A woman in her 50s arrives at a hospital’s emergency department short of breath, complaining of nausea and pain in her jaw.

Although the woman feels no chest pain, the attending physician immediately suspects a heart attack.

Because even though chest pain or discomfort are the most common symptoms of a heart attack in women and men, women are more likely to experience other symptoms, such as shortness of breath, nausea, lightheadedness, or pain in the jaw, arms, or back.

Similarly, among young women diagnosed with a heart attack, routine cardiac tests often do not reveal the typical findings of a heart attack — a blockage in the heart artery. There may be no blockages, or there may be other problems in the heart artery. In many instances, doctors do not know what caused the heart attack. Yet these nuances are not fully incorporated into the current classification system used to define different types of heart attacks. And so the diagnostic systems that currently exist may fall short of the gender-specific accuracy necessary to provide the best individualized treatment possible.

“For people who come to the hospital with a possible heart attack, all sirens go off and we activate a common set of clinical pathways to diagnose and treat,” said Dr. Erica S. Spatz, a general cardiologist and a clinical investigator at Yale’s Center for Outcomes Research and Evaluation (CORE). “But many young women, do not have the classic...
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PLANTING NEW SEEDS

The Rice Family Foundation Grows WHRY’s Research Efforts

Women’s Health Research at Yale has been awarded a five-year grant from The Rice Family Foundation to increase the reach and scope of the center’s successful Pilot Project Program.

The award will allow WHRY to provide seed funding for an additional project each year focused on advancing women’s health and providing data on sex and gender differences that offer the potential to improve health outcomes for everybody.

“Our are pleased to have earned the support of The Rice Family Foundation with our 18-year track record in choosing and funding the most innovative and promising Yale researchers dedicated to overcoming the large gap in knowledge about women’s health,” said WHRY Director Carolyn M. Mazure, Ph.D.

“This grant provides a significant boost toward true gender equality in biomedical science.”

Since its founding in 1998, WHRY has supplied a total of $5 million in seed grants that have gone on to generate more than $85 million in external funding for researchers to invest in their own labs and clinical research settings.

Women’s Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation. Women’s Health Research at Yale is a program within Yale School of Medicine. Yale University is a 501(c)(3) nonprofit organization.
In its second year, our undergraduate research training fellowship features three talented and accomplished students eager to work directly with senior faculty members and learn about women’s health and sex and gender differences.

HALEIGH LARSON will spend her time as a WHRY undergraduate fellow broadening her base of knowledge and advancing her science writing.

“I really like to write,” Larson said, adding that she plans to attend medical school in pursuit of an M.D. and a Ph.D. A junior from Fargo, N.D., Larson spent a summer in high school studying immunology at the National Institute on Aging, where she was invited to return two years later. As a Molecular Biophysics and Biochemistry major at Yale, she has worked as a research assistant at the Alzheimer’s Disease Research Center. Currently, she also works with Dr. David Schatz to explore the mechanisms of the immune system.

Larson spent the summer at a 10-week fellowship on advancing ways to preserve fertility after cancer therapy at The Jackson Laboratory in Bar Harbor, Maine. Back in New Haven, she expressed enthusiasm for plans to help WHRY increase health literacy through writing articles for a general audience as well as helping to produce entertaining, educational videos and measuring their effect on health behaviors.

“I’m curious about gender differences in science,” Larson said. “I want to be informed and to share that knowledge with others.”

MILANA BOCHKUR DRATVER sees the WHRY undergraduate fellowship as a way to bridge her passions for medicine, psychology, and public health.

“I really want to learn more about sex and gender differences as they relate to health outcomes,” Bochkur Dratver said. “In this mid-point of my time as an undergraduate at Yale, I could not create a better opportunity than this to continue to cultivate and refine my interests.”

A resident of Los Angeles, Bochkur Dratver volunteered and then worked at a lab at UCLA’s David Geffen School of Medicine on projects regarding radiation therapy for glioblastoma multiforme and a new drug for triple-negative breast cancer, a form of the disease that lacks estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2. She currently works with Dr. Clare Flannery in her laboratory in the Obstetrics, Gynecology & Reproductive Sciences Department at Yale. In addition, she writes for Yale Scientific magazine, serves on several educational and service-oriented boards and committees, and volunteers at the student-run Haven Free Clinic, motivating and educating patients about health and nutrition.

Bochkur Dratver will work with Dr. Lynn Fiellin at the Yale Center for Health and Learning Games, helping to design and develop videogame interventions and assessments.

“Through my recent lab work, I have found that the content I am most passionate about relates to women’s health,” Bochkur Dratver said. “Not having conducted clinical research in the past, I believe this fellowship can serve as an ideal environment for me to learn more about a field I am very interested in while contributing to an important project.”
WOMEN'S HEALTH RESEARCH AT YALE

ROSE DAVIS
is a junior premed student pursuing a degree in Molecular, Cellular, and Developmental Biology and a career as a surgeon.

For the past three summers, Rose has worked as an intern with a plastic surgeon near her home on Long Island, helping to run the office, organizing and maintaining the Operating Room, and observing surgical procedures. She has cultivated an interest in how the body heals and ages, and developed a strong desire to contribute to cancer research after observing breast reconstruction post mastectomy.

Davis also works as a guide at the Yale Center for British Art and a peer tutor. For a year, she served as Publicity Director for the Groove Dance Company.

As a WHRY undergraduate fellow, Rose will work with Dr. Lisa Freed, Director of Yale New Haven Hospital's Women's Heart and Vascular Program, shadowing work at the clinic and helping to formulate clinical research questions.

She expressed enthusiasm for the opportunity to gain new research and clinical insight that can eventually inform her medical career.

“A fuller and more well-rounded understanding of women’s health, will better help me treat, empathize and understand the psychological and physical factors affecting my patients,” Davis said.

“I think the mentoring experience was really valuable,” said LILLIAN BITTNER, now a senior who worked with Dr. Sherry McKee at the Forensic Drug Diversion Clinic.

“It really set me on a specific path. And a path that I’m really enjoying.”

For Bittner, her work at the outpatient center for people referred by the judicial system for substance abuse treatment reflected her first exposure to any type of scientific research. She entered data from medical files and began a project to determine if the patients’ traumatic life events affected treatment outcomes at the clinic.

“The first thing that really interested me about this area of work was the neurobiology behind addictive behaviors,” she said. “But getting to see this human experience — not just working in a lab with chemicals — but seeing how this affects people’s lives drove me to learn more about the mechanisms behind addiction.”

This year, Bittner plans to continue working on this topic in a laboratory setting with Assistant Professor of Psychiatry and of Cellular and Molecular Physiology Nii Antie Addy. She spent the summer at home in Colorado taking a certification class to become an emergency medical technician (EMT) before ultimately applying to medical schools.

“BIRUKTAWIT “BIRDY” ASSEFA credited WHRY’s undergraduate fellowship for helping to define her interests and talents.

“It taught me the kind of environment that I like to work in and in which I’m most productive,” she said.

Not only did she learn the skills needed to read, understand, and help advance the findings of scientific articles, but she reaffirmed her dedication to exploring science-based solutions for socioeconomic problems.

Biruktawit studied whether menthol smokers — who are more often black, female, and lower-income — are less likely to quit smoking than non-menthol smokers.

And this summer she worked at the Council on Foreign Relations in Washington, D.C., on the economics of health care in developing countries.

Next, she hopes to pursue a master’s degree in public health, focusing on policy.

“I love science but also want to help achieve social justice, perhaps as a lawyer,” Biruktawit said, noting her varied options and interests. “And of course, you can’t have social justice without addressing the inequities that have held back women’s health.”

THE FIRST CLASS

As Women’s Health Research at Yale welcomes these new undergraduate fellows this fall, our four inaugural students praised the program they completed last year for helping them refine their academic focus and establish a firm commitment to advancing women’s health.
Prior to becoming a WHRY undergraduate fellow, **LAURA GOULD GOETZ** worked on viral RNA structure and stability in Yale Sterling Professor Joan Steitz’s lab. And after studying the neurochemical and molecular basis of addiction and psychiatric disorders through brain imaging technology as a WHRY fellow with Dr. Kelly Cosgrove, she realized the type of science she wants to pursue.

“I love basic science,” Gould Goetz said, praising the program for helping her to better understand her passion. “And now I realize that I want to continue to study basic science that has a strong emphasis on translation into treatments that directly help people live healthier lives.”

A double-major in Molecular Biophysics and Biochemistry (MBB) and Women’s, Gender, and Sexuality Studies, she also wants to continue anthropological research she has begun on how colonization may have affected the biology of the Argentinian people.

**BENJAMIN FAIT** applied his scientific mind to the challenge of science communications. As a double major in MBB and Comparative Literature focusing on Latin American film, Fait had worked with Dr. Marina Picciotto in Yale Department of Psychiatry’s Division of Molecular Psychiatry. And with WHRY, he helped produce six videos in a public awareness campaign about issues facing women’s health.

“It was great to see how the apparatus works in a center like WHRY versus a lab,” Fait said. “You’re dealing with donors and the general public. It’s a different mode of communication about science.”

Fait spent the summer on a fellowship at The Pasteur Institute in Paris, working with a scientist who is also an experimental filmmaker on new mechanisms of RNA interference, the process in which RNA molecules inhibit gene expression.

But he won’t soon forget his experience helping to hone the messages and craft the language for videos seeking to educate the public about the need to study the differences between men and women.

“I think about women’s health a lot more now,” Fait said. “Everyone needs to understand that sex and gender must be addressed with careful analysis in all biomedical research.”

**EACH YEAR, ABOUT 1.5 MILLION PEOPLE IN THE UNITED STATES BREAK A BONE THAT HAS BEEN WEAKENED BY OSTEOPOROSIS, A DISEASE THAT AFFECTS MORE WOMEN THAN MEN. THIS VIDEO ON THE TOPIC IS ONE OF SIX VIDEOS THAT BENJAMIN FAIT HELPED TO PRODUCE AS A WHRY UNDERGRADUATE RESEARCH FELLOW IN A PUBLIC AWARENESS CAMPAIGN ABOUT ISSUES FACING WOMEN’S HEALTH. SCAN THE CODE ON THE RIGHT WITH A SMARTPHONE TO WATCH THE VIDEO.**
features of a heart attack, thus creating uncertainty about what is going on and how to classify the condition, and how best to treat it going forward. Yet despite the differences, we tend to group everyone together.”

Acute myocardial infarction (AMI), the technical term for a heart attack, occurs when blood flow to the heart is blocked so as to damage the muscle and potentially cause death. The condition leads to the hospitalization of about 40,000 women each year in the United States.

The typical mechanism for causing a heart attack is the rupture of a plaque or a blood clot in an artery. Plaques are waxy substances created by damage to the arterial wall, blocking blood flow needed to supply the heart with oxygen. Risk factors for plaque include smoking, high blood pressure, and high cholesterol. About one in five young women do not show evidence of a plaque rupture or a blood clot in an artery.

And yet women are grouped into classification systems that can obscure some patients’ disease processes while not accounting for some others.

With the help of a grant from Women’s Health Research at Yale, Dr. Spatz has begun testing a new method of sorting women who have had heart attacks into categories that more fully describe the ways in which women develop problems that might lead to a heart attack.

“Giving people a diagnosis or a label for their symptoms and disease course validates what they’ve experienced,” Spatz said. “And it provides the scientific community with a common language to communicate with one another about the distinct features of a disease, which can ultimately stimulate research and discovery of biological mechanisms and best practices to improve outcomes.”

The current classification system, known as the Third Universal Definition of MI, includes five categories of patient types:

- **Type 1** describes patients with a plaque rupture.
- **Type 2** involves a condition other than coronary artery disease (the plaque-caused hardening of arteries) contributing to an imbalance between the heart’s oxygen supply and demand, such as bleeding or a stroke.
- **Type 3** describes death of heart muscle with symptoms suggesting a lack of oxygen (ischemia).
- **Type 4a** includes problems related to a non-surgical procedure called percutaneous coronary intervention (PCI) in which a thin flexible tube (catheter) is used to place a structure called a stent in the artery to open it up.
- **Type 4b** describes a condition called stent thrombosis in which a life-threatening blood clot forms on a stent.
- **Type 5** involves complications from a surgery called coronary artery bypass graft (CABG) in which a healthy artery is connected to a blocked one, creating a new path for oxygen-rich blood to reach the heart.

But some symptoms and mechanisms of disease that are more common in women simply do not fit in this system.

“As a doctor, you take into account all the nuances of your patient to give the most fitting diagnosis and best estimates for treatment and prognosis,” Spatz said. “But sometimes we don’t have any evidence to support that labelling or those recommendations.”

Spatz’s team developed a new scheme based on a study funded by the National Institutes of Health called Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) and using clinical data describing patient symptoms and findings after the insertion of a catheter through blood vessels to evaluate heart function.

The researchers classified 2,802 men and women under 55 years old into five classes.

- **Class 1** describes a plaque rupture.
- **Class 2a** includes obstructive coronary artery disease with a mismatch in heart muscle oxygen demand and supply.
- **Class 2b** includes obstructive coronary artery disease without an oxygen supply-demand mismatch.

About one in five young women do not show evidence of the typical mechanism for causing a heart attack.

**PILOT PROJECT PROGRAM**

*(Continued from front cover)*

**What Kind of Heart Attack?**

**ABOUT THE INVESTIGATOR —**

**Dr. Erica S. Spatz** earned her M.D. from Ben Gurion University in Israel, an M.H.S. from Yale School of Medicine, and a B.S. from Vanderbilt University. She is a general cardiologist and has been an Assistant Professor of Medicine at Yale since 2013.

Dr. Spatz leads large research teams comparing cardiovascular outcomes among health systems and studies the factors that contribute to variation in outcomes with particular attention to socioeconomic disparities.
- **Class 3a** involves non-obstructive coronary artery disease with an oxygen supply-demand mismatch.
- **Class 3b** involves non-obstructive coronary artery disease without an oxygen supply-demand mismatch.
- **Class 4** covers some other identifiable mechanism such as spontaneous tearing of the artery wall, a sudden spasm leading to tightening of a blood vessel and lowering its flow rate, or a blockage caused by a blood clot, a globule of fat, gas, or an outside object (embolism).
- **Class 5** is for an undetermined cause.

Comparing the two classification systems, Spatz found that about 13 percent of women were unable to be classified using the traditional Third Universal Definition. The VIRGO taxonomy she helped create left out less than 1 percent of patients.

“People with Type 2 AMI can be very different from one another, yet we tend to treat them the same,” Spatz said of the older, more established classification system. “Maybe we can do better.”

The new WHRY-funded study will group patients with heart attack from other existing registries into the

**Coronary Artery Disease (CAD)**
A disease in which waxy substances called plaques build up on artery walls and block the flow of blood needed to supply the heart with oxygen.

**Acute Myocardial Infarction (AMI)**
A heart attack, which occurs when blood flow to the heart is blocked so as to damage the muscle and potentially cause death.

**Catheterization Laboratory**
Known as the Cath Lab, a room in the hospital with equipment to visualize the flow of blood to the heart for signs of obstruction.
We can do better... we need to develop new methods that incorporate people’s unique conditions.

Spatz aims to develop a system that clinicians can use when evaluating and treating patients that is more precisely attuned with their individual condition. For example, patients with an oxygen supply-demand imbalance may benefit from a different set of tests and different medication types.

Careful research that accounts for sex and gender is key to understanding what makes us different and how to care for each individual according to what’s best for her or him.

Women’s Health Research at Yale understands this. After 18 years, the center continues to launch investigations into vital health issues, build interdisciplinary research partnerships, train the next generation of researchers, engage the public and professionals in health education initiatives, and assert a national voice to inform public policy.

In addition, WHRY partners with community members and organizations to understand their needs and share vital health information for everyone to live happier, healthier, and more productive lives.

We are proud of our achievements. But as an independent, self-supporting center within Yale School of Medicine, we need private donations to finance this vital work.

Here are some of the important things your gift could do:

• fund another promising research project
• support meaningful mentorships to outstanding junior faculty members and students focusing on interdisciplinary research with a gender-differentiated focus
• underwrite newsletters and digital communications that feature
One of the primary missions of Women’s Health Research at Yale is training the next generation of scientists to study the influence of sex and gender. And perhaps there is no one better to voice that necessity than a member of that generation.

“I always thought it was unbelievable that people could conduct preclinical studies without reporting the sex of the animals or cells they are using,” said Yasmin Zakiniaeiz, a fourth-year graduate student pursuing a Ph.D. in neuroscience at Yale School of Medicine. “It’s a shock that this still goes on.”

In an effort to raise awareness about the importance of studying sex and gender differences, Zakiniaeiz and other editors of the student-run 88-year-old Yale Journal of Biology and Medicine (YJBM) decided to devote Volume 80, Issue 2 to topics addressing sex and gender.

“I’ve always had a drive for understanding and learning about sex differences,” said Zakiniaeiz, who studies the neural mechanisms of drug addiction with Drs. Kelly Cosgrove and Marc Potenza in a lab Cosgrove runs with Dr. Evan Morris. “I thought that by serving as deputy editor for this issue, I could expand my knowledge of sex and gender issues beyond neuroscience.”

Zakiniaeiz contacted WHRY Director Carolyn M. Mazure, Ph.D., who helped the student editors solicit and select manuscripts, targeting researchers conducting both clinical and preclinical studies.

The issue came out in June with peer-reviewed articles addressing the influence of sex and gender on smoking, stress and depression; the effect of tobacco smoking on mothers’ brains; the preferences patients show for the gender of their physicians in a hospital’s Emergency Department; the effects of gender-based violence on unwanted pregnancy and abortion; the effect of marijuana on the female reproductive system; and other topics.

In addition, Zakiniaeiz, Cosgrove, Mazure, and Potenza wrote an article together on addressing sex differences in preclinical research.

“The new NIH policy change has the potential to close the gap in knowledge that has persisted for decades,” Mazure said. “But it will largely fall on up-and-coming researchers like Yasmin to hold true to these ideals and make sure that sex and gender are fully embraced as variables in study design and fully analyzed and reported in published results.”

Already, Zakiniaeiz has convinced Dr. Michael Schwartz, Associate Professor of Neuroscience and Associate Dean for Curriculum, to add the study of sex differences in the brain to the curriculum of the first-year neuroanatomy course she helps teach.

“I think it’s a really important topic,” she said. “I realize that I could make a difference in the course I’m teaching and spur others to incorporate the study of sex and gender as a fully integrated component of a medical education.”

The impact of your gift could be priceless, eventually improving or even saving thousands of lives by fully exploring sex and gender. Help us continue to make progress.

Sincerely,

Bobbi Mark,
Philanthropy Chair
"We’re just at the beginning of understanding what we need to study, what’s important about the findings that we’re generating, and where to go from here."

In a public conversation in October with New York Times “Diagnosis” columnist and Yale Associate Professor of Medicine Dr. Lisa Sanders, Mazure traced the histories of U.S. public policy toward the inclusion of women in health research and of Women’s Health Research at Yale, the independent center she created in 1998 to speed that progress.

“You can never underestimate the power of a grassroots effort,” Mazure said. “And it can grow. People can see the value of it. They can support it. Get behind it. And it can continue to be very productive.”

Before an attentive crowd at The Maurice R. Greenberg Conference Center, Mazure explained how researchers historically excluded women from biomedical research because of a false perception that women were less affected by certain diseases and conditions or responded to the same treatments as men, the difficulty of accounting for the variables inherent in women’s hormonal cycles, and an interest in protecting women of reproductive age.

“She called on people to educate themselves and to engage their medical practitioners on how gender influences the health conditions they may face.

“In my experience, very reasonable practitioners will talk with you about what they know and what they think is reasonable in terms of sex differences,” Mazure said. “It’s important to know whether sex differences exist in conditions for which you are seeking medical care, and it’s important for you to ask about it.”

In addition, she encouraged people to speak to state and federal legislators and advocate for data-driven policies.

“I don’t think you can underestimate the importance of a group of individuals banding together and saying: ‘Look, this has got to change,’” Mazure said. “At the end of the day, I don’t know what’s too much more important than social justice and health. And that’s really what we’re talking about here.”

Mazure recalled with fondness and gratitude how The Patrick and Catherine Weldon Donaghue Medical Research Foundation donated the initial grant that allowed her to create WHRY and its competitive Pilot Project Program to fund Yale researchers asking questions to help close the gap that had grown in knowledge of women’s health. And she thanked Wendy and Thomas Naratil for their endowment gift establishing an additional annual award for studies that are highly inventive or on the cusp of a breakthrough.

Eighteen years later, the program has supplied a total of $5 million in seed grants that have gone on to generate more than $85 million in external funding for researchers to invest in their own labs and clinical research settings.
Mazure also stressed the need to study older women, younger women, transgender women, and women of different racial and ethnic backgrounds.

And she expressed optimism for the future of WHRY and women’s health in general, remarking on the long road ahead and the need to maintain the momentum the center has built since 1998.

“It may be interesting. I hoped people would come away more informed and possibly entertained. But other than the occasional email or phone call or in-person reaction, I had no way of knowing what, if any, effect I was having.

As the Communications Officer for Women’s Health Research at Yale, I arrived 18 months ago with a similar mindset. Here is an independent interdisciplinary center within Yale School of Medicine working to fill a gap in health knowledge that has left both women and men in unnecessary danger. I would share the stories of the researchers and clinicians working to optimize health care with more attention to sex and gender differences. I would explain the center’s mission and accomplishments and next steps. Just get the message out and hope for the best.

But working at a world-renowned research institution has a way of inspiring a need for advanced intellectual rigor in any endeavor. And when it comes to mass communication about health issues, there is no substitute for solid data on the reach and effectiveness of your messaging.

So I’m proud to announce that WHRY has begun to test the ability of our communications tools to impart knowledge and influence attitudes and behavior. As with any carefully considered effort, we have begun small and plan to expand as time and resources allow. Our goal is to develop a large enough body of data to obtain grant money that can be used for more extensive, specific, and reliable testing. Which will lead to more elaborate, widespread, and proven tools.

We don’t just want to shout into the cluttered and confusing media marketplace and hope for the best. We don’t just want to raise public awareness of an issue. We want to reach people and help influence their health decisions. We want to steer medical researchers and practitioners and policy-makers toward best practices that fully account for everything that distinguishes males and females.

People already trust nurses and doctors. We need to understand the best ways to amplify their messages and combine them with our own so we can help people primed to hear them. 📰
Women’s Health Research at Yale

FACTORING IN GENDER

135 College Street, Suite 220
New Haven, CT 06510

Women’s Health Research at Yale generates research on women’s health and sex and gender differences, dedicated to improving well-being for all through scientific knowledge translated into medical and personal practice.

To learn more, visit our website: www.yalewhr.org

Email us: WHResearch@yale.edu

And join us on social media: @WHRYale
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HELP WITH THE HEADLINES

According to a recent study, poor social relationships are associated with an increase in coronary heart disease and stroke.

For more information on this and other health topics in the news, join our email list or visit our website: www.yalewhr.org.

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