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. →

Women & Hypertension

A CONVERSATION WITH NEPHROLOGIST DR. SOFIA AHMED

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."