

# INNOVATIONS

## ► in Women's Health

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A QUARTERLY PUBLICATION of Women's Health Research at Yale



## A New Standard

### Improving the Diagnosis of Heart Disease in Women

Dr. Samit Shah has seen it too often.

Women come to a hospital Emergency Department or doctor's office complaining of chest pain, shortness of breath, nausea, lightheadedness, jaw pain, or other symptoms considered concerning for a heart problem. The women might undergo standard testing to see if they have a critical cholesterol blockage in their arteries, the hallmark of obstructive coronary artery disease.

But only 50 percent of women presenting with these symptoms show a blockage after cardiac catheterization – a procedure in which a long, thin tube is inserted through the blood vessels to the heart – and an angiogram – an x-ray of

the blood vessels taken to show the blood supply to the heart muscle. If a blockage is not detected, they are often sent home without additional testing or a clear diagnosis.

“Women are suffering because of this,” said Shah, an interventional cardiologist at Yale School of Medicine. “If we tell patients they have no blockages, but don't do further testing, they will have ongoing symptoms and probably end up in the ER again. If we take the extra steps that we are now learning to take, we can make accurate diagnoses and help patients better manage their disease.”

With this year's Wendy U. and Thomas C. Naratil Pioneer Award, Dr. Shah is leading a team to demonstrate

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**A New Standard** (Continued from front cover)

the effectiveness of validated, but not widely administered procedures for the many women who have reduced blood flow to the heart without blocked arteries or cholesterol build-up often associated with heart disease.

The tests are designed to detect conditions that elude the standard angiogram. One condition, known as microvascular disease, involves the smaller blood vessels that branch off the larger blood vessels to supply blood and the oxygen it carries to the heart. These smaller vessels control the amount of blood flow to the heart and can increase flow by up to four times when needed to meet increased demand while exercising.

In coronary microvascular disease – associated with high blood pressure and possibly caused by disease to the blood vessels themselves or damage from a prior heart attack – the smaller blood vessels do not open up when required, preventing the heart from receiving the blood it needs. To a patient, this could feel the same way a blockage might feel.

A second condition, known as coronary vasospasm, causes blood vessels to clamp down when they should open up, possibly triggered by cold air, smoking, or stress. To the patient this also feels like a heart attack but involves no blockage and cannot be detected by a standard angiogram or stress test.

Dr. Shah's team is studying 100 women over two years who get referred for coronary angiography to Yale New Haven Hospital and comparing outcomes for patients who receive the standard care with those undergoing the cutting-edge tests to detect coronary microvascular disease or vasospasm. His goal is to show the value of the new tests, already covered by insurance, so they become the

standard of care for patients – mostly women – who have reduced blood flow to the heart but no obstruction.

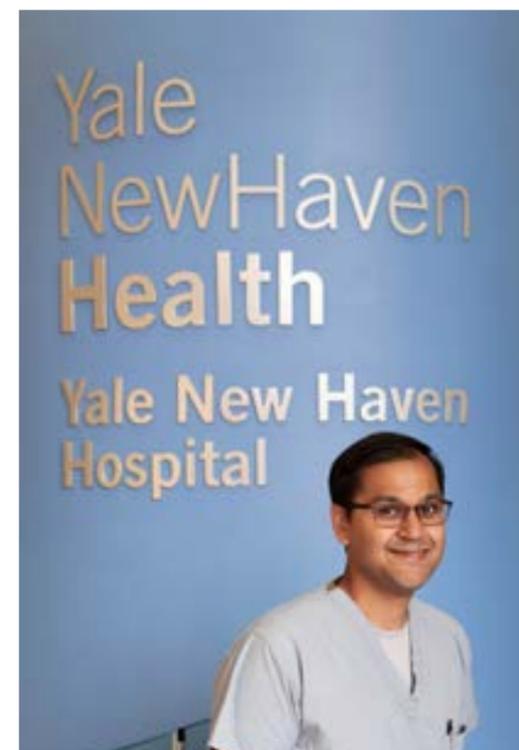
In addition, the researchers are using structured interviews to compare the patients' experiences, including their perception of their illness, ability to control symptoms, quality of life, lifestyle modification, and medication changes.

"We see patients coming back with the same symptoms, and we do not know what the toll is on them when they are left without answers," Shah said. "If we can change that experience, characterize it, and give women a diagnosis, we can avoid future invasive procedures and help them to better manage their health."

The researchers are also constructing a registry of data and procedural practice to share with other institutions, building on WHRY-funded work begun by Dr. Erica Spatz to guide future research and treatment for heart disease so that it more accurately represents the biology and experiences of women. People with microvascular disease benefit from different medications than patients with coronary vasospasm, and sometimes when you mix them together, people do worse, Shah said. By demonstrating the effectiveness of these additional tests, he hopes to better target medical therapies to meet patients' needs.

"One female patient said to me, 'I'm 55 years old and active,'" Shah said. "Why am I on the same medication as my dad who had a quadruple bypass?" Current medical practice does not have the answer to her question, but Shah expects his study to help change that.

"Beyond saving lives, getting re-admitted for the same problem is a burden on the patient and the system," he said. "We can do better." ◀



**ABOUT THE INVESTIGATOR**

**Dr. Samit Shah** earned his M.D. and Ph.D. from University of Illinois School of Medicine and his B.S. from Pennsylvania State University. At Yale, he is an Assistant Professor of Clinical Medicine and a practicing interventional cardiologist who specializes in the invasive evaluation of coronary physiology as well as coronary and peripheral vascular interventions.

Dr. Shah's scholarly work has focused on coronary physiology and peripheral vascular disease. He has active research projects at Yale regarding the invasive assessment of coronary physiology, including coronary microvascular disease and endothelial dysfunction, as well as the vascular effects of psychological stress.



## Sleepless: In a Battle Testing an Insomnia Intervention for Black Women

When Dr. Soohyun Nam meets with female members of predominantly Black churches, the conversation often shifts from her advertised topics of obesity and sleep difficulties to what the women perceive as the source of many of their health problems: stress.

“We would be talking about eating and diet, and then all of a sudden it became about stress, stress, stress,” said Nam, Associate Professor of Nursing at Yale School of Nursing. “We all have stress, but as the data have shown us, women can experience more pervasive stress, and Black women often experience pervasive stress because of daily encounters with racial discrimination. And this has a significant impact on health.”

Excessive stress can lead to insomnia, a condition that is undertreated and more common in women than men. It is defined by sleep difficulties that are associated with anxiety, moodiness,

fatigue, irritability, poor work performance, headaches, unhealthy eating, and sedentary lifestyles. People with chronic insomnia are more likely to also have cardiometabolic disease — cardiovascular disease combined with obesity and diabetes. In fact, people who have insomnia are 41 percent more likely to have a heart attack and 55 percent more likely to develop coronary heart disease or have a stroke than people without the disorder.

“Insomnia is not just a sleep problem,” Nam said. “If we provide treatment to improve insomnia, maybe we can improve cardiometabolic health and save lives.”

Currently, 30 percent of American adults suffer from some form of insomnia, but the condition affects Black women disproportionately. For example, even when studies account for socioeconomic status, Black women report shorter total sleep time than

White women and greater difficulty falling asleep and staying asleep. However, there have been no studies published to date that focus on psycho-behavioral interventions for Black women to address their sleep deficits.

The most common treatments for insomnia are sleeping pills, which carry the risks of side effects, tolerance, and dependence without addressing the underlying causes of sleeplessness. The most common non-pharmaceutical therapy for insomnia is called cognitive behavioral therapy (CBT), an evidence-based treatment that seeks to help patients develop coping skills and change the way they think, feel, and behave. While used for conditions as diverse as depression, anxiety, and substance use disorders, CBT for insomnia can be difficult for much of the public to access because of cost and its practice being largely limited to academic medical centers. In addition, although effective, CBT only prevents

recurrence of the insomnia 40 percent of the time.

With a grant from Women’s Health Research at Yale, Dr. Nam is testing — for the first time — an evidence-based stress-reduction intervention for insomnia that has shown potential for addressing the underlying causes of sleep difficulty in a manner culturally sensitive to the needs of Black women.

“When lying down in bed, someone might fixate on a troubling incident from earlier in the day, leaving her hyper-aroused and unable to sleep,” Nam said. “This triggers worries about not sleeping and not functioning the following day, which makes it even harder to fall asleep. We need to break that cycle.”

Dr. Nam’s approach uses a mindfulness-based therapy for insomnia (MBTI), an eight-week group therapy program in which participants gain an awareness of their thoughts that fuel the stress they feel and the skills to regulate their responses to stress. The program includes daily home practice and is designed to cultivate

*(Left photo) Dr. Soohyun Nam (right) meets with Ann Greene, former community research liaison for YSM’s National Clinician Scholars Program.*

### ABOUT THE INVESTIGATOR

**Dr. Soohyun Nam** earned both her master’s degree as an adult nurse practitioner and her Ph.D. in nursing from University of California, San Francisco (UCSF) and her BSN from Seoul National University in Seoul, South Korea. At Yale School of Nursing, Dr. Nam is an Associate Professor in the Adult Gerontological, Family, and Women’s Health nurse practitioner specialty and Ph.D. program.

As a member of the Steering Committee on Community Projects in the Yale Center for Research Engagement, Dr. Nam has nearly a decade of experience working closely with members of the Greater New Haven community. She has previously

non-judgement, self-compassion, and present-focused awareness.

In this study, Nam and her team are comparing the amount and quality of sleep experienced by the MBTI participants with another randomly assigned group receiving general education in healthy eating, physical activity, and proper sleeping strategies.

Participants are measuring their body weight and height using portable electronic devices and evaluating daily stresses and sleep practices through remotely conducted surveys. Participants are wearing a device on their wrist called an actigraph to detect periods of activity and rest, supplemented with a daily diary and text message reminders. The researchers are also using home saliva

kits to collect and analyze samples for levels of cortisol, a hormone associated with stress.

Dr. Nam anticipates that the group receiving the MBTI intervention will show improved sleeping results and reduced levels of stress compared with the control group. With these data, she plans to design a much larger trial to justify the widespread dissemination of this intervention for the benefit of this underserved population of women.

“Mindfulness focuses on how you live with the stress, not just get rid of it,” she said. “You regulate your emotion. And hopefully, we can help women achieve the rest they need so they can better maintain their health and well-being.” ◀



found that adults of diverse race and ethnicity can face barriers to accessing and navigating health care systems and to managing chronic diseases that often require substantial health

behavior change and self-management. Her current work focuses on reducing health disparities by addressing social determinants of health in underserved and overburdened populations.



## Opioids, Pain, and the Brain Mapping Out a Healthier Future for Women

What if we could peer into our brains and find evidence capable of predicting the future?

What if this were possible for something even as complicated as knowing the likelihood of a relapse for those recovering from a substance use disorder?

At Yale, this is not a hypothetical. And, with a new Women's Health Research at Yale-funded study on the biological intersection of pain and opioids, the future is now.

Dr. Sarah Yip, Assistant Professor of Psychiatry and Director of the Yale Imaging and Psychopharmacology Lab, is using a new technique developed at Yale by Dr. Todd Constable, Director of MRI Research, and colleagues. Dr. Yip aims to understand for the first time how patterns of brain organization might differ between women and men in the experience of pain and analgesia for the purpose of learning how to better

treat chronic pain and avoid opioid addiction.

Known as connectome-based predictive modeling, the technique provides a "brain map of connections" associated with a behavior of interest, such as future substance use following treatment for addiction. The researchers first examine a set of data involving brain images and behaviors to build a predictive model in a training dataset. Then, the researchers see if they can use the connections that they have found to predict the same behavior in an entirely new group of people — the testing dataset.

This well validated "machine learning" method is designed to avoid overfitting to any specific data set and thereby increases the likelihood their findings will be generalizable and applicable to real-world settings. Dr. Yip and her colleagues have already applied this technique to successfully predict cocaine abstinence during a 12-week treatment program.

"The goal of traditional statistical approaches is to explain the relationship between two variables," Yip said. "The goal of this new technique, guided through machine learning, is to generate predictions in novel data. It's the difference between looking backward versus looking forward."

Yip, working with co-project leader, Dr. Sarah Lichenstein, and Dr. Declan Barry, is building on her prior work with colleagues Drs. Kathleen Carroll and Marc Potenza published in the American Journal of Psychiatry and in Molecular Psychiatry. Using magnetic resonance imaging (MRI), they aim to use this form of brain mapping to identify a "neural fingerprint" that shows pathways in the brain involved in the sensation of pain and pain relief through opioids.

This study will be one of the first studies to investigate the neurobiology of pain and analgesia at the same time as investigating sex differences. Fewer

than 15 percent of participants in neuroimaging studies of opioid use disorder (OUD) have been female, and none of these studies sought to identify differences between females and males.

This is important because women account for 70 percent of Americans suffering from chronic pain and are more likely than men to become exposed to opioids when seeking medical treatment for pain. Once exposed, women are more likely than men to become addicted. Overdose deaths from opioids have grown for years and spiked substantially during the COVID-19 pandemic. The rate of increase in overdose deaths also has

grown more for women than men. Altogether, a detailed understanding of how sex influences pain and pain relief promises a better way for women to treat their chronic pain.

Moreover, researchers have developed evidence-based treatments for substance use disorders that work for some individuals. But simple clinical variables such as baseline severity and years of past use do not consistently predict treatment success. Here too, Yip's study could help identify sex-specific treatment targets for substance use based on how brain patterns of women and men process rewards and achieve abstinence. It

could also identify individuals more likely to relapse into opioid use who can then be provided additional resources that would be cost effective, such as more frequent interactions with a counselor specializing in substance use prevention.

"The current standard of addiction treatment often involves multiple failed attempts," Yip said. "Identifying the people most at need and designing treatments best suited for their individual needs would save money in the long run. More importantly, women are suffering, and science can show us how to help." ◀

Dr. Sarah Yip (left photo) meets with members of her lab studying the biological intersection of pain and opioids. (Right photo) Dr. Sarah Lichenstein (right) is also leading the project.

### ABOUT THE INVESTIGATORS

**Dr. Sarah Yip** earned her Ph.D. from The University of Oxford in England, her M.S. from University College London, and her B.A. from New York University. At Yale School of Medicine, she is an Assistant Professor of Psychiatry who uses neuropsychiatric research methods to identify the biological mechanisms of addictions and other psychiatric disorders and to investigate sex differences. Her work includes application of machine learning approaches to identify predictive neuro-markers of cocaine and opioid use and individuals' responses to different forms of medication-assisted treatments for opioid use disorder. This work has recently expanded to include predictive modeling of neuroimaging data to identify markers of alcohol initiation and misuse in youth.

**Dr. Sarah Lichenstein** earned her Ph.D. and M.S. from the University of Pittsburgh and completed a doctoral internship in clinical and community psychology and a postdoctoral fellowship in neuroimaging sciences at Yale School of Medicine. She received her B.A. in psychology from Bard College. At Yale, she is an Assistant



Professor of Psychiatry building a research program focused on neural mechanisms of risk for mood and substance use disorders in adolescence and emerging adulthood, including how sex and gender influence

the development of these disorders, neural mechanisms of cannabis-related harm, and the effects of cannabis and other substance exposure on neurodevelopment.

## What Do We Mean by Sex and Gender? By Carolyn M. Mazure, Ph.D.

At Women's Health Research at Yale, we are committed to advancing the health of a diverse society. We do this in large measure by studying the health of women and the similarities and differences in health outcomes between and among women and men. As we pursue our work, it is particularly important to use language that captures the different concepts of sex and gender so that our science and our findings can be more precise and better serve everyone.

What do we mean by sex and gender? Aren't these terms interchangeable? Perhaps at some point in time they were used as synonyms, but this is no longer true in science.

In 2001, a committee convened by the Institute of Medicine (IOM), a nonprofit think tank that took on issues of importance to the national health, addressed the question of whether it mattered to study the biology of women as well as men.

The IOM, now embedded within the National Academies of Science, Engineering, and Medicine (NASEM), concluded there was more than sufficient evidence that, beyond reproductive biology, there were major differences in the biology of women and men that greatly affected their health and influenced treatment and prevention strategies.

Importantly, the committee emphasized that neither the health of women nor men is simply a product of biology but is also influenced by sociocultural and psychological experience. To differentiate between these broad areas of investigation, the members created working definitions of "sex" – when referring to biology – and "gender" – when referring to self-representation

influenced by social, cultural, and personal experience.

The committee advised that scientists use these definitions in the following ways:

In the study of human subjects, the term **sex** should be used as a classification, generally as male or female, according to the reproductive organs and functions that derive from the chromosomal complement [generally XX for female and XY for male].

*“Neither the health of women nor men is simply a product of biology but is also influenced by sociocultural and psychological experience.”*

In the study of human subjects, the term **gender** should be used to refer to a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation.

In most studies of nonhuman animals, the term **sex** should be used.

These working definitions were a good start in recognizing the value of studying sex and gender and their interactions, yet they were always meant to evolve. Now, we are learning more about ourselves and so must

adapt our terminology to be inclusive, respectful, and more accurate.

For example, while most people are born biologically female or male, rare biological syndromes can result in genital ambiguity. Or a resistance to a sex hormone can result in traits typical of the opposite biological sex.

Moreover, while an individual's internal sense of gender can be female or male, some people identify as nonbinary – neither female nor male. Other individuals can identify as a gender that is the same as (cisgender) or different from (transgender) the one assigned at birth.

These terms are separate from an individual's sexual orientation, which describes a person's emotional, romantic and/or physical attachments (such as straight, lesbian, gay, asexual, bisexual, and more).

In science, as our understanding grows, so must the precision of our language in communicating what we know. ◀



### TERMINOLOGY

Here are some current terms defined in Yale's "Guide to Gender Identity and Affirmation in the Workplace" that can help us all be more precise and respectful of everyone.

**Cisgender:** A term used to describe an individual whose gender identity aligns with the one typically associated with the sex assigned to them at birth. This is a term that is preferable to "non-trans," "biological," or "natal" man or woman.

**Gender:** A set of social, psychological, or emotional traits, often influenced by societal expectations that classify an individual as either feminine or masculine.

**Gender nonconforming:** A person who views their gender identity as one of many

possible genders beyond strictly female or male.

**Intersex:** Describing a person whose biological sex is ambiguous. There are genetic, hormonal or anatomical variations that can make a person's sex ambiguous (e.g., Klinefelter Syndrome, Adrenal Hyperplasia).

**Sex:** Refers to biological, genetic, or physical characteristics that define males and females. These can include genitalia, hormone levels, genes, or secondary sex characteristics. Sex is often compared or interchanged with gender, which is thought of as more social and less biological, though there is some considerable overlap.

**Transgender:** A term that may be used to describe people whose gender expression does not conform to the cultural norms and/or whose gender identity is different from their sex assigned at birth. Transgender is also considered by some to be an "umbrella term" that encompasses a number of identities that transcend the conventional expectations of gender identity and expression, including transgender man, transgender woman, genderqueer, and gender expansive. People who identify as transgender may or may not decide to alter their bodies hormonally and/or surgically to match their gender identity. Sometimes shortened to the term "trans."



## It's Time to Take Women's Health Seriously By Rick Harrison

The first accounts of the disorder known as hysteria date back to ancient Greek scrolls, characterizing the cause of various symptoms in women due to the uterus somehow migrating through the body and affecting other organs.

Over millennia, the proposed cause of hysteria shifted to psychological explanations, first rooted in psychoanalytic theory, then adapted further by other schools of thought. The term was used to explain a wide variety of what we now know to be normal reproductive functioning, confident assertive behaviors, and emotional expression, as well as actual clinical symptoms, such as the loss of appetite or pleasure associated with depression.

Looking back, we also see evidence of hysteria attributed to men. However, the history of hysteria as “emotional excess” has mostly involved unsuccessful attempts to explain aspects of women's biology and behavior considered puzzling.

Ancient history, right? Not quite. Just as public laws can often survive decades after they are understood to be outdated, hysteria remained an entry in The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders until 1980. Although contemporary health providers have parted from these concepts, misperceptions about the occurrence and cause of symptoms continue, particularly regarding the health of women.

For example, heart disease is the greatest cause of death for both women and men in the United States. However, women are less likely than men to survive a first heart attack. One of the reasons for this is that women are more likely than men to show symptoms other than those

considered “typical” by standard medical protocols and the public. These other symptoms – such as nausea, lightheadedness, shortness of breath, or pain in the jaw, arms, or back – can go unrecognized as signaling heart attack.

In fact, a study published in 2020 by the Journal of the American Heart Association found that women were significantly less likely than men to receive aspirin, cholesterol-reducing statins, and blood pressure medications – common treatments for cardiovascular disease.

In addition, women comprise 70 percent of Americans suffering from chronic pain. But research has shown that the pain women experience is often taken less seriously than the pain of men.

*“Research has shown that the pain women experience is often taken less seriously than the pain of men.”*

A study from earlier this year found that people observing videos of female and male faces expressing the same self-reported amount of chronic shoulder pain would characterize the female patients' pain as less severe and less in need of medication than the male patients' pain.

For these and many other reasons, Women's Health Research at Yale leads the way toward understanding how differences in sex, gender, and race influence



health outcomes. It is why we have launched studies determining a more accurate way to diagnose heart disease in women and to understand the intersection of pain and analgesia in males and females. It is why we are testing an intervention to treat insomnia and its health consequences that addresses the high prevalence of this sleep disorder in women, notably in Black women.

Medicine certainly has come a long way from ancient eras. Yet, there's so much more we need to investigate and understand about how health is influenced by our natural differences so that, together, we can change science to make life better for all. ◀



## Making Science Better for Women, with Women

Why give to Women's Health Research at Yale? Here's one reason: When researchers study the health of women and sex-and-gender differences in health, everybody benefits.

This is because the more we know about the biology and health behavior of women and the differences between and among women and men, the more we can develop prevention and treatment strategies best suited for every person's unique needs. This principle guides WHRY in our mission to better lives through better science.

WHRY funds and guides researchers to fill in historical gaps on the health of women and to establish critical, enduring programs of study that build upon growing bodies of knowledge and leverage expertise through interdisciplinary collaborations. We have also learned that who conducts research can be as important as what's under investigation.

For example, the authors of a recent paper published in the journal Science examined all biomedical U.S. patents granted between 1976 and 2010 and found that teams composed entirely of female inventors were 35 percent more likely to concentrate their efforts

on female health issues than all-male teams. In 2020, only 13 percent of U.S. patent recipients were women, suggesting that the world is missing out on inventions that could benefit women. In addition to focusing on the goal of marketable products, the paper's authors found that female researchers were more likely to publish findings on female-oriented topics.

At WHRY, we see the same trend. Looking back over 23 years, we have funded male and female investigators, all with great commitments to studying women and health-related sex-and-gender differences. Yet, 68 percent of our principal investigators over the last five years have been women.

We support the careers and innovative science of female investigators, but the main reason for this higher percentage of female compared to male investigators is because women have been more likely to study the health of women. Going forward, we are eager to ensure all researchers have a commitment to study the health of women as well as investigate the influence of sex and gender on diagnosis, treatment, and outcomes.



Thanks to our generous donors, WHRY is leading the way to conduct new, cutting-edge science that advances the health of women. Together we are changing science in ways that benefit all. ◀

With my thanks for your support,

*Barbara*

Barbara M. Riley  
Philanthropy Chair



# Women's Health Research at Yale

► Better science, better lives ► ►



Women's Health Research at Yale is changing the landscape of medical research and practice by ensuring the study of women and examining health differences between and among women and men to improve the lives of everyone.

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