



Calorie Restriction, Obesity, and the Aging Process

Antonello Lorenzini, PhD

The question of whether the aging process is slowed by calorie restriction or accelerated by obesity has been hovering in the gerontological field for some time. Now, Correa-Burrows et al¹ present solid observations that can help formulate an answer. They analyzed 205 of the more than 1000 participants in the Santiago Longitudinal Study, a longitudinal cohort in which participants were followed up from birth to ages 28 to 31 years. The analysis focused on this subgroup because the data for these individuals were more complete and due to budget limitations. Biological age was assessed using several methods, including 2 biological age estimations by DNA methylation, methylation-based estimation of leukocyte telomere length, and cytokines, adipokines, myokines, and growth factor levels. These assessments are generally recognized as valid for estimating the progression of the aging process by the gerontological community. In these participants, the persistence of a high body mass index (BMI) since early childhood or adolescence was associated with an increase in epigenetic age compared with chronological age, ranging from 2.23 years to 4.68 years, depending on the persistence of obesity and the specific epigenetic clock used.¹

The first observations regarding the prolongevity effect of caloric restriction date back 90 years and precede the consolidation of the biology of aging as a field of research.² Over the years, caloric restriction as an experimental tool to modulate the aging process has been used on multiple experimental models (from yeast and *Caenorhabditis elegans* to fish, birds, dogs, and cows), with consistent and reproducible results. To date, there are several experimental approaches in which diet has been used to modulate the aging process—simple calorie restriction, ketogenic diets, intermittent fasting, fasting-mimicking diets, time-restricted feeding, protein restriction, and diets restricted for specific amino acids. Among all these dietary interventions, however, caloric restriction remains the common component among those with the greatest effect on lifespan.³ When caloric restriction is absent, the increase in longevity observed is usually much smaller. Since these first observations, much of the research on caloric restriction, has been conducted on rats and mice. These 2 species, thanks to the relative brevity of their lifespans, are a common choice in gerontology. Taking these 2 species as examples, an analysis of the various available strains and their response to caloric restriction clearly shows that the ability to extend longevity correlates with the ability to limit the spontaneous excess weight experienced by rats and mice fed ad libitum.⁴ Ad libitum feeding, where animals have unrestricted access to food, is widely utilized in research facilities and is often considered the conventional housing approach. To evaluate the possible effectiveness of caloric restriction in our species, the most representative experimental model—aside from ourselves—is obviously other primates. Some studies have been diligently conducted on rhesus monkeys, and in this case as well it is reasonable to assume that the effect of caloric restriction is due mainly to its ability to prevent excess weight.⁵

In humans, controlled studies on longevity are difficult, the length of our lives being the first element of difficulty. Correa-Burrows et al¹ took advantage of a long longitudinal study and, among other tests, performed DNA methylation, which currently seems to be the most accurate method to estimate biological age.⁶ There are still conflicting interpretations regarding these biological clocks, and these estimates probably do not yet have the solidity to serve as a starting point for recommendations at the individual level. In any case, they still appear to be the most reliable biological aging estimators currently available in gerontology.⁷ Looking at the key findings of the study by Correa-Burrows et al,¹ and considering the sizable sample size (89 participants with normal BMI, 43 with obesity from adolescence, and 73 with obesity from early childhood), the results speak

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for themselves.¹ The graphs of biological age assessed by the 2 epigenetic clocks used—Horvath and GrimAge—show the extent of the effect without the need for statistical analysis when superimposed on the graphs of chronological age. Biological age is probably influenced by multiple factors in addition to obesity (eg, genetic variants, quality of diet, tobacco, and environmental pollutants), and it is likely that the assessment of the epigenetic pattern is a technique that still has a fair amount of technical variability: these 2 considerations account for the ups and downs in the graphs of biological age. However, despite this variability, the average level of biological age is clearly elevated in the 2 groups experiencing lasting obesity. This elevation strongly suggests that it is time to doubt the classical interpretation that has dominated the field of biology of aging for a long time: caloric restriction slows down the aging process. It is reasonable now to hypothesize that the excess calories that precede and accompany obesity, or obesity itself as a state of modified hormonal balance, or a combination of both these aspects, may accelerate the aging process.

Gerontologists have reached agreement on the fundamental hallmarks that are associated with the aging process. Through careful bibliographic research, researchers have looked for parallels between the processes associated with aging and those associated with obesity. What they found is a clear overlap in most of these hallmarks.⁸

A new awareness of the effect of obesity in accelerating the aging process represents an additional element for educational campaigns that aim to address the *globesity* epidemic. The recipe for a long and healthy life, therefore, does not seem to require experiencing hunger, but rather simply avoiding mental and physical stress, getting an appropriate amount of physical activity, and modifying the diet to increase foods that prevent obesity while reducing those that promote it.⁹

ARTICLE INFORMATION

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Corresponding Author: Antonello Lorenzini, PhD, Department of Biomedical and Neuromotor Sciences - DIBINEM, Alma Mater Studiorum, University of Bologna, Via Irnerio 48, Bologna 40126, Italy (antonello.lorenzini@unibo.it).

Author Affiliations: Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; Biostructures and Biosystems National Institute (INBB), Rome, Italy.

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