles, soft tissues, and fluids. Every organ in the body requires this vital mineral to carry out many functions and biochemical reactions, including regulating blood pressure and blood sugar levels, supporting strong and healthy bones, synthesizing protein, contracting muscles, including the heart, and even supporting brain neurotransmitter functions.

Magnesium is an important contributor to our overall physical health and is also pivotal to our brain health.

Magnesium in our food sources has dramatically decreased over the years. The impact of modern farming practices and industrialized agriculture have had a negative impact on the minerals we've been able to acquire from the soil.

Consequently, combining this fact with the increased consumption of processed foods, high-fat and starchy meals, sugar, soft drinks, and alcohol, it is no surprise that magnesium deficiency is most prevalent in regions with such diets.

Several common medications deplete the body of magnesium, including blood pressure and cholesterol-lowering drugs, proton pump inhibitors to reduce stomach acid, and diuretics. Low magnesium levels can also make other medications ineffective.

For example, our body cannot metabolize vitamin D properly or absorb calcium if it doesn't have enough magnesium. Being aware of the impact of drug interactions is, therefore, critically important to managing our health.

Other contributing factors for magnesium depletion include stress. Releasing stress hormones like adrenaline and cortisol makes us burn through already-depleted nutrients faster. Stressors are wide-ranging and include mental (anxiety), emotional, traumatic (injuries, illness, etc.), chemical (drugs, alcohol, caffeine, environmental), nutritional (allergies) or physical (exertion, travel, lack of sleep, etc.) ones.

And according to the U.S. National Institutes of Health, anyone with certain conditions, including gastrointestinal issues or Type 2 diabetes, is more at risk of magnesium deficiency. Those with alcohol dependence are also at risk of this.

A large percentage of people in developed countries don't get enough magnesium in their diet; possibly up to three-quarters of the population, according to researchers Anne Marie Uwitonze and Dr. Mohammed S. Razzaque's 2018 article in the *Journal of Osteopathic Medicine*.

SINCE MAGNESIUM IS SO ESSENTIAL TO THE BODY'S PROPER FUNCTIONING, A MAGNESIUM DEFICIENCY THAT CULMINATES OVER A LONG PERIOD OF TIME CAN EVOLVE AND INCREASE THE RISK OF OTHER CHRONIC MEDICAL CONDITIONS LIKE HEART DISEASE, DIABETES, OSTEOPOROSIS, HIGH BLOOD PRESSURE, AND POOR BRAIN HEALTH.

In fact, *Israel Journal of Medical Sciences* published a study in 1981 that found 84% of postmenopausal women with osteoporosis were also diagnosed with a low magnesium deficiency.

Dr. Michael Del Junco, an internal medicine specialist with the healthcare organization Providence in Orange, California, has done extensive work on the correlation of magnesium and brain health and told *U.S. News & World Report* in July 2022 that magnesium plays a very important role in the body's production of energy, "because over 20% of all energy produced in the body is consumed by the brain. As such, magnesium plays a pivotal role in brain health."

COGNITIVE PERFORMANCE CAN BE REDUCED WITHOUT THE PROPER MAGNESIUM LEVELS ENSURING OPTIMAL NERVE TRANSMISSION AND NEUROMUSCULAR CONDUCTION.

"Abnormal levels of magnesium have even been linked to disorders such as migraines, depression, chronic pain, stroke, seizures, and dementia," Dr. Del Junco shared with the publication.

SYMPTOMS OF MAGNESIUM DEFICIENCY

- low appetite
- nausea or vomiting
- fatigue or weakness
- muscle spasms or tremors
- numbness or tingling in skin
- osteoporosis
- seizures
- high blood pressure
- anxiety and depression
- migraines
- abnormal heart rhythms

The journal *Nutrients* published a literature review in 2018 that looked at the role of magnesium in various neurological disorders like migraines, epilepsy, anxiety and depression, stroke, Parkinson's, and Alzheimer's.

The review found "the amount of quality data on the association of magnesium with various neurological disorders differs greatly," with the data that showed a connection between magnesium and migraines and depression being the strongest.

They also found "good potential for magnesium to be having an effect" on anxiety. The researchers noted that more research is needed to understand the role of magnesium and the other conditions.

MAGNESIUM-RICH FOODS AND WOMEN'S BRAIN HEALTH

Khawlah Alateeq, of the Australian National University's National Centre for Epidemiology and Population Health, published a study in March 2023 in *European Journal of Nutrition* that highlighted how the magnesium we have in our daily diet is linked to better brain health – especially for women.

Alateeq said, "Our study shows a 41% increase in magnesium intake could lead to less age-related brain shrinkage, which is associated with better cognitive function and lower risk or delayed onset of dementia in later life. Higher dietary magnesium intake may contribute to neuroprotection earlier in the aging process and preventative effects may begin in our 40s or even sooner."

The study measured the diet of 6,000 adults ages 40 to 73 in the United Kingdom and discovered a correlation between the consumption of magnesium-rich foods and increased brain health. ⟶

MAGNESIUM-RICH FOODS TO CONSIDER IN YOUR DIET

VEGETABLES
kale
broccoli
spinach
swiss chard
sweet potatoes

DAIRY
milk
yogurt

LEGUMES
black beans
chickpeas
kidney beans
green peas
tofu (soy beans)
peanuts
lentils

FISH
salmon
halibut

FRUITS
strawberries
blackberries
bananas
raisins
avocados

NUTS
almonds
cashews

SEEDS
pumpkin seeds
chia seeds

Specifically, MRI imaging measured participants' brain volumes. They found that the brain volume of people who got more than 550 milligrams of magnesium daily via their diet was larger than those who consumed about 350 milligrams of magnesium each day. By age 55, the former group had a brain age of someone roughly one year younger, they noted. These effects were more pronounced in women.

Alateeq told Mind Over Matter® that they "observed the neuroprotective effect of higher dietary magnesium intake appears to be greater in women than men and in post-menopausal than pre-menopausal women; this may be due to the anti-inflammatory effect of magnesium."

For recipe ideas using these various magnesium-rich foods and to learn more about what other foods are important for optimizing brain health, check out the Women's Brain Health Initiative memorymorsels.org website.

FOOD CHOICES CAN INCREASE YOUR MAGNESIUM LEVELS, BUT DIET ALONE IS NOT LIKELY ENOUGH BECAUSE OF THE MINERAL-DEPLETED SOILS USED TO GROW FOOD.

A 2020 literature review by Dr. Roberta Cazzola and colleagues in the journal *Heliyon* noted. "It is ascertained that magnesium content in fruits and vegetables dropped in the last fifty years, and about 80% of this metal is lost during food processing. As a consequence, a large percentage of people all over the world do not meet the minimum daily magnesium requirement."

The recommended dietary allowance (RDA) of magnesium is 400–420 milligrams (mg) for adult males and 310–360 mg for adult females. During pregnancy and lactation, a person's RDA will vary depending on their age.

So, if you are not getting enough magnesium in your diet and want to try and avoid the many contributing health issues, you may need to supplement to fill the gaps.

"Magnesium supplements are available in a variety of forms, including magnesium oxide, citrate, and chloride," said the U.S. National Institutes of Health in a magnesium fact sheet for health professionals.

Make sure to read the label of any supplement you choose, as that will give you information about the amount of magnesium in the product. "The Supplement Facts panel on a dietary supplement label declares the amount of elemental magnesium in the product, not the weight of the entire magnesium-containing compound," they explained in the fact sheet.

Consult your health professional before adding a magnesium supplement to your routine to make sure doing so is safe and right for you.

Dr. Carolyn Dean, a medical doctor and qualified nutritionist, naturopath, and a leading expert in magnesium deficiency and supplementation, is the author of *The Magnesium Miracle* and a big proponent of the direct link between magnesium deficiency and headaches and migraines, clearing up brain fog, improving sleep rhythm and function, and improving overall brain health.

Dr. Dean also firmly believes that one of the potential benefits of magnesium could be preventing Alzheimer's disease. She explains and offers some simple examples in a post on her website.

"Magnesium helps us to regulate our emotions and sleep better, so it stands to reason that people who get their required daily intake of magnesium regularly will have less requirement for medication to help them sleep. Adequate amounts of magnesium help alleviate stress, improve memory function, and make thought processes clearer – all these things can help ward off conditions such as dementia and Alzheimer's disease."

Brain health is a delicate balance of physical health, life stressors, genetics, experience, and body chemistry. When anything is out of alignment, health issues can develop.

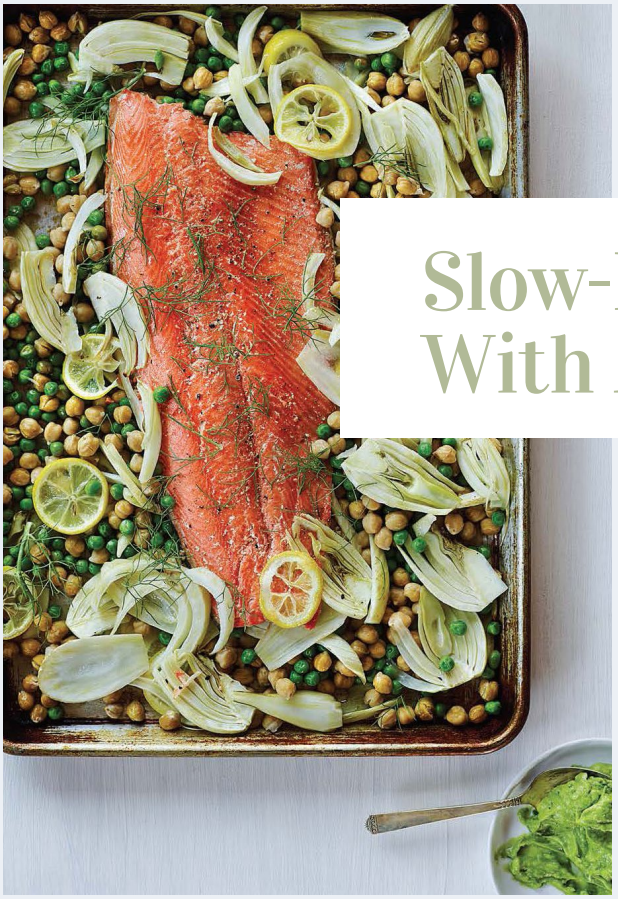
Since magnesium deficiencies can result from dietary, environmental, and drug-related issues, and, most importantly, influence so many systems within the body, including the nervous, immune, cardiovascular, and muscular systems, it can be difficult to diagnose and treat.

This is also why magnesium deficiency is often referred to as the "invisible deficiency" by many experts. If you have concerns or have questions, you can also ask your doctor to check your magnesium levels by taking a blood test.

THE BENEFITS OF HEALTHY MAGNESIUM LEVELS

- protection from heart disease
- protection from Type 2 diabetes
- lower risk of cancer (especially colorectal cancer)
- relief from headaches or migraines
- ease muscle aches
- promote bone health
- improve sleep quality
- boost mental health
- improve vitamin D absorption
- support health during pregnancy

Overall, a healthy lifestyle that includes a proper diet with magnesium-rich foods, light alcohol consumption, limited stress, and appropriate supplementation can help limit your magnesium deficiency and help you achieve proper and effective health maintenance, including stronger brain health.



SERVES 4 TO 6

Slow-Roasted Salmon With Avocado Butter

Slow-roasting salmon is not only a brain-friendlier method than cooking over higher heat, it's practically foolproof, turning out perfectly cooked salmon every time.

INGREDIENTS

- 2 small fennel bulbs (230 g), thinly sliced, fronds reserved for garnish
- Two 15-ounce (425 g) cans chickpeas, drained (about 3 cups)
- 1 large lemon, thinly sliced, seeds removed
- 1/2 cup (120 ml) water
- 1/4 cup (60 ml) extra-virgin olive oil, plus more for drizzling
- 1 teaspoon kosher salt
- One 1 1/2-pound (680 g) whole salmon fillet, skin-on (preferably wild-caught), about 1 inch (2.5 cm) thick (see Tip)
- 1/4 teaspoon freshly ground black pepper
- 1 1/2 cups (230 g) peas (fresh or frozen)
- 2 large, ripe avocados, mashed (about 1 cup)
- 3 tablespoons fresh lemon or lime juice
- 2 tablespoons unsalted butter, preferably grass-fed, at room temperature
- 2 tablespoons fresh flat-leaf parsley leaves
- 1 medium garlic clove, minced (about 1/2 teaspoon)

TIP: You can use fillets of salmon, too. Four- to 6-ounce (115 to 170 g) portions work well. Start checking for doneness after 15 minutes, especially if you prefer your salmon rare.

INSTRUCTIONS

1. Set an oven rack in the centre position and preheat the oven to 300°F (150°C).

2. Toss the fennel, chickpeas, lemon, water, 2 tablespoons of the oil, and 1/2 teaspoon of the salt on a rimmed baking sheet until evenly coated, then spread into an even layer. Top with the salmon, skin side down, and pour the remaining 2 tablespoons oil over top. Sprinkle the salmon with pepper and 1/4 teaspoon of the salt.

3. Bake for 20 to 28 minutes, stirring in the peas after 10 minutes, until the salmon is just turning opaque. (If using an instant-read thermometer, take the temperature in the thickest part of the fish: 125°F/50°C for medium-rare; up to 140°F/60°C for well done.)

4. Meanwhile, combine the avocados, lemon juice, butter, parsley, garlic, and the remaining 1/4 teaspoon salt in the bowl of a food processor. Process until completely smooth. Keep in the refrigerator until ready to eat.

5. To serve, divide the salmon and vegetables between plates and spoon a tablespoon of any pan sauce over top. Top each piece of fish with 2 tablespoons avocado butter, some of the reserved fennel fronds, and a drizzle of oil. Top with more pepper, if you like.

6. To store extra avocado butter, transfer to an airtight container with a piece of waxed paper or parchment paper pressed onto the surface of the butter to prevent browning. It will keep like this for up to 3 days in the refrigerator or 3 months in the freezer.

Simmering cashews along with the canned crushed tomatoes softens them into an easily blended, creamy soup that provides healthy fats from the nuts and boosts the nutrition of the tomatoes.

Creamy Tomato Soup

SERVES 4 AS A SIDE

INGREDIENTS

- **2 tablespoons extra-virgin olive oil, plus more to finish**
- **2 large garlic cloves, chopped (about 2 teaspoons)**
- **Two 28-ounce (988 g) cans crushed or whole peeled tomatoes (preferably San Marzano)**
- **1 cup (150 g) raw cashews**
- **1/2 teaspoon kosher salt**
- **Flaky salt (optional)**
- **1/2 cup (10 g) fresh basil leaves, plus a few small leaves for garnish**

INSTRUCTIONS

1. Heat the oil in a medium saucepan over medium heat. Add the garlic and cook until golden, 1 to 2 minutes. Pour in the tomatoes, cashews, and kosher salt. Bring to a boil then reduce to a gentle simmer, stirring often. Cook until the liquid has reduced slightly and the cashews are softened, about 30 minutes.

2. Carefully transfer the soup to a blender (cover the lid with a kitchen towel to prevent splatters) and blend on low speed for 10 seconds, then work up to high speed until the soup is more orange than red and completely smooth, 2 to 3 minutes. Add the basil and blend for about 30 seconds.

3. To serve, divide among four bowls, drizzle with olive oil, and sprinkle with flaky salt (if using). Garnish with basil.

Scan for more delicious & brain-healthy recipes created by Annie

MEMORYMORSELS®
A WOMEN'S BRAIN HEALTH INITIATIVE

This edition's recipes are courtesy of Annie Fenn, physician, chef, culinary instructor, and the author of *The Brain Health Kitchen*.

For more recipes and the latest from our Featured Foodie, **Annie**, visit: memorymorsels.org

@BRAINHEALTHKITCHEN

BRAIN BUZZ®

CONTINUING SUPPORT FOR WBHI AND WOMEN'S BRAIN HEALTH

MARCH 2023
PRESENTED BY RBC WEALTH MANAGEMENT

WBHI VANCOUVER LAUNCH

ANNE KINVIG, JUDY ROGERS, NANCY LAUGHTON, LYNN POSLUNS, MARCIA GAY HARDEN, GARY SEGAL, CHRIS OOSTHUIZEN, JOANNE KORTEN, SONIA SUNGER

APRIL 2023
PRESENTED BY CIBC

BRAINSUITE™ FEED YOUR BRAIN

DR. LAURA BEST, DR. IRWIN ADAM EYDELNANT, ALEX SAMSON, CATHY WILLIAMSON, JOANNE KORTEN, SUSANNA PETROVIC, NIKKI BALL

JUNE 2023
PRESENTED BY CIBC

BRAINSUITE™ ACTIVATE YOUR MIND

EMILY HOSTLAND, NATALIA FARQUHAR, JADE CRYSTAL, HEATHER GOODWIN

MAY 2023
PRESENTED BY RBC WEALTH MANAGEMENT

HEALTHY BODIES, HEALTHY MINDS

DR. SHERRI HAYDEN, DR. CHRISTINE SIMMONS, DR. SOFIA AHMED, DR. CARA TANNENBAUM, CHRIS OOSTHUIZEN, LYNN POSLUNS, JENNIFER PALMA, JENNIFER HILBORN, MARK LASH, JOHN HAMILTON

WOMEN'S BRAIN HEALTH INITIATIVE
BOARD OF DIRECTORS & OFFICERS

Jeanne Beker*
Journalist, Author & Fashion Entrepreneur

Dr. Vivien Brown
MDCM, CCFP, FCFP, NCMP, Assistant Professor, University of Toronto

Brenda Dee
President, Brenda Dee & Associates Inc.

Catherine Delaney*
President, Delaney Capital Management Ltd.

Terrie-Lynne Devonish*
Chief Legal Officer & Corporate Secretary, Altus Group

Arlene Dickinson*
CEO, Venture Communications

Janice Fukakusa*
Corporate Director & Chancellor, Toronto Metropolitan University

Mark Girard
CFO, Cedarpoint Investments

Susan Hodkinson
Partner & COO, Crowe Soberman LLP

JoAnne Korten
Executive Director, Women's Brain Health Initiative

Mark Lash
Founder & President, Mark Lash

Nancy Laughton
Former Managing Director, LHH Knightsbridge

Rosie MacLennan*
Olympic Gold Medalist

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

Ellen Rachlin (U.S.)
Former Managing Director, J.P. Morgan

Heather Reisman*
Founder & CEO, Indigo

Dr. Erna Snelgrove-Clarke
Vice-Dean & Director, School of Nursing, Associate Professor, Queen's University

Fran Sonshine*
National Chair, Canadian Society for Yad Vashem

Kirstine Stewart*
World Economic Forum Executive Committee

Will Stewart
SVP, Hill+Knowlton Strategies

Sarah Widmeyer
Director & Head, Wealth Strategies & Chief Marketing Officer, Richardson Wealth

*Honorary

YOU CAN SUPPORT WOMEN'S BRAIN HEALTH INITIATIVE AND BE A CHAMPION FOR WOMEN AND THEIR BRAIN HEALTH. YOUR CHARITABLE DONATION CAN FURTHER INTENSIFY OUR IMPACT, ALLOWING US TO REACH MORE AND TEACH MORE.

Women's Brain Health Initiative

Yes! I'd like to support Women's Brain Health Initiative now with my gift of:

☐ $2,000 ☐ $1,000 ☐ $500
☐ $250 ☐ $100 ☐ Other $_____

☐ I have enclosed a cheque payable to Women's Brain Health Initiative

☐ I prefer to use my credit card

You can also donate online at ***womensbrainhealth.org/donate***

DONOR NAME

ADDRESS

ADDRESS

CREDIT CARD NUMBER

EXPIRY DATE: MM/YY

CVD

NAME ON CREDIT CARD

PHONE NUMBER

E-MAIL

SIGNATURE

30 St. Clair Avenue W., Suite 900 | Toronto, Ontario | M4V 3A1 | 1-877-927-2011 | info@womensbrainhealth.org


Your valuable support powers our efforts, and
your memories
are worth the investment.
Women's Brain
Health Initiative
DONATE TODAY
SCAN QR CODE OR
VISIT WBHI.ORG
Charitable # 80099 3206 RR0001 | 501(C)(3) | Tax-exempt organization