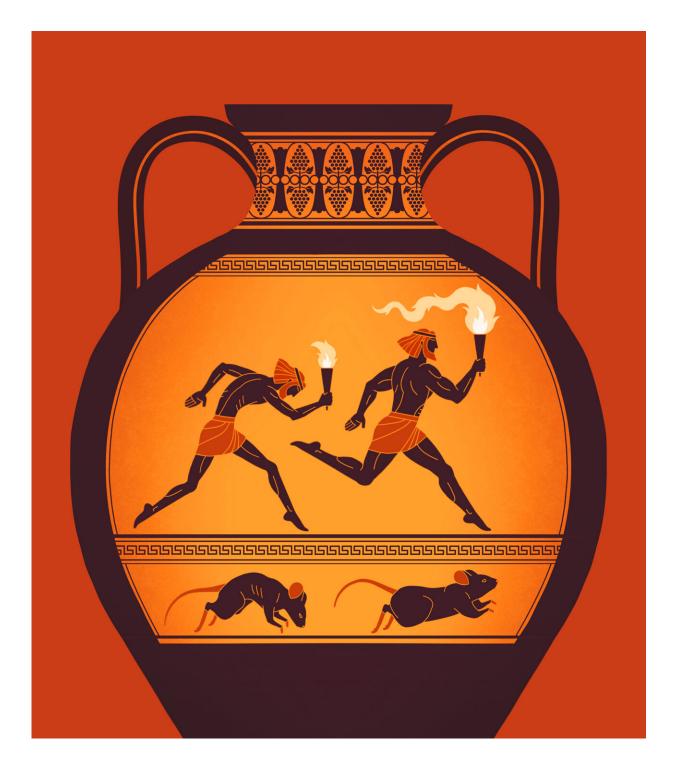


Energy deficits harm athletes' health, new research tool reveals how

September 4 2024





Depicted on a pot inspired by the ancient Greek origins of the Olympics, two torch-wielding athletes and their coinciding mouse models are shown with REDs (left) and without (right). Credit: Salk Institute



In 2014, the International Olympic Committee named a syndrome affecting many of its athletes: relative energy deficiency in sport, or REDs. It's now estimated that more than 40% of professional athletes have REDs, and the rate could be even higher in recreational athletes and exercisers.

Athletes develop REDs when they consistently expend more energy through their physical activity than they take in through their diet. Over time, this prolonged energy deficit can lead to a wide range of symptoms, including hormonal and reproductive issues, insomnia and fatigue, bone weakness and injury, and a higher risk of anxiety and depression.

Despite its high prevalence, little is known about how REDs works on a cellular and molecular level—in large part because there was no established laboratory model of the <u>syndrome</u>.

Now, researchers at the Salk Institute have created the landmark mouse model of REDs and are already using it to better understand the syndrome. Their initial investigation revealed that REDs affects organ size and gene expression patterns across the entire body. What's more, this energy deficiency appears to impact male and <u>female mice</u> differently: In males, kidney health was most significantly impacted, while in females, reproductive health and muscle mass were most affected.

The findings, published in <u>*Cell Metabolism*</u> on September 3, 2024, identify potential biomarkers to more conclusively diagnose REDs and provide new molecular targets for future therapeutics that could halt, reverse, or prevent the syndrome altogether.

"Without an animal model of the syndrome, there was no means to gain an understanding of its mechanisms on a cellular or <u>molecular level</u>,"



says Professor Satchidananda Panda, senior author of the study and Rita and Richard Atkinson Chair at Salk.

"By establishing an effective mouse model of REDs, we can now systematically ask how the syndrome affects each organ, tissue, and bone in the body and what we can do to help athletes experiencing these symptoms."

Other groups have tried to develop rodent models of REDs but have largely failed to replicate its many symptoms. Salk scientists took a new approach, and by gradually changing the animals' exercise-to-food ratio, they were able to mimic many human features of REDs, including high activity levels, low energy intake, reduced body weights, disrupted activity-rest patterns, and lowered blood sugar. They also focused on relatively young mice to model the typical age range of <u>professional</u> <u>athletes</u>, equivalent to 20-25 years old in humans.

"Our mouse model is an incredible milestone in the ongoing research on REDs," says Laura van Rosmalen, first author of the study and a postdoctoral researcher in Panda's lab. "And though it's not so great for athletes, for us scientists it is really interesting—and shocking—to see how the whole body is impacted by this syndrome."

Using this new <u>mouse model</u>, the scientists measured how REDs affects the anatomy and gene expression levels of 19 different organs. Mice with REDs showed significant shrinkage of vital organs, including kidney and reproductive organs, and deterioration of bone quality.

The experiments also revealed several molecular changes in the blood that could potentially be used as biomarkers to test patients for REDs—a far more effective diagnostic approach than the current questionnaire-based methods.



The scientists also found several elevated markers of stress in the REDs mice, including the activation of a brain-body hormone network known to contribute to anxiety and depression, with larger effects observed in females. What some athletes may write off as pre-competition jitters, adds Panda, may in fact be deeper-rooted psychological changes related to the syndrome.

The new model and initial findings stem from Panda's work with the <u>Wu</u> <u>Tsai Human Performance Alliance</u>—a collaborative team of researchers that studies peak human performance and athleticism with the intention of "enabling all people to achieve optimal health and well-being" and an <u>emphasis on female athletes</u>.

"The recipe for health is not 'eat less food, do more exercise,'" says Panda. "In fact, combining these two independently reasonable habits doesn't seem good if you are already healthy. But so far it seems the solution for REDs is not as simple as increasing caloric intake. We now have much to explore with this model to determine exactly what our clinical recommendations should be, and I look forward to continuing that now-possible exploration."

Beyond the scope of athletes, REDs can also affect others with negative energy balances, such as those with eating disorders like anorexia nervosa. Future inquiry into the prevention and treatment of REDs will positively influence these populations and athletes alike, promoting an overall healthier population in alignment with the Wu Tsai Human Performance Alliance's mission.

More information: Laura van Rosmalen et al, Multi-organ transcriptome atlas of a mouse model of relative energy deficiency in sport, *Cell Metabolism* (2024). DOI: 10.1016/j.cmet.2024.08.001



Provided by Salk Institute

Citation: Energy deficits harm athletes' health, new research tool reveals how (2024, September 4) retrieved 5 September 2024 from <u>https://medicalxpress.com/news/2024-09-energy-deficits-athletes-health-tool.html</u>

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