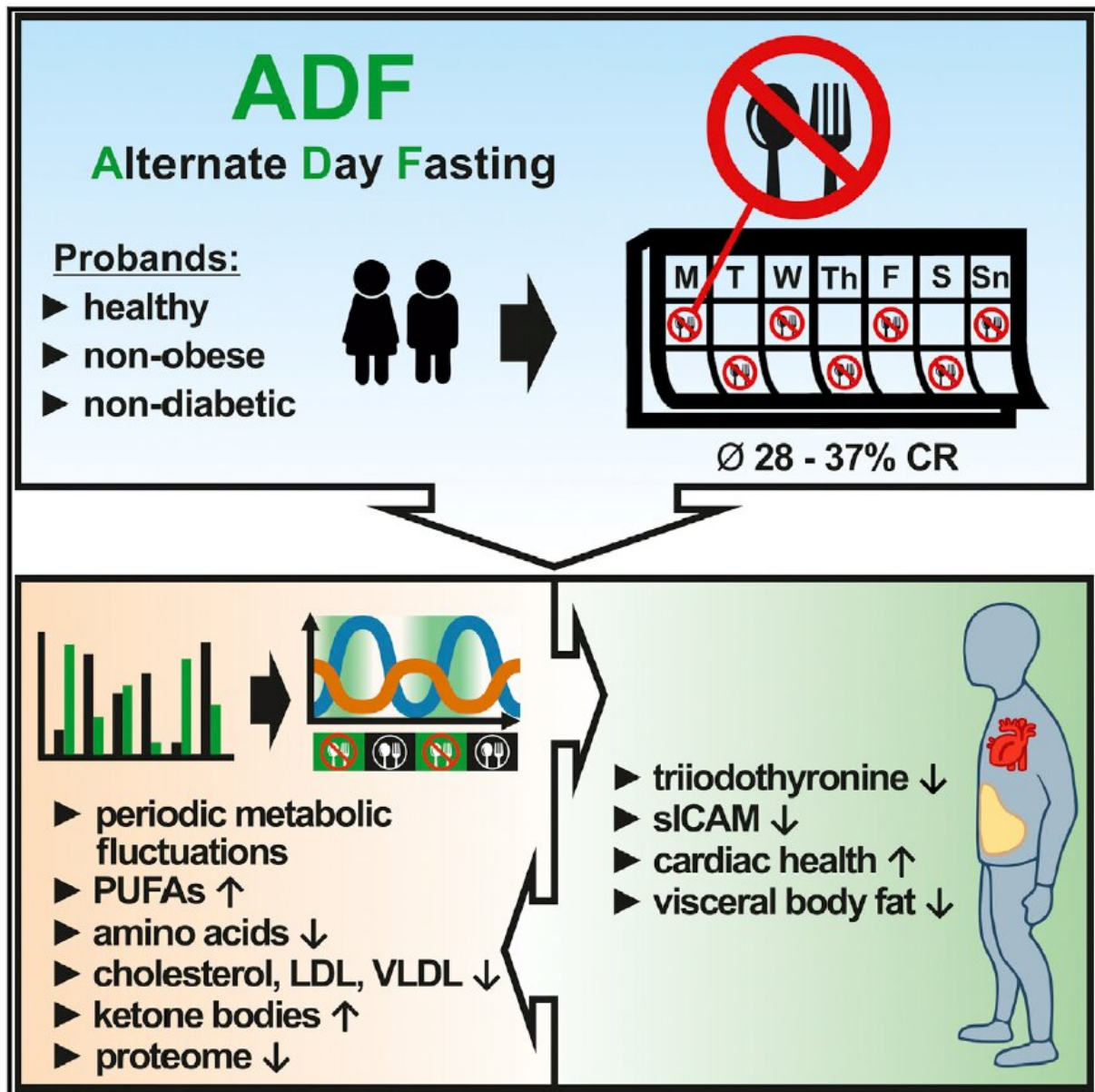


Clinical trial shows alternate-day fasting a safe alternative to caloric restriction

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This visual abstract reflects the finds of Stekovic et al., who show in the clinic that alternate day fasting (ADF) is a simple alternative to calorie restriction and provokes similar improvements on cardiovascular parameters and body composition. ADF was shown to be safe and beneficial in healthy, non-obese humans, not impairing immune function or bone health. Credit: Stekovic et al./*Cell Metabolism*

In recent years there has been a surge in studies looking at the biologic effects of different kinds of fasting diets in both animal models and humans. These diets include continuous calorie restriction, intermittent fasting, and alternate-day fasting (ADF). Now the largest study of its kind to look at the effects of strict ADF in healthy people has shown a number of health benefits. The participants alternated 36 hours of zero-calorie intake with 12 hours of unlimited eating. The findings are reported August 27 in the journal *Cell Metabolism*.

"Strict ADF is one of the most extreme diet interventions, and it has not been sufficiently investigated within randomized controlled trials," says Frank Madeo, a professor of the Institute of Molecular Biosciences at Karl-Franzens University of Graz in Austria. "In this study, we aimed to explore a broad range of parameters, from physiological to molecular measures. If ADF and other dietary interventions differ in their physiological and molecular effects, complex studies are needed in humans that compare different diets."

In this randomized controlled trial, 60 participants were enrolled for four weeks and randomized to either an ADF or an ad libitum control group, the latter of which could eat as much as they wanted. Participants in both groups were all of [normal weight](#) and were healthy. To ensure that the people in the ADF group did not take in any calories during fast days, they underwent continuous glucose monitoring. They were also asked to

fill in diaries documenting their fasting days. Periodically, the participants had to go to a research facility, where they were instructed on whether to follow ADF or their usual diet, but other than that they lived their normal, everyday lives.

Additionally, the researchers studied a group of 30 people who had already practiced more than six months of strict ADF previous to the study enrollment. They compared them to normal, healthy controls who had no fasting experience. For this ADF cohort, the main focus was to examine the long-term safety of the intervention.

"We found that on average, during the 12 hours when they could eat normally, the participants in the ADF group compensated for some of the calories lost from the fasting, but not all," says Harald Sourij, a professor at the Medical University of Graz. "Overall, they reached a mean calorie restriction of about 35% and lost an average of 3.5 kg [7.7 lb] during four weeks of ADF."

The investigators found several biological effects in the ADF group:

- The participants had fluctuating downregulation of amino acids, in particular the amino acid methionine. Amino acid restriction has been shown to cause lifespan extension in rodents.
- They had continuous upregulation of ketone bodies, even on nonfasting days. This has been shown to promote health in various contexts.
- They had reduced levels of sICAM-1, a marker linked to age-associated disease and inflammation.
- They had lowered levels of triiodothyronine without impaired thyroid gland function. Previously, lowered levels of this hormone have been linked to longevity in humans.
- They had lowered levels of cholesterol.
- They had a reduction of lipotoxic android trunk fat

mass—commonly known as belly fat.

"Why exactly calorie restriction and fasting induce so many beneficial effects is not fully clear yet," says Thomas Pieber, head of endocrinology at the Medical University of Graz. "The elegant thing about strict ADF is that it doesn't require participants to count their meals and calories: they just don't eat anything for one day."

The investigators point to other benefits that ADF may have, compared with continuous calorie restriction. Previous studies have suggested calorie-restrictive diets can result in malnutrition and a decrease in immune function. In contrast, even after six months of ADF, the immune function in the participants appeared to be stable.

"The reason might be due to evolutionary biology," Madeo explains. "Our physiology is familiar with periods of starvation followed by food excesses. It might also be that continuous low-calorie intake hinders the induction of the age-protective autophagy program, which is switched on during [fasting](#) breaks."

Despite the benefits, the researchers say they do not recommend ADF as a general nutrition scheme for everybody. "We feel that it is a good regime for some months for obese people to cut weight, or it might even be a useful clinical intervention in diseases driven by inflammation," Madeo says. "However, further research is needed before it can be applied in daily practice. Additionally, we advise people not to fast if they have a viral infection, because the immune system probably requires immediate energy to fight viruses. Hence, it is important to consult a doctor before any harsh dietary regime is undertaken."

In the future, the researchers plan to study the effects of strict ADF in different groups of people including people with obesity and diabetes. They also plan to compare ADF to other dietary interventions and to

further explore the molecular mechanisms in animal models.

More information: *Cell Metabolism*, Stekovic, Hofer, and Tripolt et al.: "Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans." [www.cell.com/cell-metabolism/f ... 1550-4131\(19\)30429-2](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30429-2) , DOI: [10.1016/j.cmet.2019.07.016](https://doi.org/10.1016/j.cmet.2019.07.016)

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