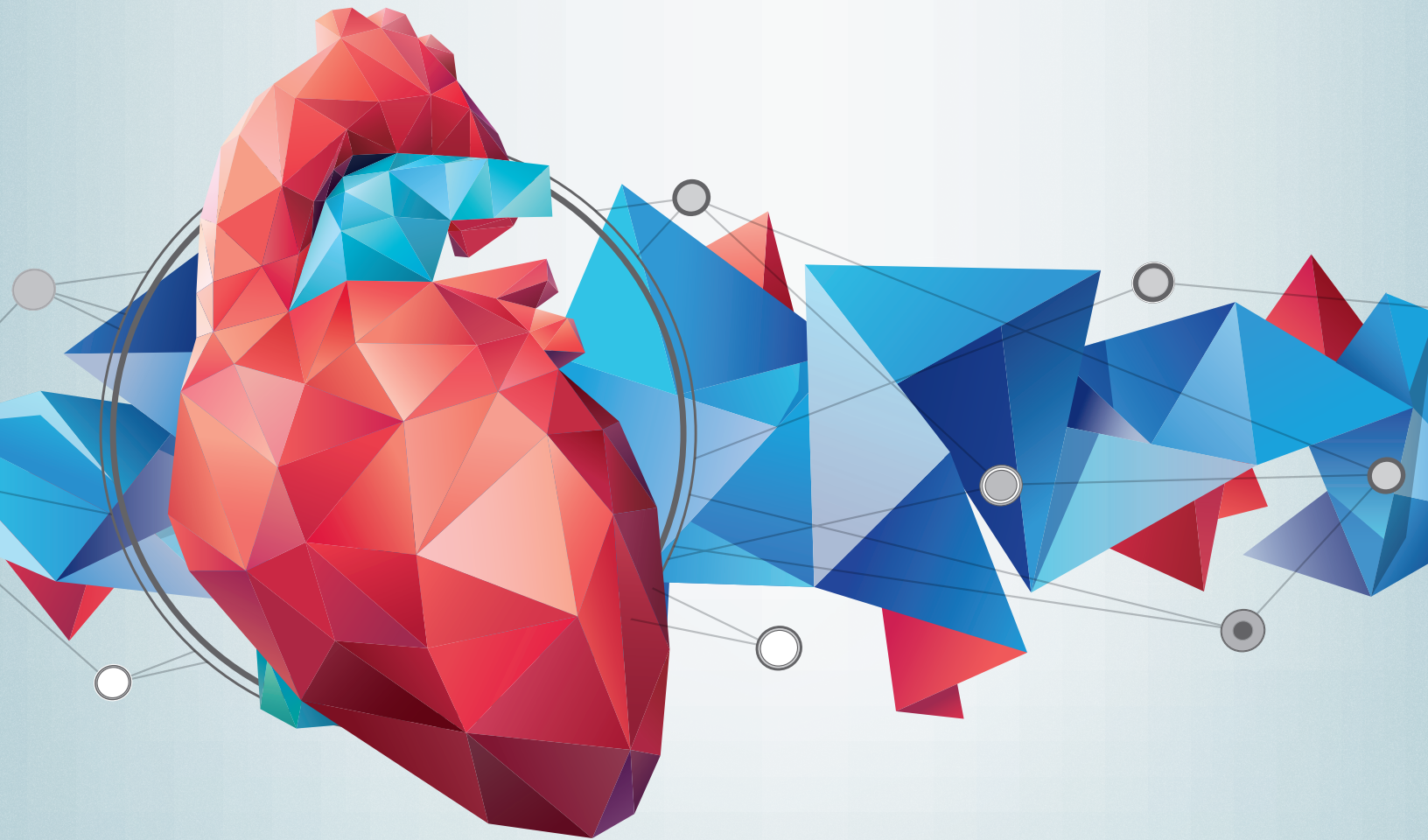




American
Heart
Association.

END OF NETWORK REPORT

O B E S I T Y



STRATEGICALLY FOCUSED RESEARCH NETWORK

For nearly 100 years, the American Heart Association has been dedicated to fighting cardiovascular disease, the No. 1 killer worldwide.

At the center of its mission is research. Since 1949, the organization has invested more than \$5 billion to spur scientific innovations that help people live longer, healthier lives. As science evolves, the AHA's research has grown and evolved to keep pace.

In 2014, the AHA established the Strategically Focused Research Networks (SFRN), a unique venture that brings together scientists from multiple institutions to study a common topic from different perspectives. Collaboration across disciplines helps create new ideas, approaches and knowledge. The AHA Board of Directors chooses the topic of each SFRN.

As obesity rates continue to worsen in the U.S. and around the world, the AHA committed \$15 million to establish the Obesity SFRN. The network gave researchers the critical opportunity to explore complex questions about obesity and its relationship to cardiovascular health



Dr. Annabelle Volgman
Oversight Advisory
Committee Chairperson

The AHA awarded \$3.7 million to each of four Centers beginning in 2017:

Johns Hopkins University, to study the role of time-restricted feeding on obesity and cardiometabolic health.

New York University Medical Center, to examine the translational and therapeutic opportunities of braking inflammation in obesity and metabolic dysfunction.

The University of Alabama at Birmingham, to investigate how women with obesity, metabolic syndrome and gestational diabetes may influence their children's weight and health long after birth.

Vanderbilt University Medical Center, to develop precision medicine approaches to treating obesity while reducing cardiovascular disease risk.

Each center was required to include a basic science, clinical science and population science research component. Each center also designed a two-year research postdoctoral training program for three fellows, who built relationships with faculty across multiple disciplines within their own institution and throughout the research network.

"These four centers were amazingly enthusiastic and collaborative as we set out to better understand obesity and its relationship with

cardiovascular disease. Working together, they helped advance the knowledge so we can find better treatments and improve people's health," said Oversight Advisory Committee Chairperson **Annabelle Volgman, M.D., FACC, FAHA.**

"More than one-third of Americans have obesity, so this is a big problem we're tackling, and we asked a lot of big questions," she said.

"Our centers explored everything from genetic predispositions to maternal transmission of obesity to their offspring. As a result of all their hard work, I think we could eventually see new drugs and innovative new therapies that will help decrease obesity in patients. Indeed, we are extremely pleased that this SFRN initiated 10 additional clinical trials that will continue to produce translatable outcomes related to obesity. This is exactly the type of impact envisioned when the SFRN model was put in place."

Obesity SFRN Awardees and Oversight Advisory Committee



SFRN CENTERS: OBESITY

Johns Hopkins University

Center Director: **Jeanne Marie Clark, M.D., M.P.H.**

In recent years, researchers have been puzzling over an intriguing question about obesity: Is it caused solely by how many calories you consume and metabolize? Or does the timing of when you eat also impact body weight and metabolism?

To delve further into that question, scientists at Johns Hopkins University used novel approaches to better understand the role of time-restricted feeding on obesity and cardiometabolic health.

In the basic science project, researchers confirmed that restricting the feeding time for obese mice “protects them against weight gain and some metabolic effects like glucose tolerance, which is partly due to the up-regulation of a molecule called AMP-activated protein kinase (AMPK),” said Center Director **Jeanne Marie Clark, M.D., M.P.H.**



Dr. Jeanne Clark

But in the clinical science project, time-restrictive feeding in humans didn't seem to cause weight loss or improve glucose, blood pressure or lipids. The population science project showed similar results. It used a mobile app to look at eating and sleeping patterns in a large group, but again, those patterns did not seem to influence weight changes.

While the results were the opposite of what researchers had hypothesized, they're important because they show that time-restrictive feeding for losing weight doesn't live up to its early promise.

“Our research adds to the literature and helps us move away from the time-restrictive feeding option by saying, ‘It's not really the time that you eat the food, it's *what* you eat,’” Clark said. “The quality of the diet and the calories still are the biggest drivers of weight.”

She commended the American Heart Association for putting together a research network that was unified “despite being four teams with completely different focuses and approaches to such a big problem.”

“We received a lot of good feedback from the other investigators and especially from the Oversight Advisory Committee, who were really effective. I was impressed by how engaged and motivated they were to produce the best science possible,” she said.

New York University Medical Center

Center Director: **Ann Marie Schmidt, M.D.**

Researchers at New York University (NYU) zeroed in on two questions countless people ask themselves every day: Why is it so hard to lose weight? And why is it also very hard to keep the weight off?

To find answers, they looked at one potential problem area: The body's natural “brakes” that block energy use after weight loss, including the receptor for advanced glycation endproducts (RAGE).

NYU scientists modified the receptors in both mice and humans and found potential benefits for blocking the RAGE pathway either through medicine or genetic tools, said Center Director **Ann Marie Schmidt, M.D.**

“There's every reason to believe that very exciting biomarkers and pharmaceuticals for weight loss success will come from that,” she said.

In the population science project, researchers looked beyond one-size-fits-all approaches to diets and weight loss and focused on alternative tech-supported behavioral weight loss programs.

New York University Center



Dr. Ann Marie Schmidt

“People have a broad spectrum of risks for obesity,” she said. “It's very likely we will have to tailor weight loss to particular people now and advise them individually about what's the best recipe for them to lose weight and keep it off.”

As productive as the research was, Schmidt said the AHA's SFRN on Obesity also fired up NYU fellows and scientists to make future breakthroughs.

“Many times, when the grant's over, everybody goes their own way but that's not the case here. It's really synergized and brought people together and energized them to continue to work together. It sets up a lot of future directions, and you can attribute a lot of that to the encouragement and insightful suggestions the Oversight Advisory Committee gave us,” she said.

“Hats off to the AHA for creating such a wonderful network and setting a tone for successful research. I'm thrilled to be able to take part in it.”

University of Alabama at Birmingham

Center Director: **W. Timothy Garvey, M.D.**

Scientists already know mothers with obesity tend to give birth to children with obesity, who often pass it on to the next generation. But they don't know why – or how to stop the endless cycle.

At the University of Alabama at Birmingham (UAB), researchers looked closely at events in the womb to learn how these mechanisms help determine body weight in children and increase risk for diabetes and heart disease.

The basic science project studied how different forms of stress during pregnancy change the metabolism of rats when they become adults. UAB scientists fed the mothers different types of diets to learn more about how that impacts pathways of metabolism as well as satiety hormones, which lead to sensations of hunger or of feeling full.

In the clinical science project, researchers delved deep into how a mother's pregnancy affects the first three months of a human baby's life, including their metabolism, body composition and insulin resistance.

The third project, focused on population science, shifted attention to the mother-child pairs to understand how a mother's weight, diabetes



Dr. Tim Garvey

and genes contribute to the inter-generational transmission of obesity and related health risks.

The results of all three projects told a similar story, said Center Director **W. Timothy Garvey, M.D.**

"The main message is that we really need to pay more attention to maternal health prior to conception, and not just focus on risk factors for cardiovascular disease in adulthood," he said.

"If we can get mothers to achieve a healthier body weight before they get pregnant, we can mitigate some of the generational transmission of obesity."

The UAB fellows who worked on the SFRN benefited from "a very creative multidisciplinary training experience. It made them think beyond the limits of their own research and gave them a broad translational reach," Garvey said.

"I've taken part in research projects before, but not one with this level of breadth of research, with all the projects interrelated and synergistic," he said.

"The American Heart Association has designed a research network where the projects are greater together than the sum of their individual parts."

Vanderbilt University Medical Center

Center Director: **Kevin Niswender, M.D., Ph.D.**

Before you can develop precision medicine, first you must know precisely what you're dealing with.

At Vanderbilt University, researchers set out to better understand the nuts and bolts of glucagon-like peptide 1 receptor (GLP1-R), which could be the key to fighting obesity and improving cardiometabolic health.

In the basic science project, researchers used mouse models to develop important preliminary data about genetics and molecular pharmacology that could, one day, translate into a simple pill for humans to manage their weight.

In the clinical science project, scientists looked at GLP1-R drugs to find new ways of decreasing inflammation and other cardiometabolic disorders. For the population science project, researchers studied electronic health records of more than 900,000 people treated at Vanderbilt to shed new light on the intersection of GLP1-R, genetics, obesity and a wide range of health problems. (All of the records were randomized and participants were de-identified.)

"We're really beginning to get a much more nuanced picture of what the clinical phenotypes of obesity are, and how precision medicine can improve outcomes," said Center Director **Kevin Niswender, M.D., Ph.D.**



Dr. Kevin Niswender

"We have one group that is very obese but also seems to be very metabolically healthy and may not need a lot of resources. Another group may not be as obese but has the features of people who develop severe terrible cardiovascular and metabolic disease. In that case, using algorithms, we'd be able to intervene much, much earlier, before it's too late," he said.

Niswender commended the AHA for paving the way for a revolution in obesity prevention and treatment.

"It's an incredibly brilliant concept, so well-managed and executed. A more typical funding mechanism is a single investigator swimming upstream in a sea of funding, but this SFRN concept pulls people together with very different skill sets so they work together and create powerful synergy, new ideas and creativity," he said.

"When it comes to obesity, we're in a brand-new day," he said. "And I think this SFRN is going to steamroll the way toward precision medicine and targeted therapies to reduce this burden of cardiovascular disease."

University of Alabama at Birmingham Center



THE FELLOWS: A CLOSER LOOK

The Fellowship Program

The fellowship program is an integral part of the Obesity Strategically Focused Research Network. It's also an important step toward the future, as the American Heart Association trained and mentored 10 postdoctoral fellows to be part of an innovative new generation of obesity investigators.

Fellows were assigned to specific teams at each SFRN center. They forged relationships with scientists and mentors inside and outside of their centers as they conducted research on new ways to prevent and treat obesity. The fellows also advanced their careers by networking and presenting research at AHA conferences and meetings.

"I was very impressed by this diverse group of fellows, who did a great job of helping us move obesity science forward," said Dr. Annabelle Volgman, who chaired the Obesity Strategically Focused Research Network Oversight Advisory Committee.

She said the AHA made it a point to prepare the fellows for a lifetime of developing new strategies to fight obesity and cardiovascular disease.

"It's not always just what they're finding that's important. It's the process of learning how to

conduct good research and ask further questions. That's the beauty of science: When you get an answer, you get 10 more questions. So we're teaching the fellows the process of rational thinking and ethical, meaningful research," she said.

Dr. Ann Marie Schmidt, who directed the SFRN Center at NYU, called the fellowship an "extraordinary opportunity" for young researchers.

"The American Heart Association provided the fellows with so many means to network, build a group of colleagues and present their research to the (then) president of the AHA, Dr. Ivor Benjamin," she said.

"Just as importantly, the fellows got to work on an exciting research project and learn from so many other scientists. I think it was a fabulous opportunity for them to learn new ways of answering important questions about diabetes and obesity."



Dr. Ruth-Alma Turkson-Ocran

Here are the stories of four of the fellows:

Ruth-Alma Turkson-Ocran, Ph.D., M.P.H., R.N.

Johns Hopkins University

SFRN Obesity Fellow 2019–2021

Although COVID-19 curtailed many in-person collaborations during the Obesity SFRN, **Ruth-Alma Turkson-Ocran, Ph.D., M.P.H., R.N.** was thrilled to attend several AHA meetings to share ideas and network with colleagues.

"Presenting my work at an AHA conference actually enabled me to get the faculty position I have now," said Turkson-Ocran, an instructor at Harvard Medical School and Beth Israel Deaconess Medical Center.

"This fellowship has played a tremendous role in my career, and I'm really, really grateful."

Turkson-Ocran's presentation at the American Heart Association's EPI|Lifestyle Scientific Sessions included research she conducted in the Obesity SFRN on time-restricted feeding in obese adults. Her work on the clinical project examined blood pressure patterns among adults who eat 80% of their calories before 1 p.m.

Her results found that time-restricted feeding did not reduce blood pressure compared to usual feeding patterns – an outcome that was the opposite of what she had hypothesized.

"That's the interesting part of research: You answer some questions, but then you end up raising more questions, which leads to future work in that area," she said.

Before she joined the Obesity SFRN, Turkson-Ocran had focused on cross-sectional studies. The fellowship gave her a whole new skill set.

"Learning to do clinical studies really improved my research methodology," she said. "I learned so much about troubleshooting and about the details that go into a successful trial, from data analysis skills to measuring the food in the metabolic kitchen."

The fellowship also gave her a chance to study a predominately Black population – a population that historically has been excluded from research. She applauded the AHA for its progressive thinking in all aspects of the SFRN.

"I really love the fact that they were focused on diversifying their training and a diversity of thought," she said. "It really gave me an opportunity to also shine as a fellow."

Johns Hopkins University Center



Henry Ruiz, Ph.D.

New York University School of Medicine
SFRN Obesity Fellow, July 2018–June 2020

Like all centers in the Obesity SFRN, NYU was required to have separate research components in basic science, clinical science and population science.

For Henry Ruiz, Ph.D., three was definitely better than one.

“I had never been exposed to a setup like that before, and I really appreciated how research improves when people with different perspectives target the same questions,” he said.

As part of the basic science project, Ruiz studied how obesity may be worsened by a receptor in the body that brakes energy-burning as a way for humans to survive when food is scarce.

“But we now live in a society with an excess of foods and nutrients, so what used to be a good braking mechanism is now actually a bad player that helps us store fats when we really don’t need them,” he said.



Dr. Henry Ruiz

Working with mouse models, Ruiz focused on blocking the braking system known as RAGE, an acronym for receptor for advanced glycation endproducts. As a result of the blockage, mice boosted their energy expenditure and became less obese.

The findings may one day translate into new drugs and therapies to prevent obesity or help people keep pounds off after they lose them, Ruiz said.

As a result of his SFRN fellowship, Ruiz won an NIH career development grant, or “K award,” and published papers in *Cell Reports* and *The International Journal of Obesity*. The second paper was the result of a project he started with Dr. Coleen McNamara of the University of Virginia after the two met during an AHA meeting during his fellowship.

“One of the things I valued most from the SFRN was being able to sit down and network with Ph.D.s and M.D.s and interact with leaders in the field. I learned a lot and I really grew as a scientist because of that.”



Dr. Samantha Martin

Samantha Martin, Ph.D.

University of Alabama at Birmingham
SFRN Obesity Fellow 2018–2020

Like a lot of scientists, Samantha Martin, Ph.D. began her career in a laboratory researching cells. To break up the solitude, she’d occasionally talk to the cells.

“But they didn’t talk back to me,” she said with a laugh. Eventually, the isolation got to her, “and I found myself not really being happy.”

Everything changed when she met Paula Chandler-Laney, a teacher at UAB who told her about a fellowship researching mothers and their children for the Obesity SFRN.

“I’ve always had a passion for working with moms and kids. This was my ideal path, and I wanted desperately to join, so I interviewed and got the position,” she said.

Martin worked on UAB’s population science project on the intergenerational transmission of obesity in mother-child dyads. One big takeaway from her work is that even though maternal obesity and gestational diabetes are often lumped together, they have different outcomes.

“These are essentially two different groups of women, so we identified the need to develop different interventions for both groups,” she said. “It’s important to really empower clinicians and investigators to come up with new strategies to prevent cardiovascular disease for these groups of women.”

Her work on the Obesity SFRN was accepted in several publications, including *Journal of the American Heart Association*. Her fellowship also helped her secure a faculty-level position in UAB’s Department of Obstetrics and Gynecology.

“This SFRN has really been amazing for my career development,” she said.

“I met so many great collaborators and incredible mentors at UAB, like Paula Chandler-Laney and Dr. Tim Garvey, who gave me so much advice and support and really pushed me beyond the limits of what I thought I was capable of. The AHA did such a great job of connecting me with a network of people. It really opened doors for me.”

Megan Shuey, Ph.D., M.Sc.

Vanderbilt University Medical Center

SFRN Obesity Fellow: July 2018–June 2020

Megan Shuey, Ph.D., M.Sc. was already an experienced investigator at Vanderbilt University when she joined the Obesity SFRN. But the fellowship opened her eyes to the power of teamwork and thinking outside the box.

“It was truly the first time I was able to take a lead on a collaborative project with others who were doing completely different work than I was,” she said. “It taught me to be really creative about how to communicate with others.”

Diving deep into the world of genetics and precision medicine for obesity and cardiovascular disease, Shuey not only worked with scientists from the other three SFRN centers, but she also compared data with scientists from other AHA SFRNs, including those on atrial fibrillation and vascular disease.

Shuey combed through a huge population database, cleaning the data and identifying different cardiovascular phenotypes. The next steps were to “ask a ton of different questions about the impacts of obesity and obesity-related phenotypes on a patient’s overall health and precision medicine,” she said.



Dr. Megan Shuey

She successfully zeroed in on coronary artery disease, heart attack, atrial fibrillation and peripheral artery disease “and quantified the individual risk of each of these different components of metabolic syndrome,” she said. “We found that getting early control of high blood pressure and some of these other components, independent of weight, can really have an impact.”

The research will help medical professionals prioritize which areas to focus on and assist them in counseling patients about weight loss and weight management, she said.

Her work from the SFRN was published in several medical journals, including *Obesity Science & Practice* and the AHA’s *Atherosclerosis, Thrombosis, and Vascular Biology*. Shuey said the fellowship inspired and prepared her for her goal of one day running her own university research lab.

“It’s a really unique and valuable fellowship. I think the AHA has done an incredible job of taking a multi-pronged approach across disciplines and training fellows in a very holistic manner.”

COLLABORATIONS

Above all, the Obesity SFRN was an alliance of scientists partnering to share data, methods and models to push research forward.

“These four centers had a brilliant synergy among the different projects,” said Dr. Annabelle Volgman, who chaired the Obesity Strategically Focused Research Network Oversight Advisory Committee.

“Not only was there a lot of collaboration among the scientists within individual universities, but they helped each other out across the universities. It’s hard, sometimes, but collaboration is the best way to advance knowledge in any disease.”

Dr. W. Timothy Garvey, Center Director at University of Alabama at Birmingham, said he was pleased by some key information-sharing efforts between UAB, Vanderbilt and Johns

Hopkins, as well as between UAB scientists working on the center’s basic, clinical and population projects.

“Data was constantly flowing among all of these projects,” Garvey said.

The joint efforts across the Obesity SFRN had a profound impact on Samantha Martin, a fellow at UAB.

“I loved seeing how well and effortlessly people worked together. I’ve never seen anything like it,” she said.

“Other fellows and postdocs I’ve talked to outside the SFRN tell me they haven’t been as fortunate as I was as far as collaboration. But my takeaway from this SFRN is that teamwork is really important. I want to model my own research program based on what I experienced with the AHA.”

Vanderbilt University Center



CONCLUSION

The need for obesity research is urgent. Obesity affects more than a third of the U.S. population, and the epidemic continues to grow and affect the health of people of all ages, regions and demographic groups.

But the Obesity SFRN came with an enormous challenge: the Covid-19 pandemic, which struck partway through the program.

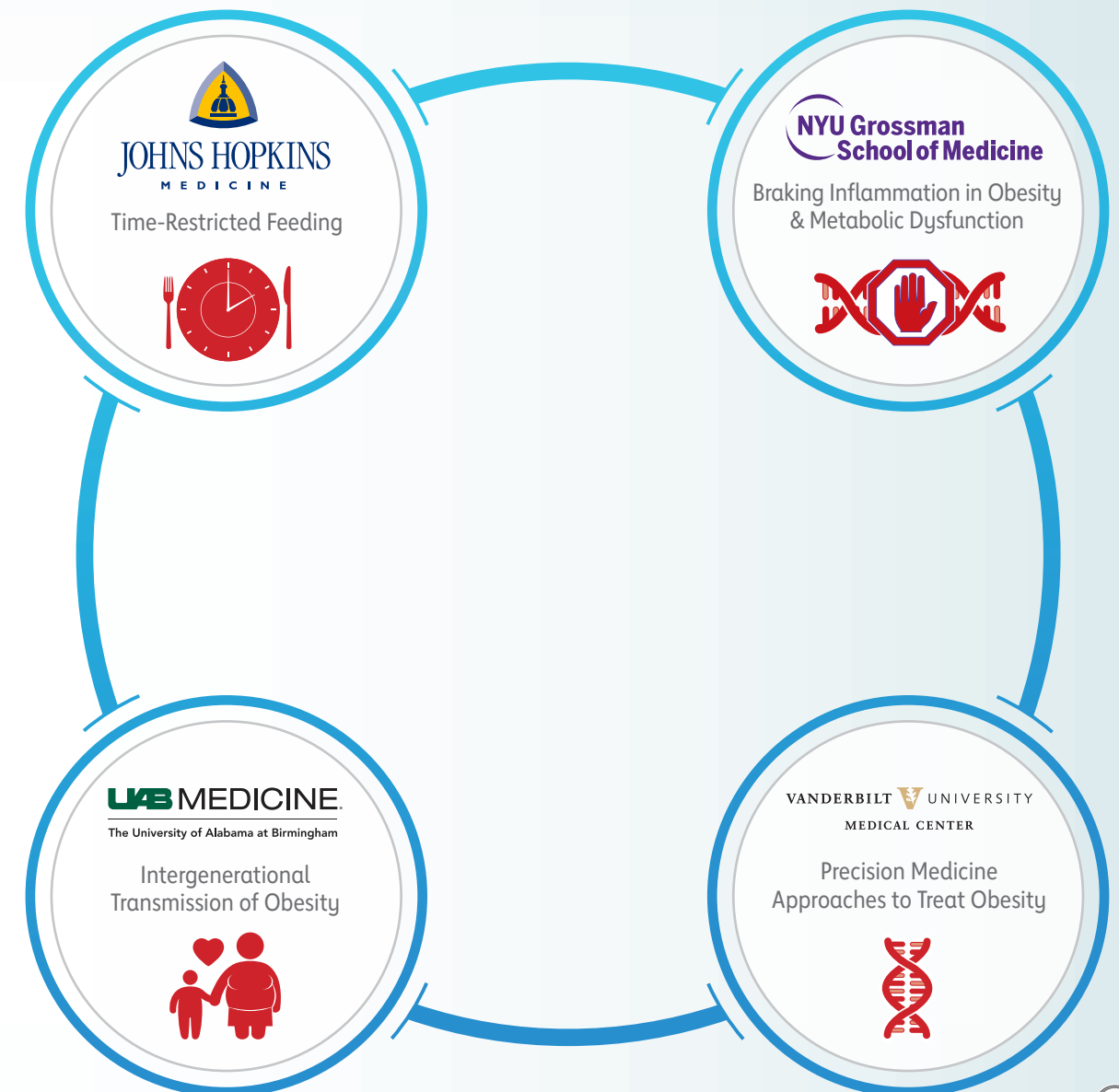
All of the Obesity scientists did a “remarkable job of quickly pivoting and transitioning to a virtual world when needed. They really rose to the challenge,” said Dr. Annabelle Volgman, the Oversight Advisory Committee Chairperson.

“We are so grateful to the American Heart Association for thinking up this innovative SFRN model,” Volgman said. “Thanks to the AHA, we now have a better understanding of obesity and how it contributes to cardiovascular disease.”

Since the first SFRN launched in 2014, the AHA has created 14 strategically focused research networks, including ones on Prevention, Hypertension, Disparities in CVD & Stroke, and Go Red For Women.

In addition to Obesity, other networks have focused on Heart Failure, Children, Vascular Disease, Atrial Fibrillation, Arrhythmias & Sudden Cardiac Death, Cardiometabolic Health & Type 2 Diabetes, Health Technologies & Innovation, Disparities in Cardio-Oncology, and the Science of Diversity in Clinical Trials.

All of AHA’s strategically focused research networks share common goals, such as training new investigators, producing new research and identifying programs and policies to reduce cardiovascular and cerebrovascular disease.





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