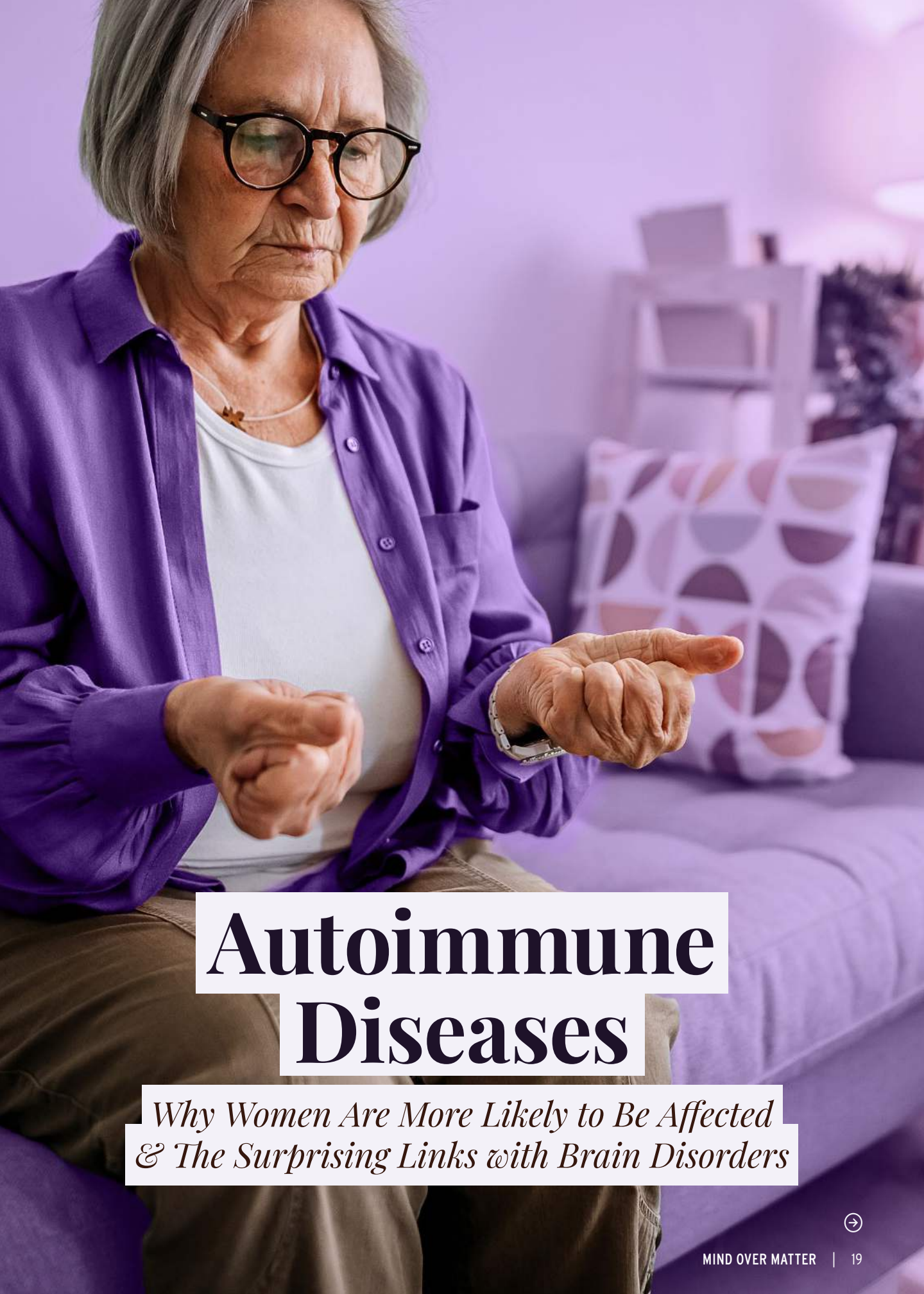

Autoimmune Diseases

Why Women Are More Likely to Be Affected & The Surprising Links with Brain Disorders

Selma Blair, the *Legally Blonde* and *Cruel Intentions* actress, posted on Instagram in May 2018 that she experienced four years of postpartum depression and crippling anxiety after her son's birth in 2011.

Later in 2018, Selma was diagnosed with multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system that damages the protective covering around nerves in the brain and spinal cord. MS symptoms are unpredictable and include trouble walking, muscle weakness in the arms and legs, spasticity, fatigue, and blurred vision.

Women account for almost 80% of people affected by autoimmune diseases, conditions in which the body's immune cells mistakenly attack healthy cells.

MS is one of more than 100 autoimmune diseases that predominantly affect women.

To understand why these diseases disproportionately plague women, researchers have found compelling clues in sex chromosomes, sex hormone changes during pregnancy, and immune responses. They have also found surprising links between autoimmune diseases and depression, dementia, and Alzheimer's disease (AD), which also affect more women than men.

"It's essential to understand the underlying factors driving sex-related differences in autoimmune diseases and brain disorders," said Dr. Hilary Brown, an associate professor in the Department of Health and Society at the University of Toronto Scarborough.

"Greater understanding of how risk factors for both disease categories arise in women over their lifespans will hopefully lead to better screening, earlier diagnoses, and greater access to treatments.

X-RELATED DIFFERENCES

Chromosomes contain genes that, when activated, provide instructions for making proteins that perform functions inside the body's cells. Female and male embryos have 22 identical pairs of chromosomes plus an additional pair of

AUTOIMMUNE DISEASES IN WOMEN

Autoimmune diseases are the fourth leading cause of disability in women under 65, typically arising between the ages of 15 and 60. Examples of some of the most common autoimmune diseases affecting women are as follows:

AUTOIMMUNE DISEASE	MAJOR AREAS AFFECTED	RATIO WOMEN: MEN	AVERAGE AGE OF ONSET/DIAGNOSIS
Sjögren's syndrome	Eyes and mouth	9:1	40-60
Systemic lupus erythematosus (lupus)	Skin, joints, kidneys, brain	7:1	15-55
Rheumatoid arthritis	Fingers, wrists, feet, and ankle joints	3:1	30-60
Systemic sclerosis	Skin and internal organs	3:1	20-50
Multiple sclerosis	Nerve sheath tissue in brain and spine	2:1	20-49

sex chromosomes; females have an XX pair, and males have an XY pair.

During in-utero development, only female embryos undergo X inactivation, a process that silences the expression of genes on one of the two X chromosomes. In some cells, the X chromosome inherited from the father is inactivated, in others, the X chromosome inherited from the mother is silenced.

The process is random, occurring on a cell-by-cell basis. If X inactivation didn't happen, women could make twice the amount of proteins needed, which could be toxic.

PROBLEMS CAN ARISE WHEN SOME GENES AVOID X INACTIVATION, RESULTING IN AN EXCESS PRODUCTION OF PROTEINS THAT PROMOTE INFLAMMATION AND AUTOIMMUNE DISEASE.

Incomplete X inactivation – where some genes remain active on both X chromosomes – is one of the leading theories about the cause of lupus, according to a narrative review published in *Cureus* in 2020.

Dr. Howard Chang, a professor of genetics and dermatology at Stanford Medicine, led a recent study that provided new insights into the X inactivation process. Dr. Chang and colleagues discovered that when hundreds of RNA molecules called Xist coat an X chromosome to silence it, the process triggers the production of antibodies that latch onto the Xist molecules and their protein partners.

These molecular bundles trigger strong responses by immune cells when they move out of the cell nucleus in response to stress, injury, or cell death.

To demonstrate that these bundles increased autoimmunity regardless of sex hormones, the investigators created male mice that made Xist. The male mice showed signs of autoimmune disease similar to female mice.

Dr. Chang and his team also found that blood from people with autoimmune diseases was more likely to have autoimmune antibodies that recognized Xist-protein bundles than blood from healthy people. Their study was published in *Cell* in February 2024.

Other X-related differences between men and women trace to differences in genes. The X chromosome contains more immune-related and immune-regulatory genes than the Y chromosome.

WHILE THIS DIFFERENCE MEANS WOMEN MOUNT STRONGER IMMUNE RESPONSES TO INFECTIONS AND VACCINES, AND TEND TO CLEAR INFECTIONS SOONER THAN MEN, IT ALSO RESULTS IN A HIGHER PREDISPOSITION FOR DEVELOPING AUTOIMMUNE DISEASES.

Genes on the X chromosome are called X-linked genes, and some are directly tied to autoimmune disorders. For example, hyperactivation of the gene *TLR-7* is associated with early-onset lupus, type 1 diabetes, and Sjögren's syndrome.

But why do women have all of these X-related differences in the first place? Dr. Melissa Wilson, a computational evolutionary biologist at Arizona State University, and colleagues proposed that incomplete X inactivation and X-linked genes evolved as a way for women to withstand dramatic shifts in immune states during pregnancy. Their paper was published in *Trends in Genetics* in 2019.

SEX HORMONE DIFFERENCES

Women undergo significant and dynamic changes in sex hormones during pregnancy. For example, estrogens increase about 300-fold by week 30 and remain elevated until dropping sharply after giving birth.

Dr. Liisa Galea, the Treliving Family Chair in Women's Mental Health at the Centre for Addiction and Mental Health in Toronto, along with Dr. Brown, described how the immune state in a woman's body changes dramatically during the three trimesters of pregnancy in their review paper published in *Psychoneuroendocrinology* in February 2025:

- at the beginning of the first trimester, an increase in **the Type 1 Helper (TH1)-immune response creates a pro-inflammatory state that facilitates embryo implantation**. Think of the TH1 immune response as the first reaction to an invading virus or injury, signalling immune cells to launch an immediate attack;

- after implantation, **an increase in the TH2 immune response results in an anti-inflammatory state that lasts most of the pregnancy**. Think of the TH2 immune response as the one that focuses on rallying the production of antibodies and autoantibodies, which attack cells made by the body; and

- **just before birth, the immune system returns to a pro-inflammatory state, facilitating the onset of labour**. This state continues for a few months postpartum.

"These swings in inflammatory states are necessary to protect the health of the baby and the mother during pregnancy," said Dr. Brown.

> *Population studies, however, show that pregnancy may be linked to an increased future risk of developing autoimmune diseases.*

For women with pre-existing MS, rheumatoid arthritis, Graves' disease, and Hashimoto's thyroiditis, symptoms tend to improve during the second trimester and relapse in the postpartum period, as these diseases are driven more by TH1 immune responses. On the other hand, women with systemic sclerosis and lupus, which are driven more by TH2 immune responses, tend to experience worse symptoms in the second trimester.

Another plot twist? Experiencing a pregnancy complication ramps up the risk of developing an autoimmune disorder. A separate population study of more than 1.7 million single births in Ontario, led by Dr. Brown and postdoctoral fellow Dr. Natalie Scime, found that pregnancy complications were associated with a 3.1% incidence of developing a new autoimmune disorder for up to 19 years after delivery compared to a 2.6% incidence for women who did not have pregnancy complications.

The elevations in risk in the pregnancy complications group were modest, but the difference between groups was significant, Dr. Brown said. The largest increases in risks of developing an autoimmune disorder were found within the first three years after delivery in women who experienced pre-eclampsia (22% elevated risk), stillbirth (36%), and spontaneous preterm birth (30%). The study was published in the *International Journal of Epidemiology* in August 2024.

"Our study found that the higher risk of developing new-onset autoimmune diseases after experiencing pregnancy complications plateaued but remained elevated over the long term compared to individuals not experiencing pregnancy complications. Again, inflammation could be a common factor driving these associations," said Dr. Brown.

> *We hope that our findings raise the awareness of pregnancy experiences on women's lifetime risk of developing chronic autoimmune disorders.*

"There has been a lot of research on reducing autoimmune-related health risks through lifestyle behaviours, which are important. However, our research suggests women with a history of pregnancy complications should be monitored closely for symptoms of autoimmune disease. Likewise, healthcare providers evaluating women for autoimmune diseases should ask them about their past pregnancy experiences."

LINKS WITH BRAIN DISORDERS

The changes in inflammatory states during pregnancy increase the short- and long-term risks of psychiatric and neurodegenerative disorders, said Dr. Brown. For example, the risk of developing a new psychiatric disorder is seven times higher during the early postpartum period compared to about a year after birth.

Dr. Galea and Dr. Brown's research has also revealed that some pregnancy characteristics may increase the risk of psychiatric and neurodegenerative disorders:

- **carrying a male fetus is associated with increased inflammation** and may be a contributing factor to depressive symptoms experienced during pregnancy;
- **carrying a male fetus is associated with a higher risk of postpartum depression** than depression that occurs during the pregnancy; and
- paradoxically, **never having given birth and having five or more children are both associated with an increased longer-term risk of AD**. Having five or more children is associated with a 1.7 times higher risk of AD than fewer pregnancies.

> *Remember that these findings are associations, not causal relationships.*

"There are many other factors associated with the number of pregnancies and the development of mental disorders like depression and chronic diseases like Alzheimer's," continued Dr. Brown.

Beyond these pregnancy-related associations, recent population studies have found significant, bidirectional links between autoimmune diseases and mental health disorders.

A Danish study of more than 64,000 people found that those with autoimmune diseases had a 13% increased risk of developing a subsequent mental health disorder, and

Neurologic symptoms can manifest in any autoimmune disease that affects joints and tissues. However, MS, lupus, rheumatoid arthritis, celiac, and Grave's disease are more often linked with many psychiatric symptoms, including anxiety, depression, and psychosis.

people with mental health disorders had a 27% higher risk of developing a subsequent autoimmune disease. The paper was published in *Brain, Behavior, and Immunity* in January 2021.

A population study from Sweden found that among people with dementia, those who also had rheumatoid arthritis experienced faster cognitive decline and had a 15% greater risk of death compared to their counterparts without rheumatoid arthritis. The study was published in *Neurology* in March 2025.

IS ALZHEIMER'S AN AUTOIMMUNE DISEASE?

Dr. Donald Weaver – a professor of chemistry, medicine/neurology, and pharmaceutical sciences at the University of Toronto and a senior scientist at University Health Network's Krembil Brain Institute – and colleagues proposed that AD may be an autoimmune disease. Their paper was published in *Translational Research & Clinical Interventions* in April 2022.

Their theory is that the buildup of amyloid beta in the AD process begins as a protective mechanism of the brain's immune system in response to a trigger, like a head injury, excessive air pollution, or an infection. Trouble occurs when the amyloid beta mistakenly attacks healthy neurons. As the dying neurons fall apart, they release substances that increase inflammation, causing a vicious cycle of neurodegeneration over time.

DIAGNOSIS TIPS

Getting a proper diagnosis for an autoimmune condition can be challenging because symptoms can come and go and affect different parts of the body. While autoimmune disease symptoms vary by disease, many share the following in common, according to Johns Hopkins Medicine:

- fatigue;
- joint pain and swelling;
- skin problems;
- abdominal pain or digestive issues;
- recurring fever; and
- swollen glands.

A survey by the Autoimmune Association found that most people who were eventually diagnosed with a serious autoimmune disease had significant problems getting a correct diagnosis. Many were incorrectly diagnosed and told their symptoms were "all in their heads" or stress-related.

Disturbingly, 45% of patients with autoimmune disease had been labelled as chronic complainers.

On average, people saw four different doctors over four years before being diagnosed. A surprising reason why getting a diagnosis is so difficult may trace back to Xist, which only forms in women in the presence of two X chromosomes. The standard test for detecting autoimmune disease, the antinuclear antibody test, does not recognize Xist because it was developed using a male cell line as a reference, explained Dr. Chang in a Stanford Medicine *Health Compass* podcast.

ADVOCATING FOR CHANGE

Selma Blair's 2021 documentary *Introducing, Selma Blair* chronicled her struggles with debilitating fatigue, difficulty walking, muscle weakness, spasticity, and the challenging treatments she underwent to achieve remission.

One of those treatments was a stem cell transplant with her own stem cells to establish a new immune system. Similar to restoring your computer's operating system to an earlier point in time, the procedure aims to restore the immune system to an earlier time before it started recognizing self-cells as foreign invaders.

Over the last 25 years, stem cell transplantation has increasingly been used to treat severe autoimmune diseases like MS. This intensive treatment is only used when the benefits outweigh the risks.

Selma's treatment plan helped her achieve remission. She still requires immunosuppressant medication to keep relapses at bay, and her rheumatologist continues to monitor her progress closely.

But she's back in the spotlight, appearing in designer looks at Paris Fashion Week in June 2024 and walking across the red carpet without a cane at the Daily Front Row Fashion Los Angeles Awards in April 2025. She is also a spokesperson for the manufacturer of her medication, raising awareness about the importance of paying attention to symptoms, seeking a diagnosis, and accessing treatments.