Q&A: How gaps in scientific data lead to gaps in care for aging women

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Menopause, the time that marks the end of a female's menstrual cycles, is a significant transition that comes with aging. This change has health effects, but researchers don't properly consider it in 99% of studies of

the biology of aging, as highlighted in a recent perspective in *Nature Aging*.

This gap in research translates to gaps in women's health care. Fabrisia Ambrosio, the article's senior author and an HMS associate professor of physical medicine and rehabilitation at Spaulding Rehabilitation Hospital, along with colleagues from HMS, the University of Pittsburgh, the University of Minnesota, and Spaulding, emphasize the importance of better basic research models of menopause and other female-specific traits.

For example, one of the issues in studying menopause's role in healthy aging is the lack of reliable animal models of menopause.

Ambrosio, who is the director of the Musculoskeletal Recovery Cente at Spaulding, discusses the challenges and opportunities for building a better understanding of female aging.

What do we know about the role menopause, pregnancy, breastfeeding, and giving birth play in aging?

Menopause is inextricably intertwined with aging in female individuals. On average, females will live about a third of their lives postmenopausal. We lack data to understand how menopause affects aging and how it might contribute to disease or age-related declines. In preclinical models, it's something that we just haven't effectively addressed, and so we haven't been able to study it well.

Similarly, when we think about pregnancy, about 86% of female individuals will give birth at some point. And in the clinic, pregnancy, childbirth, and breastfeeding can have long-term health effects. In some

cases, it is protective. In other cases, it may contribute to disease.

Again, this is a variable prevalent in humans but largely ignored in animal studies—most of the animals we use have never given birth.

I feel an overwhelming sense of urgency when I think about this. The science has so much catching up to do. Hundreds of years of research studies have been dominated by male animal models and male humans.

How does this gap impact health care outcomes?

Our health care system lacks data on how to treat age-related diseases in females. In the clinic, we're falling behind and can't treat aging females as effectively as we would like. It represents a significant gap in clinical practice.

And the consequences are tangible. Females live longer, but they live with more physical declines, cognitive declines, and cardiovascular issues. For example, we know that the number of misdiagnoses of a heart attack in females is higher than in males. And the same is true for a stroke.

In the example from our research, females get osteoarthritis more frequently than males, starting from around the time of menopause, which contributes to greater declines in physical mobility into older age. And yet, when we look at aging female rodent models, they display a relative protection against the loss of cartilage health with aging.

Alzheimer's disease is another example. The incidence is higher in females than in males. But it has been difficult to recapitulate this sex difference in our animal models

How often is menopause considered in studies of age-related health issues?

When we look at age-related diseases, over 75% of them are likely influenced by menopause in one way or another. But the great majority of preclinical biology research in aging studies fail to consider menopause in their experimental setup. In our new paper, we found that less than 1% of published studies considered menopause. The fact that we're not including menopause or other female-specific traits in preclinical models is a big missed opportunity.

Why is it important what animal models studies use?

There's no doubt that clinical (human) studies are critical for understanding disease. But much of our scientific understanding of the mechanisms by which diseases develop relies on animal models, which let us understand the fundamentals of disease in a way that we can't with humans.

Why don't we have an animal model of menopause?

Unlike humans, female rodents do not always have a persistent menopause phase. For many rodents, their hormone levels stay constant or increase even into older age. In fact, humans are quite unique in this way. Some monkeys undergo menopause, but that's pretty much right at the end of their life span, though a new study indicates that some chimpanzees may undergo menopause in midlife. Other than that new work, the literature has found that only humans and some types of whales spend a good amount of their life span post-menopause.

What's needed to address this gap?

There's been a lot of emphasis by the National Institutes of Health for researchers to do better in considering sex as a biological variable in their studies. And that's based on the recognition that so much research to date has been done only in males.

Of course, aging is another crucial biological variable. So now we're thinking about the intersection of sex and aging and the need to ensure that our aging models are capturing human trajectories.

The first step is increased recognition of the limitations of the current models and consideration of the contribution of menopause to aging and disease. I hope we'll start seeing more studies take menopause and other female-specific traits into account, to better understand aging and disease in human females.

We need a mechanism to bring aging researchers together to share their ideas on understanding aging in the postmenopausal population. And then we need additional funding for research that considers female-specific traits and uses some of these new models.

I hope in the coming years, we'll see some dedicated funds and resources for this type of work.

More information: Gabrielle Gilmer et al, Female aging: when translational models don't translate, *Nature Aging* (2023). DOI: 10.1038/s43587-023-00509-8

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