

Why do women live longer than men?

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Steven Austad. Credit: UAB

Women live longer than men. This simple statement holds a tantalizing riddle that Steven Austad, Ph.D., and Kathleen Fischer, Ph.D., of the University of Alabama at Birmingham explore in a perspective piece published in *Cell Metabolism* on June 14.



"Humans are the only species in which one sex is known to have a ubiquitous survival advantage," the UAB researchers write in their research review covering a multitude of species. "Indeed, the sex difference in longevity may be one of the most robust features of human biology."

Though other species, from roundworms and fruit flies to a spectrum of mammals, show lifespan differences that may favor one sex in certain studies, contradictory studies with different diets, mating patterns or environmental conditions often flip that advantage to the other sex. With humans, however, it appears to be all females all the time.

"We don't know why <u>women</u> live longer," said Austad, distinguished professor and chair of the UAB Department of Biology in the UAB College of Arts and Sciences. "It's amazing that it hasn't become a stronger focus of research in human biology."

Evidence of the longer lifespans for women includes:

- The Human Mortality Database, which has complete lifespan tables for men and women from 38 countries that go back as far as 1751 for Sweden and 1816 for France. "Given this high data quality, it is impressive that for all 38 countries for every year in the database, female life expectancy at birth exceeds male life expectancy," write Austad and Fischer, a research assistant professor of biology.
- A lifelong advantage. Longer female survival expectancy is seen across the lifespan, at early life (birth to 5 years old) and at age 50. It is also seen at the end of life, where Gerontology Research Group data for the oldest of the old show that women make up 90 percent of the supercentenarians, those who live to 110 years of age or longer.
- The birth cohorts from the mid-1800s to the early 1900s for



Iceland. This small, genetically homogenous country—which was beset by catastrophes such as famine, flooding, volcanic eruptions and disease epidemics—provides a particularly vivid example of female survival, Austad and Fischer say. Over that time, "life expectancy at birth fell to as low as 21 years during catastrophes and rose to as high as 69 years during good times," they write. "Yet in every year, regardless of food availability or pestilence, women at the beginning of life and near its end survived better than men."

• Resistance to most of the major causes of death. "Of the 15 top causes of death in the United States in 2013, women died at a lower age-adjusted rate of 13 of them, including all of the top six causes," they write. "For one cause, stroke, there was no sex bias, and for one other, Alzheimer's disease, women were more at risk."

Cell Metabolism invited Austad to contribute this perspective paper, "Sex differences in lifespan."

Austad first became interested in the topic when Georgetown University asked him to lecture on it in 2003. Although lab models like the roundworm *C. elegans*, the fruit fly *Drosophila melanogaster* and the mouse *Mus musculus* are intensively used in scientific studies, people in those fields are not very aware of how longevity patterns by sex can vary according to genetic backgrounds, or by differences in diet, housing or mating conditions, Austad says.

Those uncontrolled variables lead to different results in longevity research. A survey of 118 studies of laboratory mice by Austad and colleagues in 2011 found that 65 studies reported that males outlived females, 51 found that females outlived males, and two showed no sex difference.



But if variables are carefully controlled, mice may prove to be a useful model to study sex differences in the cellular and molecular physiology of aging, Austad and Fischer write.

This understanding will be helpful as researchers start to develop drugs for human use that affect aging, Austad says. "We may be able to develop better approaches," he said. "There is some complicated biology underlying sex differences that we need to work on."

Differences may be due to hormones, perhaps as early as the surge in testosterone during male sexual differentiation in the uterus. Longevity may also relate to immune system differences, responses to oxidative stress, mitochondrial fitness or even the fact that men have one X chromosome (and one Y), while women have two X chromosomes.

But the female advantage has a thorn.

"One of the most puzzling aspects of human sex difference biology," write Austad and Fischer, "something that has no known equivalent in other species, is that for all their robustness relative to men in terms of survival, women on average appear to be in poorer health than men through adult life."

This higher prevalence of physical limitations in later life is seen not only in Western societies, they say, but also for women in Bangladesh, China, Egypt, Guatemala, India, Indonesia, Jamaica, Malaysia, Mexico, the Philippines, Thailand and Tunisia.

One intriguing explanation for this mortality-morbidity paradox is a possible connection with health problems that appear in later life. Women are more prone to joint and bone problems, such as osteoarthritis, osteoporosis and back pain, than are men. Back and joint pain tends to be more severe in women, and this could mean chronic



sleep deprivation and stress. Thus, the <u>sex differences</u> in morbidity could be due to connective tissue maladies in women, and connective tissue in humans is known to respond to female <u>sex</u> hormones.

But this is just one of several plausible hypotheses for the mystery of why women live longer, on average, than men.

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