

# Update on Human Calorie Restriction Research<sup>1–3</sup>

Susan B. Roberts<sup>4\*</sup> and John Speakman<sup>5</sup>

<sup>4</sup>Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA; and <sup>5</sup>School of Biological Sciences, University of Aberdeen, Aberdeen, Scotland

## ABSTRACT

The United States population is aging rapidly, and understanding the potential impact and feasibility of lifestyle interventions on the aging process is of central importance for addressing future population health and health care costs. This symposium addressed the question of whether caloric restriction may be a feasible strategy to improve human health by reductions in rates of primary and secondary aging in humans, viewed from the perspective of existing data in animal models, and by using emerging data from the human Comprehensive Assessment of Long-Term Reduction in Energy Intake trial, which is a randomized trial of human caloric restriction in free-living men and women. *Adv. Nutr.* 4: 563–564, 2013.

## Animal Studies of Caloric Restriction

Caloric restriction (CR) experiments on animals have been performed for almost the past 100 y, since the pioneering paper that demonstrated that restricting food intake of rats resulted in extension of life span. Since then CR has been applied to many species, almost universally (with some notable exceptions such as the housefly), resulting in an increase in life span. Studies in small rodents have been the most popular, and a linear relationship has been found between the extent of restriction and the extension of life span in such animals, at least up to a restriction of 65%. Beyond this amount it is uncertain whether further restriction would increase or shorten life span, but one thing is certain, restricting food intake by 100% leads to death within a few days for most small rodents. Hence, somewhere between 65 and 100% restriction, the increase in life span must reverse and then decrease. The increase in life span of rodents as restriction increases is mirrored by an improvement in health span. This improvement is most noticeable in the reduction in the prevalence of cancer, including reductions in both the initiation and progression of tumor growth. The effect is apparent in multiple forms of cancer, including breast, liver,

pituitary, skin, colon, and lymphatic cancers [reviewed in (1)]. In addition to cancer, insulin sensitivity and immune function improves in rodents, although the ability to clear a parasite infection appears to be impaired. Effects on cardiovascular responses are less clear from the rodent studies, and there seems to be a consensus that the long-term impact on bone health in rodents is largely negative.

Perhaps one of the most startling results in rodent studies of CR in the past few years has been the studies of a recombinant inbred series of 43 different mouse strains: the ILS-XISS mice. These studies found that, far from a universal positive effect, a whole range of different responses occurred up to 40% restriction across the different strains. These responses ranged from life extension, to no impact, to substantial life shortening. Exactly how this effect comes about is unclear, but it is possible that it reflects differences in the point at which the restriction transfers from being beneficial to detrimental. Hence, less severe restriction may still provide a universal benefit. More studies are needed to clarify this issue. Two additional observations are worth making with respect to these data. The first is that the impact of CR, across the strains, was different between males and females. Although a broad correlation exists between the responses across the sexes, the  $r^2$  for the relationship was only 0.215 (1). This number suggests that the impact of CR may be different between the sexes, and if so, this difference would have profound implications for the application, and study, of CR in humans. Even more intriguing is that the responses to CR were very different across the two labs that studied them, pointing also to an unknown environmental impact on the effects of CR.

<sup>1</sup>Supported by NIH grant U01-AG022132 and USDA agreement 58-1950-0-014.

<sup>2</sup>This article is a summary of the symposium "Caloric Restriction in Humans: Is It Feasible, Effective and Safe?" held April 20, 2013, at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2013 in Boston, MA. The symposium was sponsored by the American Society for Nutrition (ASN) and the National Institute of Aging. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, editor, or editorial board of *Advances in Nutrition*.

<sup>3</sup>Author disclosures: S. B. Roberts and J. Speakman, no conflicts of interest.

\*To whom correspondence should be addressed: E-mail: susan.roberts@tufts.edu.

Finally, consistent data are lacking from studies of the effects of CR in nonhuman primates in the past 20–25 y. Specifically, a Wisconsin study reported an increase in life span and health outcomes in the CR group, but a NIH National Institute on Aging study reported only improved health outcomes and no impact on life span. In trying to explain this difference, researchers have focused attention on the different diets used in these two studies, a finding that has important implications for recommendations for CR in humans. However, many factors are potentially involved, and in the light of the different results from the studies on the recombinant inbred mouse strains, we should perhaps not be surprised that environmental factors have also affected the nonhuman primate studies. The implications of this work for the human application of CR is that how CR is implicated may be a critical factor in determining the results of the intervention.

### CR in Humans

One small randomized trial reanalyzed by Stunkard (2) suggested beneficial effects of human CR (a regimen consisting of reduced energy intake provided by milk and fruit on alternate days) in a small population of nursing home residents, and the Biosphere studies (3,4) have also indicated beneficial short-term effects of CR that also involved modulation of dietary composition. Additionally, cross-sectional studies (5) have suggested that voluntary CR is associated with longevity, and factors such as high insulin sensitivity that have been associated with beneficial effects of CR in animal models have also been associated with longevity in humans. These observations, combined with the recent suggestion of active alterations in aging processes by antiaging genes, suggest the potential for extensive beneficial effects of CR in humans consistent with the effects emerging in the nonhuman primate studies. However, some theoretical analyses alternatively suggest that CR may have only a limited potential to extend life span and reduce morbidity in humans. Moreover, potential adverse effects of CR in humans that would render it unacceptable even if metabolic benefits were detected (such as adverse alterations in mood and cognition) have received almost no attention to date.

This symposium was conducted to give an overview of the current state-of-the-art research on human CR, including the NIH-funded Comprehensive Assessment of Long-Term Reduction in Energy Intake (CALERIE) trial. Three 6- to 12-mo pilot studies were previously conducted by the team (6–8) to define the protocol for a powered clinical trial. The pilots indicated the broad feasibility of long-term human CR trials that are generally consistent with emerging data from the CR trials in nonhuman primates and provided data for power calculations for key variables, including metabolic rate, oxidative stress, and insulin sensitivity. Based on these studies, a 2-y multisite CALERIE trial randomizing 220 nonobese men and women to an assessment-only control or CR intervention has recently been completed (site PIs Eric Ravussin, Susan Roberts, John Holloszy with William

Krauss as Principle Investigator (PI) of the study coordinating center).

Data from the trial were presented by Susan B. Roberts and Sai K. Das, with Leanne Redman, and by Eric Ravussin, Dennis Villareal, and Edward Saltzman, with William Krauss. The protocol of CALERIE and design of the intervention have been previously published (9,10). Collected data are currently being analyzed, including data on adherence to the CR regimen determined by the doubly labeled water method; adverse events, such as self-reported sicknesses; and safety parameters of particular concern, based on previous studies, such as bone mineral density, metabolic adaptation (changes in resting metabolic rate and total energy expenditure in relation to changes in body composition), body temperature, and biomarkers of aging (e.g., immune function, oxidative stress, and growth factors). Whether CR is feasible, safe, and effective for reducing primary or secondary aging in humans is not known, and publication of these comprehensive data from the CALERIE trial will go a long way toward providing suitable information for evaluation.

### Acknowledgments

All authors read and approved the final manuscript.

### Literature Cited

1. Speakman JR, Mitchell SE. Caloric restriction. *Mol Aspects Med.* 2011; 32:159–221.
2. Stunkard AJ. Nutrition, aging and obesity. In: Rockstein M, Sussman ML, editors. *Nutrition, longevity, and aging.* New York: Academic Press; 1976. p. 253–84.
3. Weyer C, Walford RL, Harper IT, Milner M, MacCallum T, Tataranni PA, Ravussin E. Energy metabolism after 2 years of energy restriction: the Biosphere 2 experiment. *Am J Clin Nutr.* 2000;71:946–53.
4. Walford RL, Weber L, Panov S. Caloric restriction and aging as viewed from Biosphere 2. *Receptor.* 1995;5:29–33.
5. Holloszy JO, Fontana L. Caloric restriction in humans. *Exp Gerontol.* 2007;8:709–12.
6. Das SK, Gilhooly CH, Golden JK, Pittas AG, Fuss PJ, Cheatham RA, Tyler S, Tsay M, McCrory MA, Lichtenstein AH, et al. Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am J Clin Nutr.* 2007;85:1023–30.
7. Racette SB, Weiss EP, Villareal DT, Arif H, Steger-May K, Schechtman KB, Fontana L, Klein S, Holloszy JO. One year of caloric restriction in humans: feasibility and effects on body composition and abdominal adipose tissue. *J Gerontol A Biol Sci Med Sci.* 2006;61:943–50.
8. Heilbronn LK, de Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, Rood J, Nguyen T, Martin CK, Volaufova J, Most MM, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA.* 2006;295:1539–48.
9. Stewart TM, Bhaskar M, Das S, Galan K, Martin CK, McAdams L, Pieper C, Redman L, Roberts S, Stein RI, et al. Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy Phase 2 (CALERIE Phase 2) screening and recruitment: methods and results. *Contemp Clin Trials.* 2013;34:10–20.
10. Rickman AD, Williamson DA, Martin CK, Gilhooly CH, Stein RI, Bales CW, Roberts S, Das SK. The CALERIE Study: design and methods of an innovative 25% caloric restriction intervention. *Contemp Clin Trials.* 2011;32:874–81.