INSIDE STANFORD MEDICINE

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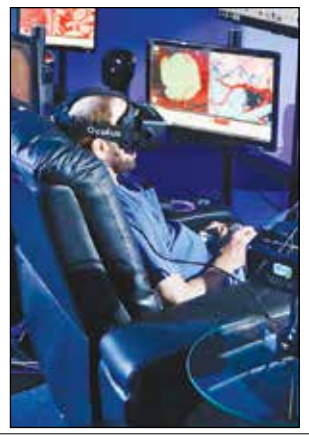

A new software system combines imaging from MRIs, CT scans and angiograms to create a 3-D model.

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Painkiller linked to kidney injury in runners

By Tracie White

People who take the painkiller ibuprofen while running very long distances double their risk of acute kidney injury, according to a study by researchers at the School of Medicine and several other institutions.

As many as 75 percent of ultramarathoners use the nonsteroidal anti-inflammatory drug, or NSAID, in this fashion, according to Grant Lipman, MD, clinical associate professor of emergency medicine at Stanford and director of Stanford Wilderness Medicine. And while most cases of acute kidney injury appear to resolve spontaneously, the condition has the potential to progress to renal failure, he said.

Lipman is lead author of the study, which was published online July 5 in *Emergency Medical Journal*. Brian Krabak, MD, a sports and rehabilitation medicine specialist at the University of Washington-Seattle, is the senior author.

PAUL SAKUMA

Grant Lipman (above) and his colleagues found that runners who took ibuprofen during ultramarathons doubled their risk for kidney injury.

"Running these races tends to hurt," said Lipman, who has served as the medical director of RacingThePlanet ultramarathon events, which are held in various parts of the world, including China, Antarctica and Chile. Lipman said he has seen firsthand how common it is for runners to take ibuprofen both before, during and after these races to relieve pain and reduce joint swelling.

Decreasing blood flow to kidneys

"In medical school, we were all taught to be careful of ibuprofen because it decreases blood flow to the kidneys," he said. However, almost all previous studies looking at the effect of the drug on the kidneys in running events have shown no negative effects, he said.

Lipman and his colleagues conducted the first randomized, placebo-controlled, double-blinded study to test the use of ibuprofen in ultramarathoners. They hypothesized that ibuprofen would not result in an increased rate of acute kidney injury compared to placebo.

The 89 participants who completed the trial were randomized to take either ibuprofen or a placebo during a 50-mile section of one of four different seven-day, 155-mile ultramarathons. They were required to refrain from taking ibuprofen at least 12 hours prior to the 50-mile section. They ran in ultramarathons either in China, Chile, Ecuador or Sri Lanka. They ran through wilderness terrain with few roads and varying topography, and they carried all their personal items for the duration of the race, including all their gear, food and clothing.

The morning of the 50-mile section, the participants were weighed, and each was given a baggie of either sugar pills or 400-milligram ibuprofen pills. They were told to take one pill every four hours.

Rates of kidney injury

Twelve- to 36-hours later, depending on the speed of the runners, the participants were met by the researchers at the medical tent. There, they were weighed, and their electrolyte levels and renal functioning were measured.

Forty-seven percent of the participants took ibuprofen, and 53 percent took the placebo. Results showed that about 39 of the 89 participants had acute kidney injury at the end of the 50-

See IBUPROFEN, page 7

Among humans in Europe and Asia, evolution favored shorter bones — with a painful trade-off, study finds

By Krista Conger

A single genetic change linked both to a reduction in human height and an increase in osteoarthritis risk might seem like it would quickly be kicked to the evolutionary curb. After all, how could it be an advantage to be both shorter and less mobile in the cutthroat competition for scarce resources and fickle mates? Darwin's finches would be appalled.

Now, researchers at the School of Medicine and at Harvard have shown that, despite its association with the painful joint disease, this genetic variant was repeatedly favored as humans migrated out of Africa and into colder northern climates. At least half of Europeans and Asians harbor the gene variant, which is relatively rare in African populations.

"Because it's been positively selected, this gene variant is present in billions of people," said David Kingsley, PhD, professor of developmental biology at Stanford. "So even though it only increases each person's risk by less than twofold, it's likely responsible for millions of cases of arthritis around the globe. This study highlights the intersection between evolution and medicine in really interesting ways, and could help researchers learn more about the molecular causes of arthritis."

NICOLAS PRIMOLA / SHUTTERSTOCK.COM

Humans in Europe and Asia evolved to have shorter bones and an increased risk of osteoarthritis. (Above) A depiction of a Neanderthal.

Cold may have played a part

A more compact body structure due to shorter bones could have helped our ancestors better withstand frostbite and reduce the risk of bone fracture from falling, the researchers speculate. These advantages in dealing with chilly temperatures and icy surfaces may have outweighed the threat of osteoarthritis, which usually occurs after prime reproductive age.

"The gene we are studying shows strong signatures of positive selection in many human populations," said Kingsley, who is also a Howard Hughes Medical Institute investigator and a member of Stanford Bio-X. "It's possible that climbing around in cold environments was enough of a risk factor to select for a protective variant even if it brought along an increase likelihood of an age-related disease

See ARTHRITIS, page 6

Tests help identify relative risk of 25 gene mutations associated with cancer

By Krista Conger

No one wants to hear that they have a mutation in their DNA associated with the development of cancer. But it may be even more difficult to accept that, in many cases, clinicians can't say whether or by how much that mutation might increase a person's actual risk of developing the disease. This uncertainty causes anxiety and clouds treatment decisions.

Now, in the largest study of its kind, researchers at the School of Medicine and at Fox Chase

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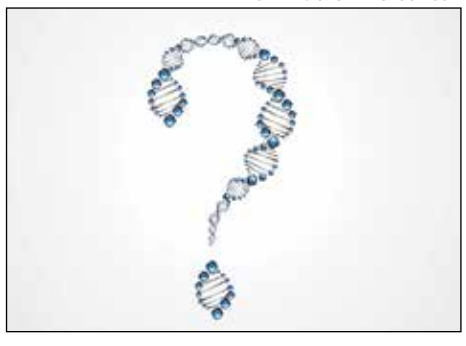

Sleep disturbances predict higher risk for suicidal symptoms

By Erin Digitale

Sleep disturbances can warn of worsening suicidal thoughts in young adults, independent of the severity of an individual's depression, a study from the School of Medicine has found.

Sleep problems among young adults at risk for suicide — especially variation in when they went to sleep and when they woke up — emerged as a warning sign of worsening suicidal thoughts in the following days and weeks, the study showed.

The study was published online June 28 in the *Journal of Clinical Psychiatry*. The lead author is suicidologist Rebecca Bernert, PhD, Stanford assistant professor of psychiatry and behavioral sciences. The senior author is Thomas Joiner, PhD, professor of psychology of Florida State University.

Suicide is the second leading cause of death among young adults, according to the U.S. Centers for Disease Control and Prevention.

"Suicide is the tragic outcome of psychiatric illness interacting with multiple biological, psychological and social risk factors," Bernert said. "Sleep disturbances stand apart from other risk factors because they are visible as a warning sign, yet nonstigmatizing and highly treatable. This is why we believe they may represent an important treatment target in suicide prevention."

Measuring sleep quality

Sleep disturbances have previously been evaluated as a risk factor for suicide, but no prior study has objectively investigated disturbed sleep as a short-term indicator of risk in young adults.

The study collected both objective and self-reported sleep characteristics among young people at a high risk for suicide. The study participants were 50 young adults, ages 18-23, selected from among almost 5,000 undergraduate students enrolled in a university research pool. The participants had a history of suicide attempts or recent suicidal ideation, meaning thoughts of suicide.

The subjects' sleep was objectively assessed for one week, during which participants wore watchlike devices containing an accelerometer to measure their wrist movements while asleep or trying to sleep. The device had been previously validated as an accurate way to distinguish sleep-wake patterns and generate a variety of sleep metrics.

At the start of the study, and seven and 21 days later, participants also answered questionnaires to measure the severity of their suicidal symptoms, insomnia, nightmares, depression and alcohol use.

Study participants who had a high degree of variability in the times at which they fell asleep for the night and the times at which they woke in the morning were more likely to experience suicidal symptoms at the seven- and 21-day marks, the researchers found. Falling asleep at very different times each night was especially predictive of an increase in suicidal symptoms, they said.

> "We believe poor sleep may fail to provide an emotional respite during times of distress."

The relationships between sleep and suicidal symptoms held even when researchers controlled for the severity of participants' depression, substance use and the severity of their suicidal symptoms at the start of the study.

Participants with a lot of variation in when they fell asleep also reported more insomnia and nightmares, which themselves independently predicted more suicidal behaviors.

"Insomnia and nightmares beget more variability in when we are able to then fall asleep on subsequent nights, which speaks to the way in which insomnia develops," Bernert said. "Sleep is a barometer of our well-being, and directly impacts how we feel the next day. We believe poor sleep may fail to provide an emotional respite during times of distress, impacting how we regulate our mood, and thereby lowering the threshold for suicidal behaviors."

Important to evaluate stand-alone risk factors

"Sleep disturbances and suicidal ideation are both symptoms of depression, making it critical to disentangle these relationships and evaluate factors that stand alone to predict risk," Bernert said.

Her team is currently conducting two suicide-prevention clinical trials to test the efficacy of a brief, non-medication insomnia treatment for suicidal behaviors.

"Treatments tested for suicidal behaviors are alarmingly scarce in comparison with need and remain mismatched to the acute nature of a suicidal crisis," she said. "Compared to other risk factors for suicide, disturbed sleep is modifiable and highly treatable using brief, fast-acting interventions. Because sleep is something we universally experience, and we may be more willing to openly talk about it relative to our mental health, we believe its study may represent an important opportunity for suicide prevention."

Stanford research assistant Naomi Iwata was also a co-author. The research was supported by the John Simon Guggenheim Foundation and the National Institutes of Health.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. **ISM**

NORBERT VON DER GROEBEN

Rebecca Bernert and her colleagues studied young adults at risk for suicide and found that when their sleep patterns varied a lot, their suicidal symptoms increased.

Anyone who is experiencing symptoms of suicide can receive help by calling the National Suicide Prevention Lifeline at (800) 873-TALK, or by texting the Crisis Text Line (text HOME to 741741). All helplines offer free, confidential support 24 hours a day.

Study shows which children with autism respond best to oxytocin treatment

By Erin Digitale

Oxytocin treatment produces more improvement in social behavior among children with autism who have low levels of the hormone to begin with, according to a new study by researchers at the School of Medicine.

The study, which was published online July 10 in the *Proceedings of the National Academy of Sciences*, is the first to consider how baseline oxytocin levels influence autistic children's responses to the substance.

"Our results suggest that some children with autism will benefit from oxytocin treatment more than others, and that blood oxytocin levels might be a biological sign that will allow us to predict if a child will respond maximally or not," said lead author Karen Parker, PhD, associate professor of psychiatry and behavioral sciences. The trial, in 32 children, was relatively small and needs to be replicated, she said.

"We are finally narrowing down whom oxytocin could be beneficial for," said Antonio Hardan, MD, professor of psychiatry and behavioral sciences and senior author of the study. "This is what precision health looks like for autism."

Although the effect of oxytocin was modest, the results are exciting because no other medications now exist to treat any of the core features of autism, Hardan added.

Oxytocin levels vary

Autism is a developmental disorder characterized by poor social ability and verbal communication skills, as well as restrictive and repetitive behaviors. Not all children with the disorder are equally affected; symptoms range in severity. In 2014, Parker and Hardan and their colleagues discovered that oxytocin levels vary greatly in children both with and without autism, and that those with low oxytocin have more social impairment regardless of whether they have autism.

That discovery made the researchers wonder if oxytocin's benefits as an autism therapy might be confined to kids whose levels were low to begin with. Other trials of oxytocin in autism have produced mixed results but did not take subjects' baseline levels into account.

The new study included 32 children with autism who were randomly assigned to receive an intranasal oxytocin spray or a placebo spray twice daily for four weeks. The children's blood oxytocin levels were measured before and after the four-week period. The children's behavior was assessed at the beginning and end of the trial using a standardized questionnaire completed by their par-

See OXYTOCIN, page 3

NORBERT VON DER GROEBEN

Karen Parker and her colleagues found that among children who received doses of oxytocin in a clinical trial, those starting off with the lowest levels of the brain hormone experienced the greatest improvements in social behavior.

INSIDE STANFORD MEDICINE

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STANFORD MEDICINE

Brother and sister breathe easier following double-lung transplants

By Julie Greicius

Before being wheeled into surgery for a double-lung transplant in March, David Diaz, 9, benefited from the knowledge of a close adviser: His older sister had gone through the same rare surgery just three years earlier.

"She told him, 'David, don't be scared. I've been through this, and you don't feel pain or anything. They give you medicine so you can go to sleep,'" recalled their mother, Corina. "She was a very big help to him and answered all his questions."

David's big sister, Doris, now 12, was diagnosed with cystic fibrosis in 2006, when she was 6 months old. In 2007, 1-month-old David was also diagnosed with CF. Their mother and father, David Diaz Sr., became experts in the daily care their children required, from administering medications to performing airway clearance to making regular doctor's visits with the pulmonology team at Lucile Packard Children's Hospital Stanford.

"Both of these kids had very severe cystic fibrosis," said Carol Conrad, MD, medical director of the Pediatric Lung and Heart-Lung Transplantation Program and Pediatric Pulmonary Function Lab at the hospital. "Despite thorough and adequate treatment at home, and despite everybody's best efforts, they both developed end-stage lung disease quite early in life."

> "They both developed end-stage lung disease quite early in life."

Rare surgery in young patients

In June 2014, Doris underwent a double-lung transplant at Packard Children's, which has the only pediatric lung and heart-lung transplant program on the West Coast. Yet at the same time the Diaz family was celebrating Doris' successful surgery and quick recovery, David's health was declining rapidly. His pulmonologist, Carlos Milla, MD, associate professor of pediatric pulmonary medicine at the School of Medicine, kept a close eye on David's case as his parents continued providing home care as long as they could.

"When David would cough, or his lips would turn purple, or when he started to cry, Doris was scared," Corina said. "She would say to me, 'Every day he seems worse than me.' But to David, she said, 'David please be faithful. Remember how I looked before? Look at me now.'"

In late 2016, David was admitted to Packard Children's, where he was hospitalized for two months. He needed around-the-clock oxygen and the support of a bi-level positive airway pressure machine. Katsuhide Maeda, MD, clinical associate professor of cardiothoracic surgery at the School of Medicine, sat with Milla in the pediatric intensive care unit as they examined David's chest X-ray.

At 'much higher risk' than his sister

Although David clearly needed an intervention, the decision to do a lung transplant was not an easy one. "His right lung was completely collapsed and not working at all," Maeda said. "He was surviving only with his left lung, which was also very sick and had expanded, pushing his heart to the other side of his chest."

When it comes to transplants, doctors must carefully consider whether a patient is too sick to survive the procedure, in which case the rare, much-needed donor lungs — for which most pediatric patients wait a year or more — should be allocated to another patient.

Maeda had done Doris' high-risk, double-lung transplant, as well as several others. But David "was much higher risk than Doris was, or anybody we've ever known," said Conrad, who is also an associate professor of pediatric pulmonary medicine at the School of Medicine.

Milla and Maeda weighed the risks and benefits. "Then, finally," Maeda said, "we decided to accept him as a transplant candidate."

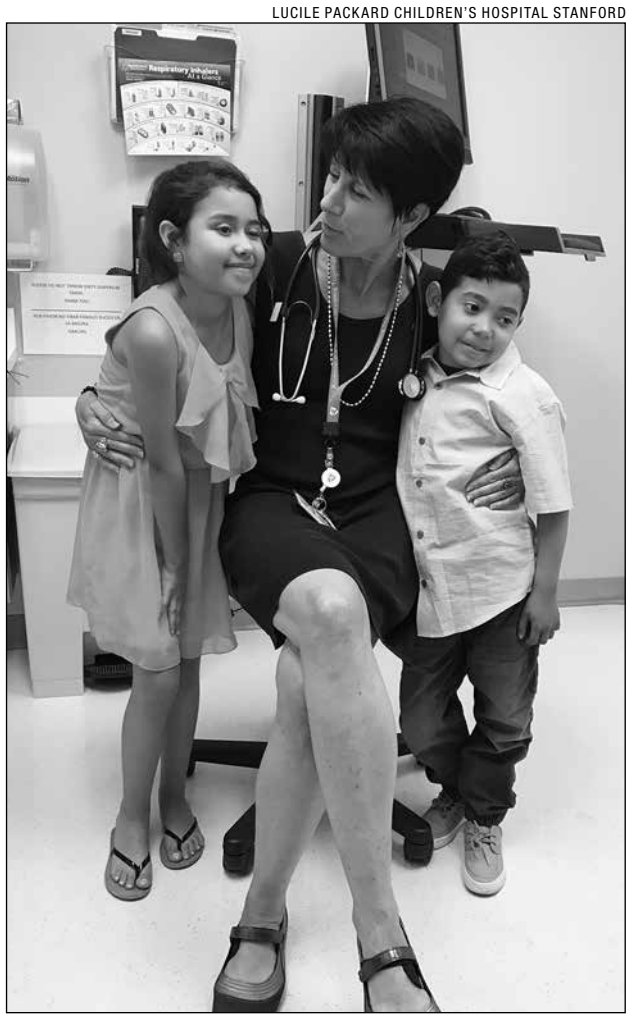
In mid-January, David's doctors put him on the national organ transplant waiting list. Then, in March, the family learned that donor lungs were available for him. "He was so happy. When the doctor told him the news, he started crying," Corina said.

Going into surgery, "David looked more comfortable than other patients," Maeda said, "because he knew his sister had done the same surgery, and she was doing just fine."

DOUGLAS PECK

In May, Doris and David Diaz attended the annual prom that's held for students and former students of the K-12 school at Lucile Packard Children's Hospital Stanford.

LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD



Doris and David with pediatric pulmonologist Carol Conrad, who has cared for both siblings at Packard Children Hospital.

David's surgery began at 7 p.m. in the evening and lasted 12 hours. "It was exactly as I expected when I opened up his chest," Maeda said. "But every time we started dissecting the right lung, we lost blood pressure, and David became very hemodynamically unstable," meaning he had unstable blood pressure.

"So we had to use the cardiopulmonary bypass machine, even for the lung dissection," Maeda said. "After that was completed, we pushed his heart back into normal position and put in the two new, healthy lungs. And, luckily, those two lungs functioned very well."

'An amazing surgeon'

Conrad had advised David's parents not to expect David's recovery to be as rapid as Doris' had been. "I just didn't expect that to happen with David," Corina said. "But Dr. Maeda is such an amazing surgeon, he has such excellent technique, and he's so fast. And David was amazing, just the perfect little patient. He had been listening very hard to what he needed to do prior to surgery, and afterwards he just set out to get better. And he did great."

David's recovery was remarkable given how fragile he had been just days before the surgery. His breathing tube was removed within 24 hours of the surgery, and he was discharged from the hospital within two weeks.

A week after discharge, he was playing soccer with other kids at the Ronald McDonald House at Stanford, where his family stayed through most of June to be close by during his follow-up care.

Corina said that with his two new lungs, David is like a new kid. "I see my kids healthy and playing like normal kids, which is something amazing," she said. "It's funny; sometimes it's 8 or 9 o'clock at night, and David still wants to kick the ball around." ISM

Oxytocin

continued from page 2

ents. The hormone was found to be safe, with no adverse events reported.

As in many trials, the researchers saw some improvement even in children given the placebo, though the effect was less pronounced than it was in the oxytocin group. Children who had low oxytocin at baseline received more benefit from placebo than those who began with high oxytocin — and their bodies' own production of the hormone rose modestly. This unexpected finding suggests a possible biological explanation for the placebo effect, which is common in studies of psychological and psychiatric treatments, Parker said. The idea that increases in natural oxytocin production might explain how patients benefit from a placebo merits future research, she added.

Among the children who got oxytocin, those with the lowest oxytocin levels at the beginning of the trial experienced the greatest improvements in social behavior. Oxytocin's effects were specific: the hormone did not change the frequency of repetitive behaviors, nor did it affect children's anxiety levels.

A large trial of oxytocin for children with autism is now underway at several institutions across the United States, and Hardan and Parker are curious about whether the bigger trial will replicate their findings. Hardan, who treats children with autism at Lucile Packard Children's Hospital Stanford, is not advocating that physicians start prescribing oxytocin for their patients yet.

> "We are finally narrowing down whom oxytocin could be beneficial for."

"If our findings are replicated in the large NIH-funded trial, then I might consider doing baseline oxytocin measurements as part of my clinical practice to try to determine if specific patients will respond," he said, noting that this could be difficult because, at present, blood oxytocin levels are not measured routinely in clinical labs. Oral or sublingual administration of oxytocin would not necessarily produce the same results as the intranasal oxytocin tested, he also cautioned.

"Hopefully, this is a first step to identifying the characteristics of people with autism who respond to specific treatments," Hardan said. "Because of the heterogeneity of the disorder, we need to start doing clinical trials not to see if there will be a response, but more to see who will respond to possible treatments."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford-affiliated authors of the paper are postdoctoral scholars Ozge Oztan, PhD, and Debra Karhson, PhD; medical student Jacqueline Summers; clinical research coordinator Robin Libove; undergraduate students Raena Sumiyoshi and Lisa Jackson; Kyle Hinman, MD, clinical assistant professor of psychiatry and behavioral sciences; Kara Motonaga, MD, clinical assistant professor of pediatric cardiology; Jennifer Phillips, PhD, clinical associate professor of psychiatry and behavioral sciences; former postdoctoral scholar Dean Carson, PhD; and Joseph Garner, DPhil, associate professor of comparative medicine.

Parker, Hardan and Garner are members of Stanford's Child Health Research Institute.

The research was supported by grants from the Mosbacher Family Fund for Autism Research, Stanford's Child Health Research Institute, the Yani Calmidis Memorial Fund for Autism Research, an Autism Speaks Meixner Postdoctoral Fellowship in Translational Research, a Stanford University School of Medicine Dean's Postdoctoral Fellowship and the National Institute of Mental Health.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

Early cardiology care linked to lower risk of stroke in patients with A-fib

By Tracie White

The risk of stroke was significantly reduced in patients newly diagnosed with a heart condition known as atrial fibrillation who received early care from a cardiologist, according to a study by researchers at the School of Medicine.

Mintu Turakhia

Cardiology care within three months of diagnosis was associated with a 9 percent reduction in the risk of stroke, the most common adverse outcome of atrial fibrillation, and an 11 percent reduction in risk of death, the study found. Patients treated by cardiologists were more likely to have been prescribed anticoagulants, blood-thinning medications used to prevent blood clots, which appeared to lower the risk of stroke.

"The important message here is that getting early cardiology care was associated with early prescription of drugs specifically for preventing stroke," said Mintu Turakhia, MD, associate professor of cardiovascular medicine, director of research at the Center for Digital Health at Stanford, and director of cardiac electrophysiology at the Palo Alto Veterans Affairs Health Care System. "These findings show that it is important to think of these interventions at the time of diagnosis."

Turakhia noted that previous research has shown the importance of starting patients on the right medications early for other heart conditions. "But because A-fib is treated by so many different types of doctors and has complicated treatment guidelines, it was important to see if this held true for A-fib, which is incredibly common as people get older," he said.

Turakhia is senior author of the study, which was published online June 26 in the *Journal of the American College of Cardiology*. Alexander Perino, MD, a fellow in cardiovascular medicine, is the lead author.

Common condition

Atrial fibrillation, an irregular and often rapid heart rhythm, is a common condition that affects between 3 million and 5 million Americans. It increases the risk of stroke and other heart-related complications. There are many treatment options, each with varying complexity and risk, and treatment may differ based on the care setting, the study said.

To determine variations in treatments and outcomes based on whether patients received care from a general practitioner or a cardiologist, Turakhia and his team analyzed records from the U.S. Department of Veterans Affairs health care system for 184,161 patients newly diagnosed with atrial fibrillation between 2004 and 2012. Within 90 days of diagnosis, 40 percent received cardiology care and 60 percent received primary care without being referred to a cardiologist.

Results showed that those seen by cardiologists had a lower adjusted risk of stroke and death, and that the lower risk of stroke appeared to be connected to higher rates of anticoagulant prescriptions.

"When you account for everything under the sun — age, other conditions and medications, insurance coverage and even how far patients lived from these clinics — there was still a reduction in stroke and mortality," Turakhia said. "To start, the patients who received cardiology care were also a whole lot sicker at baseline, so you'd expect their outcomes to be worse. In fact, we saw the opposite."

Study results also showed that, somewhat paradoxically, patients who received early cardiology care were hospitalized at a higher rate. Turakhia said this could be because this group of patients tended to be sicker or that perhaps therapies requiring hospitalization may have been beneficial.

'Not all hospitalization is bad'

"We tend to equate hospitalization as a bad outcome," he said. "But not all hospitalizations are bad."

Researchers also noted that many VA patients live in rural areas and must travel farther to get specialty care, since most VA cardiologists work at medical centers in urban areas. The patients who received specialty care lived on average 7 miles closer to the cardiologists than those who received primary care.

"That makes the case that proximity may be a big factor in access to care," Turakhia said. "One of the solutions may be virtual visits or similar options."

The study is observational and, unlike a randomized trial, does not provide evidence that cardiologists rather than primary care physicians should be treating all patients with atrial fibrillation, he said.

"We're not saying that we just need to clone more cardiologists — that is exactly the wrong solution," Turakhia said. "Rather, this research indicates that we need to fill gaps in care and find smarter ways to deliver it so it doesn't matter who a patient sees or how far away they live."

Other Stanford co-authors of the study are Sanjiv Narayan, MD, PhD, professor of cardiovascular medicine; and Paul Wang, MD, professor of cardiovascular medicine; and former postdoctoral scholars Daniel Kaiser, MD, and Christopher Swan, MD.

A researcher from the Mayo Clinic was also a co-author of the study, which was supported by the VA and the American Heart Association.

Stanford's Department of Medicine also supported the work. ISM

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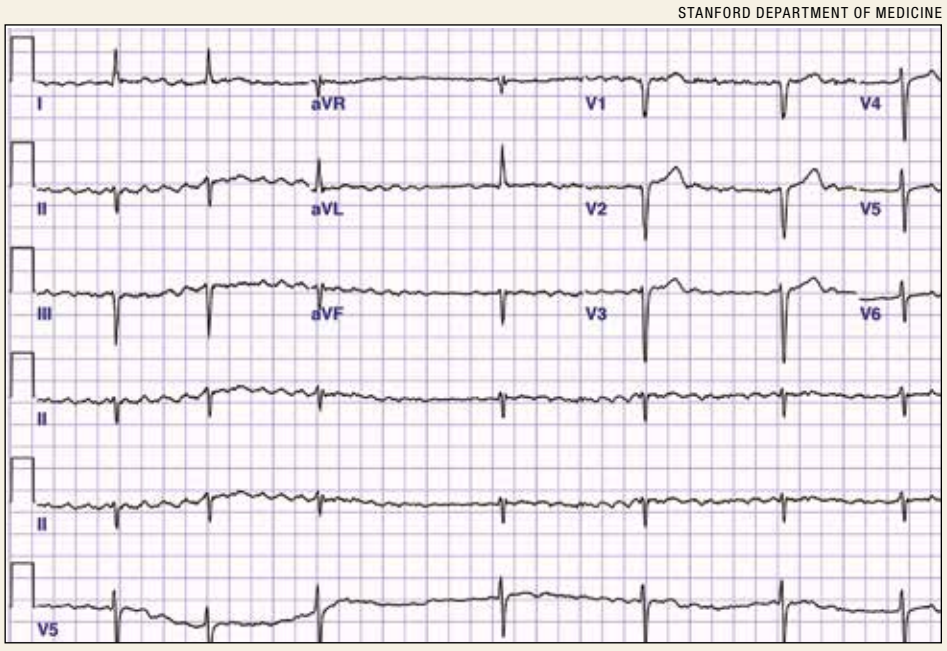


Electrical activity in the heart of a patient with atrial fibrillation is depicted here in an electrocardiogram.

Virtual reality system helps surgeons and reassures patients

By Mandy Erickson

Having undergone two aneurysm surgeries, Sandi Rodoni thought she understood everything about the procedure. But when it came time for her third surgery, the Watsonville, California, resident was treated to a virtual reality trip inside her own brain.

Stanford Medicine is using a new software system that combines imaging from MRIs, CT scans and angiograms to create a three-dimensional model that physicians and patients can see and manipulate — just like a virtual reality game.

PAUL SAKUMA

The virtual reality system is helping train residents, assist surgeons in planning upcoming operations and educate patients. It also helps surgeons in the operating room, guiding them in a three-dimensional space.

After donning a headset connected to the VR system, Rodoni could clearly see the ballooning blood vessel, as well as the spot where her neurosurgeon, Gary Steinberg, MD, PhD, would place a clip to repair it. "Because I had been through this before, I thought I knew it all until I saw this," she said. "I felt better knowing it was so clear to the doctor."

Created by the Colorado startup Surgical Theater, the VR system is helping train residents, assist surgeons in planning upcoming operations and educate patients. It also helps surgeons in the operating room, guiding them in a three-dimensional space.

For the residents, class is held in a room in the hospital basement. Under low lighting, and surrounded by three massive screens, the residents settle into reclining chairs complete with drink holders — all promising a comfortable ride inside the human skull.

Once the residents don headsets, an instructor — who shows up as an avatar in a white coat — can lead them inside the brain of a patient. The system allows instructors to highlight different components of the brain, such as arteries to show an aneurysm, bones to show skull deformities or tissue to show a tumor, while rotating the view to illustrate how a tumor or aneurysm looks from different angles. They can also progress, as avatars, through the steps for removing a tumor or fixing an aneurysm, starting outside the skull.

'A window into the brain'

Surgeons make their way down to the Neurosurgical Simulation Lab to practice an upcoming operation. Because they're practicing on images from the actual patient, rather than a generic brain, they can map out the surgery ahead of time. "It's a window into the brain — and a window into the brain of the particular patient we're going to operate on," said Anand Veeravagu, MD, an assistant professor of neurosurgery and the head of the Stanford Neurosurgical Simulation Lab.

The three-dimensional aspect of the imagery eases surgeons' planning and improves the accuracy of the surgery, with the aim of producing safer procedures. "We can plan out how we can approach a tumor and avoid critical areas like the motor cortex or the sensory areas," said Steinberg, professor and chair of neurosurgery. "Before, we didn't have the ability to reconstruct it in three dimensions; we'd have to do it in our minds. This way it's a three-dimensional rendering."

Steinberg noted that in Rodoni's case, an artery was attached to the top of the aneurysm. "You couldn't see it on conventional imaging," he said. "Had I not known about it, it could have been a real disaster."

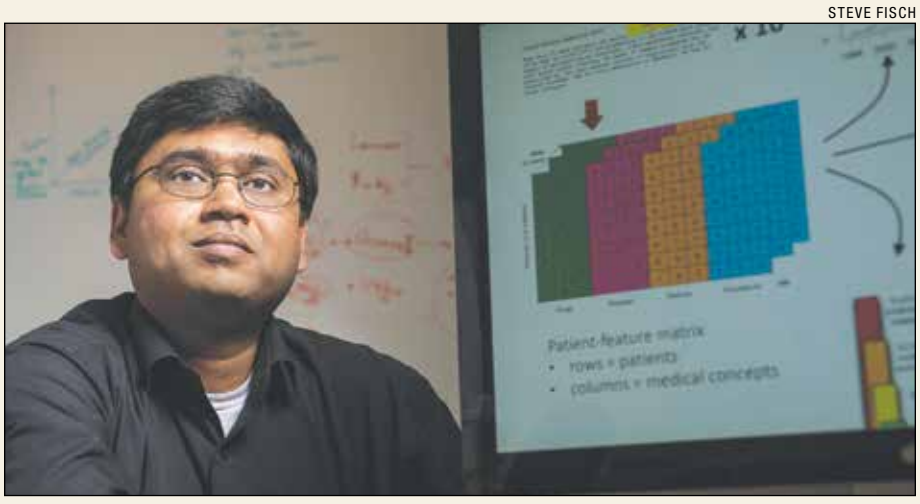
To show patients what's going on inside their skulls, Malie Collins, MS, senior program lead for the VR program, rolls a mobile unit, complete with headset, into an examination or hospital room. Being able to see the problem in three dimensions **See VIRTUAL, page 5**

Researchers help develop method for assessing risk of A-fib, second stroke

By Jennie Dusheck

One stroke is dangerous, and a second, even more so. One important risk factor for that perilous second stroke is an irregular heart rhythm called atrial fibrillation.

STEVE FISCH



Nigam Shah and his collaborators used data from thousands of stroke patients to develop an algorithm to help predict which patients should be monitored for a second stroke.

If doctors could identify the stroke patients who are most likely to experience atrial fibrillation, they could start treatments that would help prevent a second stroke.

But which stroke patients are at risk for the condition has been hard to predict without costly 24/7 monitoring for the hundreds of thousands of people who have a first stroke every year.

Now, a team led by researchers at the School of Medicine and Santa Clara Valley Medical Center has used electronic medical records to predict the likelihood of a person experiencing atrial fibrillation after either of two kinds of strokes: a cryptogenic stroke or a transient ischemic attack.

'Unique collaboration'

A paper describing their findings were published online June 28 in *Cardiology*. The senior authors are Nigam Shah, MBBS, PhD, associate professor of biomedical data science at Stanford, and Susan Zhao, MD, of Valley Medical Center. Stanford graduate student Albee Ling and Valley Medical Center internist Calvin Kwong, MD, share lead authorship.

"This work resulted from a unique collaboration," said Shah, "where a need for risk stratification was identified by Dr. Susan Zhao, and followed up jointly by an informatics student and a clinical fellow to derive a risk estimate for a population for which we don't have good scoring methods."

Stroke patients are typically monitored for atrial fibrillation while they're in the hospital. "But once they go home — after about a week — clinicians aren't usually too vigilant about monitoring them for atrial fibrillation," said Kwong. But if doctors monitor stroke patients for even 30 days after they go home, atrial fibrillation can be picked up if it's happening. And, indeed, the American Heart Association recommends 30 days of heart rhythm monitoring to detect atrial fibrillation within six months of an initial stroke. The problem, said Kwong, is that such monitoring is expensive and not appropriate for every patient.

Shah and his colleagues decided they needed a way to predict which patients should be monitored. There had to be a way to tell the patients who were at high risk for atrial fibrillation and should be monitored from the ones who were at low risk and didn't need to be monitored.

List of seven risk factors

The team did a retrospective cohort study using data from thousands of stroke patients from Stanford's Translational Research Integrated Database Environment. Of the 9,589 stroke patients in the database, 482 of them, or 5 percent, went on to be diagnosed with atrial fibrillation.

The team had already developed a text-processing pipeline for analyzing clinical data and clinical-diagnosis coding. Using that pipeline, the team extracted information from clinical notes, flagging, for example, phrases such as "ruled out stroke" and classifying data according to whether it referred to the patient or came from a family history section. The result was a list of biomedical facts about each patient — including age, body mass index and so on.

Then, by ranking the clinical attributes of patients whose medical records indicated they went on to be diagnosed with atrial fibrillation, the team was able to assemble a set of seven risk factors that, when combined, predicted which stroke patients were the most likely to develop the condition and should be monitored after hospitalization. The risk factors — age, obesity, congestive heart failure, hypertension, coronary artery disease, peripheral vascular disease and disease of the heart valves — are the basis of a scoring system that assigns patients to one of three risk groups.

"The scoring system we developed is simple to use and the results could help physicians tailor treatment to individual patients," said Ling.

It can help physicians decide which patients to monitor. Once it's known that patients have a high risk of atrial fibrillation, they can wear a heart monitor at home to see if they actually are experiencing bouts of atrial fibrillation and then, if they are, treated with the appropriate drugs to try to prevent a second stroke.

Scoring system online

"Our system needs to be further validated in studies using other independent data sources," said Ling. She said she expects that clinicians and researchers will further validate and improve the scoring system and that, hopefully, it will one day be adopted in everyday practice. "On the other hand, there will surely be more clinical studies conducted using electronic health records, not just at Stanford but in other medical institutions, as well," she added.

The study is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Studies like this one can be done quickly using preexisting patient data in just a matter of days, and provide a way to score patients' individual risk so that treatment can be partly customized.

Researchers at the University of California-San Francisco also co-authored the study.

This study was supported by the National Institutes of Health, Janssen Research and Development and by a Stanford Graduate Fellowship.

Stanford's departments of Medicine and of Biomedical Data Science also supported the work **ISM**

Virtual

continued from page 4

reassures them, she said, adding that it's especially useful for young patients or those who don't understand English well. She can also download the imagery onto a thumb drive and give it to the patient as a souvenir.

"Traditionally, doctors can show their patient a standard physical model of the brain or of the spine and say, 'On this model, imagine your tumor is located here,'" she said. "But with VR, we are able to immerse patients in their own anatomy, so they can very clearly get a sense of what's going on."

Stanford Medicine doctors are using the VR technology for the brain and spinal cord because these organs are stable and lend themselves to imagery — unlike other body parts, which move with blood flow and breathing. Collins said the technology may soon be available for the rest of the body.

'Much, much more detail'

Surgeons typically use video feeds while they are operating, but the new VR technology adds a three-dimensional view which they can superimpose on the real-time video. "It has much, much more detail," said Steinberg, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences. For Rodoni's surgery, "I had the 3-D rendering of her anatomy and could match that up with the surgical microscopic view, something I can't do with any other technology."

Veeravagu said some patients have chosen Stanford over other nearby hospitals solely because of the VR technology. "This software really helps them understand what it is they are about to undergo," he said. "Seeing it on the screen, in 3-D, really helps put a patient's mind at ease."

It certainly did for Rodoni. Knowing where her aneurysm lay, and how Steinberg would repair it, helped calm her as she faced her third brain surgery. "I knew that Dr. Steinberg would be able to see the same thing I saw, and he wasn't going to run into any surprises," she said. Rodoni's surgery went smoothly and she was discharged from the hospital within two days, her aneurysm gone. **ISM**

KRIS NEWBY

Supersize your ideas at the HIVE

Brian Tempero, a data visualization specialist at the Stanford Research Computing Center, demonstrates the HANA Immersive Visualization Environment, a state-of-the-art audio-visual classroom equipped with a 10-by-24-foot ultra-high-resolution display and a three-zone, 10-speaker sound system. He is standing in front of a brain-wiring image created by measuring the movement of water molecules through neural pathways using diffuse tensor magnetic resonance imaging technology.

The HIVE, which accommodates as many as 40 people, can be reserved by university faculty, staff and students for uses such as interactive instruction, teleconferences, presentations and thesis defenses. Many researchers use its image magnification capabilities for collaborative data analysis, simulations and visualization.

The HIVE is in Room 050 of the Jen-Hsun Huang Engineering Center. It can be reserved at https://icme.stanford.edu/resources/hive. ISM

Cancer

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Cancer Center in Philadelphia have analyzed the genetic test results, family histories and disease status of nearly 95,600 women who underwent genetic testing for 25 mutations associated with the development of breast and ovarian cancer. Some of the women had cancer; many did not. Seven percent of the women in the study carried at least one of the mutations, the researchers found.

Allison Kurian

The researchers hope the study is the first step to providing much-needed clarity to women and their physicians as they struggle to interpret the results of genetic testing. It may also help guideline-making organizations such as the American Cancer Society recommend when additional or more-frequent screening tests might be appropriate.

"The results of this study will help to personalize our risk estimates and recommendations for preventive care," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "A better understanding of cancer risks can help women and their clinicians make better-informed decision about options to manage cancer risk."

For example, Kurian said, some women with a high risk of developing breast cancer might consider preventive mastectomy, whereas those with lower risk — for example, a twofold elevation over the average risk — might instead pursue intensive regular screening, including breast magnetic resonance imaging.

Kurian is the lead author of the study, which was published online June 27 in *JCO Precision Oncology*. Michael Hall, MD, associate professor of clinical genetics at the Fox Chase Cancer Center, is the senior author. The study was funded by Salt Lake City-based Myriad Genetics Inc., which performed the genetic testing.

What does a mutation mean?

Increasingly, women who are tested for a panel of cancer-associated mutations are given a mixed bag of results. Advances in DNA sequencing have made it quicker, easier and cheaper to identify mutations in an ever-growing panel of cancer-associated genes. With the exception of a few well-studied mutations such as BRCA1 and BRCA2, however, the exact effect of most of these remains murky because few large-scale studies have been completed.

The researchers assessed the mutation status of 95,561 women with and without the disease who chose to have their genome tested by Myriad Genetics for the presence of 25 cancer-associated mutations between September 2013 and September 2016. They matched the women according to their ages, ethnicity and family history of cancer to assign a relative risk of developing cancer to each of the mutations.

> "This large sample size provided a reliable data set on real people."

Kurian and her colleagues found that eight of the mutations were positively associated with the development of breast cancer, and 11 were positively associated with ovarian cancer. Increased cancer risk for women carrying the mutations ranged from two to 40 times that of a woman without the mutations.

'Significant advantage'

"This large sample size provided a reliable data set on real people," said Hall. "This is a significant advantage as we work to identify the strength of association between mutation and risk."

In many cases the researchers' findings dovetailed with what had already been surmised from smaller studies. But there were some surprises. One mutation assumed to increase a woman's risk of breast cancer was shown to instead increase the likelihood of ovarian cancer. Three other mutations thought to increase the risk of breast cancer seem instead to have little effect.

"One surprising finding was the association of an increased ovarian cancer risk with mutations in a gene called ATM," said Kurian. "Although this risk was relatively small numerically, it was statistically significant, and to our knowledge it had not previously been published. Additional studies will be important to determine the robustness and clinical relevance of this finding, and to expand the evidence base that we use to counsel our patients."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Kurian has received research funding from Myriad Genetics, Invitae, Ambry Genetics, GeneDX and Genomic Health. Hall has received research funding from Myriad Genetics and has other relationships with Foundation Medicine and Invitae. Other authors were employed by Myriad Genetics at the time of the study and received salary and stock options as compensation.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. **ISM**

IMAGE POINT FR/SHUTTERSTOCK.COM

A large study has assigned levels of risk to 25 mutations associated with breast and ovarian cancer. The results may be helpful in guiding treatment and screening recommendations.

Arthritis

continued from page 1

like arthritis, which typically doesn't develop until late in life."

A paper describing the research was published online July 3 in *Nature Genetics*. Kingsley is the senior author. Harvard graduate student Jiaxue Cao and former Stanford postdoctoral scholars Terence Capellini, PhD, and Hao Chen, PhD, share lead authorship. Capellini is now an associate professor of human evolutionary biology at Harvard, and Chen is an associate clinical scientist at Genentech Inc.

The researchers were studying a gene called GDF5 that Kingsley's laboratory first linked to skeletal growth in the early 1990s. GDF5 is involved in bone growth and joint formation, and mutations in the coding portion of the gene have been shown to cause malformations in leg-bone structure in mice. In humans, GDF5 mutations are associated with shorter stature and joint problems; in particular, two nucleotide changes immediately upstream of the gene have been strongly associated with a 1.2- to 1.8-fold increase in the risk of osteoarthritis.

In the new study, the researchers were interested in learning more about how the DNA sequences surrounding GDF5 might affect the gene's expression. Often, these noncoding sequences contain key regulatory regions known as promoters and enhancers. Capellini, Chen and Cao were able to identify a previously unknown enhancer region they termed GROW1, which is several thousand nucleotides downstream of GDF5.

STEVE FISCH

David Kingsley and his colleagues speculate that a more compact body structure due to shorter bones could have helped humans in Eurasia better withstand frostbite and reduce the risk of bone fracture from falling.

When the researchers analyzed the sequence of GROW1 in the 1,000 Genomes Project database, which collects and compares sequences from many human populations around the globe, they identified a single nucleotide change that is highly prevalent in Europeans and Asians but that rarely occurs in Africans. When they introduced this nucleotide change into laboratory mice, they found that it decreased the activity of GDF5 in the growth plates of the long bones of fetal mice.

> "This study highlights the intersection between evolution and medicine in really interesting ways."

A common thread

Further research showed that this nucleotide change has been repeatedly favored during human evolution. Modern humans migrated from Africa between 50,000 and 100,000 years ago. But they weren't the first to leave the continent. Neanderthals and Denisovans moved north into Europe and Asia about 600,000 years ago. Interestingly, the researchers found that the same GROW1 variant was found in the DNA of both ancient and modern humans in Europe and Asia.

However, there's a dark side to this stocky, hardy body type: The GDF5 variant that reduces bone length comes hand-in-hand with the two upstream nucleotide changes known to confer an increased risk for osteoarthritis.

"It's clear that the genetic machinery around a gene can have a dramatic impact on how it works," said Capellini. "The variant that decreases height is lowering the activity of GDF5 in the growth plates of the bone. Interestingly, the region that harbors this variant is closely linked to other mutations that affect GDF5 activity in the joints, increasing the risk of osteoarthritis in the knee and hip."

"The potential medical impact of the finding is very interesting because so many people are affected," said Kingsley. "This is an incredibly prevalent, and ancient, variant. Many people think of osteoarthritis as a kind of wear-and-tear disease, but there's clearly a genetic component at work here as well. Now we've shown that positive evolutionary selection has given rise to one of the most common height variants and arthritis risk factors known in human populations."

Researchers from the University of Waterloo in Ontario, Canada, also contributed to the study.

The research was supported by the National Sciences and Engineering Research Council of Canada, the Arthritis Foundation, the National Institutes of Health, the Howard Hughes Medical Institute, the Milton Fund of Harvard, the China Scholarship Council and the Jason S. Bailey Fund of Harvard.

Stanford's Department of Developmental Biology also supported the work. **ISM**

Ibuprofen

continued from page 1

mile section of the race. There was an 18 percent higher rate of kidney injury among those who took the drug compared to those who didn't, the study found.

Grant called this an impressive difference.

"Basically, for every five runners who took ibuprofen, there was one additional case of acute kidney injury. That's a pretty high rate," he said.

Ultramarathon races have increased in popularity in recent years. The number of races worldwide reached 1,357 in 2015, with over 70,000 runners finishing these races every year, the study said.

"With ultramarathon running increasing in popularity, it is important to study how commonly used medications may affect physiology and performance in this population," said Brandee Waite, MD, associate professor of sports medicine at UC-Davis, who was not connected with the study. "This information can help runners make an informed choice about whether or not to use an NSAID for pain management during an ultramarathon and is a step toward helping physicians establish evidence-based recommendations for their ultra-running patients."

This study should cause endurance athletes and distance runners pause before taking ibuprofen while competing, but does not infer that the average athlete would necessarily face similar effects from taking the drug, Lipman said.

"I would generalize to say, yes, caution should be warranted taking ibuprofen during long distance runs or other endurance sports events," he said. "But I would not push that caution to the general lay population. This study's conclusions are for endurance athletes."

Risk for long-distance runners

Acute kidney injury is common in these athletes due to the high rates of dehydration that cause reduced blood flow and rhabdomyolsis — a breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood, which is harmful to the kidney and often causes kidney damage, Lipman said. In fact, acute kidney injury has been recorded in 34 to 85 percent of all ultramarathoners, the study said.

This study shows that adding ibuprofen into this mix further increases the danger of kidney damage, Lipman said.

"Studies show that for most people, this acute kidney injury is usually resolved within a day or two after the race," he said. "However, numbers of runners have ended up being hospitalized from renal failure."

Two years ago, an athlete participating in the Boulder Ironman triathlon died three days later due to kidney failure caused by dehydration and rhabdomyolysis associated with excessive exercise. He was 40 years old.

"We hypothesized that we were going to say ibuprofen is safe," said Lipman, an endurance runner himself who regularly used the pain reliever during races. "We thought we'd be able to say 'Go forth and run and have no pain.'"

"I felt surprised and a little shocked that it really is as bad for you as we found," said Lipman, who has now switched to using acetaminophen, such as Tylenol, for pain relief and taking ice baths after racing. "I feel it's ironic to preach moderation in extreme sports, but moderation is probably a safe approach. If something hurts, these athletes might want to consider taking acetaminophen instead."

Other Stanford co-authors were wilderness medicine fellows Kate Shea, MD, clinical instructor of emergency medicine and Mark Christensen, DO, clinical instructor of emergency medicine; and Rebecca Higbee, MD, Stanford-Kaiser emergency medicine resident.

Researchers at the University of Colorado, Harvard University and Washington University in St. Louis, also contributed to the study.

The study was funded by a research grant from RacingThePlanet; diagnostic equipment was donated by Abbott, which was returned at the end of the study.

Stanford's Department of Emergency Medicine also supported the work. ISM

COURTESY OF GRANT LIPMAN

Grant Lipman has served on the medical team of RacingThePlanet ultramarathon events, which takes place in various parts of the world, including the Atacama Desert in Chile (above).

Mike Baiocchi wins Rosenkranz Prize for statistics work in Africa

By Beth Duff-Brown

In the slums of Nairobi, where sexual assault is as commonplace as it is taboo to discuss, a team of Kenyan counselors is teaching kids that no means no.

The girls learn to shout "Hands off my body!" and throw an elbow jab or a kick to the groin. The boys are encouraged to stand up for the girls and fight against the social traditions that have normalized rape. Through a series of role-playing exercises, the children also learn how to talk themselves out of precarious situations, use diversions and speak loudly when faced with potential attackers.

The behavioral intervention appears to be working. Observational studies have inferred that the incidence of rape has dropped dramatically — perhaps even by half.

But how do those who are devoted to protecting these girls from sexual violence prove to themselves and their donors that their efforts and dollars are making a difference?

This is where Mike Baiocchi comes in. His innovative approach to applying math to a real-world problem has earned him the 2017 Rosenkranz Prize for Health Care Research in Developing Countries.

Baiocchi, PhD, assistant professor of medicine at the Stanford Prevention Research Center, and his team are conducting a large, randomized trial to gather quantitative evidence about the effectiveness of the rape-prevention program No Means No Worldwide. Baiocchi plans to use the $100,000 prize to help fund the work.

"That's what I specialize in: messy, real-world data where you try to prove the cause-and-effect relationship," he said

Baiocchi and his team have designed a closed-cohort study that will track the behavior of about 5,000 girls and 1,000 boys in Kenya who are enrolled in No Means No Worldwide, which is training 300,000 girls and boys in Africa to prevent rape and teen pregnancy.

"The entire Rosenkranz selection committee was highly impressed both with the rigor of Mike's work — which he publishes in top journals in the field of statistics — as well as his unconventional and potentially very impactful work on the prevention of gender-based violence in illegal settlements around Nairobi," said Grant Miller, PhD, associate professor of medicine and a core faculty member at Stanford Health Policy.

NICHOLE SOBECKI

Mike Baiocchi, winner of the 2017 Rosenkranz Prize, and his colleague Clea Sarnquist conduct research on the ground in Nairobi, Kenya, to determine whether a rape prevention program is truly making a difference.

Miller chairs the committee that selects the winners of the annual prize, which goes to promising young Stanford researchers who are investigating ways to improve health care and health policy in developing countries. The award's namesake, George Rosenkranz, who holds a doctorate in chemistry, first synthesized cortisone in 1951, and later progestin, the active ingredient in birth control pills. He went on to establish the Mexican National Institute for Genomic Medicine. His family created the Rosenkranz Prize in 2009.

Overwhelming prevalence of sexual violence

The World Health Organization estimates that globally, one in three women experience sexual or physical violence.

In Kenya, national surveys reveal that as many as 46 percent of Kenyan women experience sexual assault as children.

"In the roughest part of the Nairobi slums, 20 to 25 percent of high school girls will be raped this year," said Baiocchi. "This program, however, looks like it is having the ability to cut that in about half. Our job is to tease out the evidence through careful measurement and design of experiment."

To do this, Baiocchi and other members of the Stanford Gender-Based Violence Collaborative have traveled to Nairobi to collect baseline data. His partner on the project is Clea Sarnquist, DrPH, senior research scholar for the Global Child Health Program in the Department of Pediatrics.

An evaluation of the program, published in 2014 in *Pediatrics*, found that more than half of 2,000 high school girls who had completed the self-defense course had used their newfound skills to fend off sexual harassment or rape.

But Lee Paiva, the San Francisco-based founder of No Means No Worldwide, wanted more definitive proof. In a 2016 interview with Stanford Medicine magazine, she said that since establishing training in 2010 she often wondered about the true effectiveness of the program.

"A little voice inside me said, 'What did you teach them?'" she said. "What did those kids actually get? What is that money really going to do?"

She determined that she wasn't going to move forward on the program until she could answer those questions. That is when she turned to Stanford.

Baiocchi and Sarnquist spent several months last year working with their Kenyan partners, Ujamaa-Africa and the African Institute for Health and Development, in 90 schools in the poorest parts of Nairobi to establish the largest randomized trial of its kind.

They interviewed the girls who have taken part in the six-week empowerment and self-defense program taught by Kenyans who grew up in the same neighborhoods and are familiar with the local culture.

"It's hard not to be extraordinarily excited when you watch these girls; they're play-acting and just being kids, but you are also watching them evolving and creating new ways to deal with these situations," said Baiocchi. The team is now tracking a fixed group of 5,000 girls and 1,000 boys, ages 10 to 16, over two years. This will give the researchers a better understanding of just how the girls are adopting the training and readapting to societal demands.

"Doing a randomized trial is slow, expensive and — if I'm being totally honest — anxiety-inducing because everything is laid so bare and you put things in motion today that won't be resolved for another two years," Baiocchi said. "But the reward is extraordinarily high-quality data that helps you understand what's really going on. We need this level of evidence if we're going to take on such a difficult problem." ISM

Lynn Koegel, who developed prominent autism therapy, joins Stanford

Autism expert Lynn Koegel, PhD, who developed a widely-used autism therapy called pivotal response treatment, joined the clinical faculty of the School of Medicine on July 1.

Koegel comes from the University of California-Santa Barbara, where she has been clinical director of the Koegel Autism Center. She co-founded the center with her husband, Robert Koegel, PhD, who will soon join the Stanford autism program as a senior researcher. A speech-language pathologist by training, Lynn Koegel holds a PhD from UC-Santa Barbara in educational psychology and has worked for more than 20 years with her husband to develop intervention techniques for individuals on the autism spectrum.

Pivotal response treatment is based on the idea that targeting certain "pivotal" areas of a child's behavior — such as motivation — with early, intensive treatment can produce global improvements in autism symptoms. More recent research has found that the PRT techniques were effective for adolescents and adults. Autism is a developmental disorder whose core features are problems with social communication and a tendency to engage in repetitive or restrictive behaviors.

"Having the Koegels here will allow us to further develop our early intervention research program in autism, and having the infrastructure of Stanford available to them will help them to disseminate the intervention much more widely," said Antonio Hardan, MD, professor and chief of child and adolescent psychiatry at Stanford. He also directs the Autism and Developmental Disabilities Clinic at Lucile Packard Children's Hospital Stanford.

Once they arrive, Lynn and Robert Koegel will continue conducting research on PRT. Their early work focused on delivering the treatment to children ages 3-10. More recently, the couple and their colleagues have been testing whether PRT also helps other age groups, such as adolescents, adults and younger toddlers.

"Stanford has so many brilliant, hard-working people who are doing interesting research," Lynn Koegel said. "It's a great opportunity for me to work with people I really admire."

Lynn Koegel

Koegel will also treat patients at Lucile Packard Children's Hospital Stanford who need speech therapy for autism, and will work to train other autism professionals in using PRT techniques with children.

"We're very excited that Stanford will be able to make this training available to more clinicians and help disseminate this intervention that has a reasonable evidence base to support its effectiveness," Hardan said. ISM

Counting steps via smartphones yields clues about obesity trends

By Tom Abate

Stanford researchers using smartphones to track the activity levels of hundreds of thousands of people around the globe made an intriguing discovery: In countries with little obesity, people mostly walked a similar amount per day. But in countries with higher levels of obesity, there was a big gap between people who walked a lot and those who walked very little.

The researchers used data captured from smartphones to analyze the physical activity of 717,527 men and women from 111 countries, whose steps were studied for an average of 95 days. A paper describing the findings was published online July 10 in *Nature*. The lead author is graduate student Tim Althoff. The senior author is Jure Leskovec, PhD, associate professor of computer science.

"If you think about some people in a country as 'activity rich' and others as 'activity poor,' the size of the gap between them is a strong indicator of obesity levels in that society," said study co-author Scott Delp, PhD, professor of bioengineering and of mechanical engineering and the James H. Clark Professor in the School of Engineering. Delp also directs the Mobilize Center at Stanford.

The researchers dubbed this phenomenon "activity inequality" to evoke the well-established concept of income inequality.

A related finding was the powerful role that gender played in country-to-country differences. Prior studies of physical activity, done mainly in the United States, have shown that men walk more than women, and this was borne out in the global findings. What surprised researchers, however, was how greatly this gender step gap varied from country to country, with negative consequences for women.

"When activity inequality is greatest, women's activity is reduced much more dramatically than men's activity, and thus the negative connections to obesity can affect women more greatly," Leskovec said.

The researchers, who are sharing their findings on an activity inequality website, hope their work will help improve public health campaigns against obesity, and support policies to make cities more "walkable."

Smartphones and steps

Smartphones are equipped with tiny sensors called accelerometers that can automatically record stepping motions. The researchers acquired the data for this study from the Azumio Argus app, which tracks physical activity and other health behaviors. Azumio de-identified the data but provided key health demographics: age, gender, height and weight. The last two data points enabled the researchers to calculate each person's body mass index.

The findings leaned most heavily on data from the 46 countries for which Azumio provided at least 1,000 de-identified users — enough to form the basis for statistically valid inferences. The analysis disclosed strong correlations among activity inequality, the gender-activity gap and obesity levels.

"For instance, Sweden had one of the smallest gaps between activity rich and activity poor, and the smallest disparity between male and female steps," Althoff said. "It also had one of the lowest rates of obesity."

Meanwhile, the United States ranked fourth from the bottom in overall activity inequality, indicating a large gap between activity rich and activity poor. It was fifth from the bottom in the gender step gap, and it has high levels of obesity.

Walkable cities

To better understand the causes and consequences of activity inequality in urban settings, the researchers analyzed a large subset of data from the United States to investigate how the built environments of 69 cities related to activity, obesity and health.

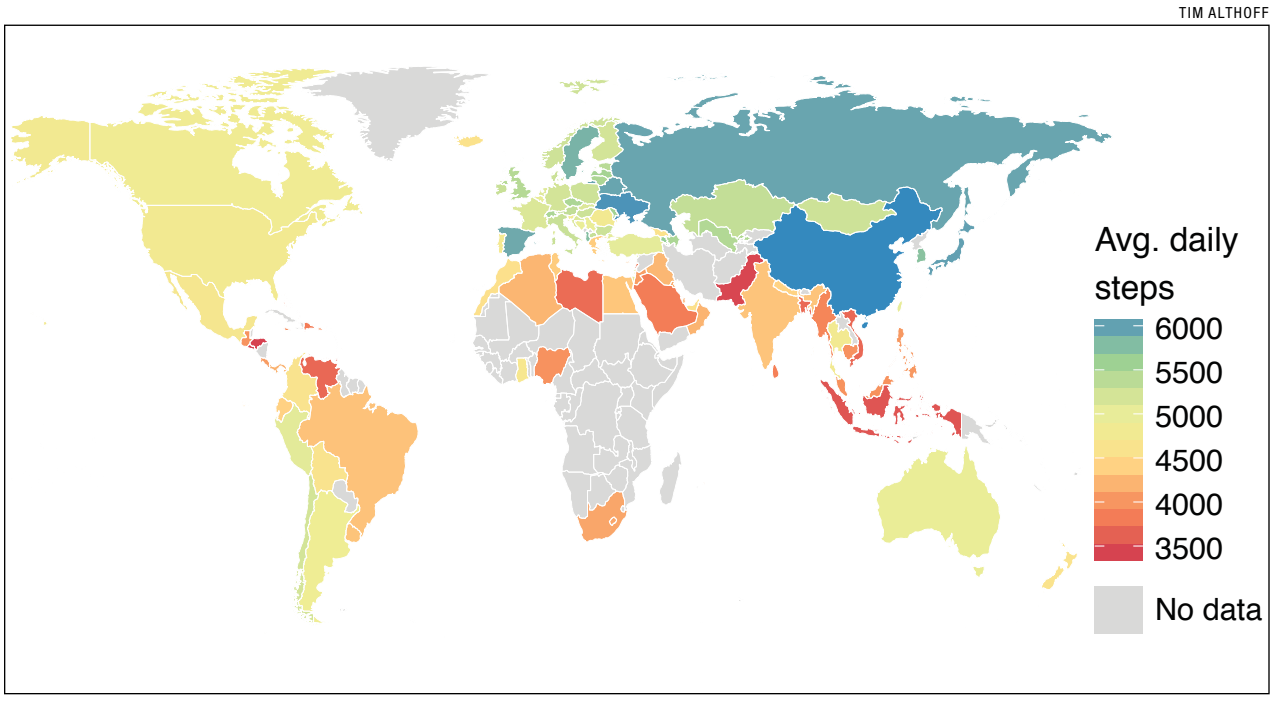
Co-author Jennifer Hicks, director of data science for the Mobilize Center, said the results make clear that city design has health impacts: The cities that were most conducive to walking had the lowest activity inequality.

Rok Sosic, PhD, a senior research engineer in computer science, and Abby King, a professor of medicine and of health research and policy, also co-authored the paper.

The research was supported by the National Institutes of Health, SAP, the National Science Foundation and the Stanford Data Science Initiative. SM

Glen Martin, a freelance science writer, and Raymond MacDougall, lead communications specialist at the National Institute of Biomedical Imaging and Bioengineering, contributed to this article.

TIM ALTHOFF



Using step data captured by smartphones, researchers have defined a new public health risk they call "activity inequality." This occurs when large gaps develop inside a country between people who walk a lot and those who walk very little, leading to unhealthy levels of obesity.

OF NOTE

reports on significant honors and awards for faculty, staff and students

MICHAELA LIEDTKE, MD, was promoted to associate professor of medicine, effective May 1. She co-directs the Stanford Adolescent and Young Adult Cancer Program. Her clinical focus is on acute lymphoblastic leukemia, multiple myeloma and amyloidosis.

VINIT MAHAJAN, MD, PhD, was appointed associate professor of ophthalmology, effective May 15. His research interests include the identification and understanding of genetic contributors to eye disease and blindness and of proteins associated with vitreoretinal disease, with the goal of developing personalized therapies.

LATHA PALANIAPPAN, MD, was appointed professor of medicine, effective May 1. Her research interests include diabetes, physical activity and health disparities. Her clinical focus is on the use of genetic and pharmacogenetics testing in primary care for precision health.

RYAN RIBEIRA, MD, a resident in emergency medicine, was elected as the resident-and-fellow representative to a two-year term on the board of the American Medical Association. His interests include health policy, quality improvement and health care operations.

VANILA SINGH, MD, clinical associate professor of anesthesiology, perioperative and pain medicine, has been appointed the chief medical officer to the Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services. She will advise the assistant secretary on public-health policy. Her interests include health policy, chronic pain, opioid use and misuse, ultrasound-guided procedures for regional anesthesia and early recognition of persistent pain in the post-operative period. ISM

Michaela Liedtke

Latha Palaniappan

Ryan Ribeira

Vanila Singh