Massive biomolecular shifts occur in our 40s and 60s, researchers find

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If it's ever felt like everything in your body is breaking down at once, that might not be your imagination. A new Stanford Medicine study shows that many of our molecules and microorganisms dramatically rise or fall in number during our 40s and 60s.

Researchers assessed many thousands of different molecules in people

from age 25 to 75, as well as their microbiomes—the bacteria, viruses and fungi that live inside us and on our skin—and found that the abundance of most molecules and microbes do not shift in a gradual, chronological fashion. Rather, we undergo two periods of rapid change during our life span, averaging around age 44 and age 60. A paper describing these findings appears in *Nature Aging*.

"We're not just changing gradually over time; there are some really dramatic changes," said Michael Snyder, Ph.D., chair of genetics and the study's senior author. "It turns out the mid-40s is a time of dramatic change, as is the early 60s. And that's true no matter what class of molecules you look at."

Xiaotao Shen, Ph.D., a former Stanford Medicine postdoctoral scholar, was the first author of the study. Shen is now an assistant professor at Nanyang Technological University Singapore.

These big changes likely impact our health; the number of molecules related to cardiovascular disease showed significant changes at both time points, and those related to immune function changed in people in their early 60s.

Abrupt changes in number

Snyder, the Stanford W. Ascherman, MD, FACS Professor in Genetics, and his colleagues were inspired to look at the rate of molecular and microbial shifts by the observation that the risk of developing many age-linked diseases does not rise incrementally along with years. For example, risks for Alzheimer's disease and cardiovascular disease rise sharply in older age, compared with a gradual increase in risk for those under 60.

The researchers used data from 108 people they've been following to

better understand the biology of aging. Past insights from this same group of study volunteers include the discovery of four distinct "ageotypes," showing that people's kidneys, livers, metabolism and immune system age at different rates in different people.

The new study analyzed participants who donated blood and other biological samples every few months over the span of several years; the scientists tracked many different kinds of molecules in these samples, including RNA, proteins and metabolites, as well as shifts in the participants' microbiomes. The researchers tracked age-related changes in more than 135,000 different molecules and microbes, for a total of nearly 250 billion distinct data points.

They found that thousands of molecules and microbes undergo shifts in their abundance, either increasing or decreasing—around 81% of all the molecules they studied showed non-linear fluctuations in number, meaning that they changed more at certain ages than other times. When they looked for clusters of molecules with the largest changes in amount, they found these transformations occurred the most in two time periods: when people were in their mid-40s, and when they were in their early 60s.

Although much research has focused on how different molecules increase or decrease as we age and how biological age may differ from chronological age, very few have looked at the rate of biological aging. That so many dramatic changes happen during our early 60s is perhaps not surprising, Snyder said, as many age-related disease risks and other age-related phenomena are known to increase at that point in life.

The large cluster of changes in the mid-40s was somewhat surprising to the scientists. At first, they assumed that menopause or perimenopause was driving large changes in the women in their study, skewing the whole group. But when they broke out the study group by sex, they

found the shift was happening in men in their mid-40s, too.

"This suggests that while menopause or perimenopause may contribute to the changes observed in women in their mid-40s, there are likely other, more significant factors influencing these changes in both men and women. Identifying and studying these factors should be a priority for future research," Shen said.

Changes may influence health and disease risk

In people in their 40s, significant changes were seen in the number of molecules related to alcohol, caffeine and lipid metabolism; cardiovascular disease; and skin and muscle. In those in their 60s, changes were related to carbohydrate and caffeine metabolism, immune regulation, kidney function, cardiovascular disease, and skin and muscle.

It's possible some of these changes could be tied to lifestyle or behavioral factors that cluster at these age groups, rather than being driven by biological factors, Snyder said. For example, dysfunction in alcohol metabolism could result from an uptick in alcohol consumption in people's mid-40s, often a stressful period of life.

The team plans to explore the drivers of these clusters of change. But whatever their causes, the existence of these clusters points to the need for people to pay attention to their health, especially in their 40s and 60s, the researchers said. That could look like increasing exercise to protect your heart and maintain muscle mass at both ages or decreasing alcohol consumption in your 40s as your ability to metabolize alcohol slows.

"I'm a big believer that we should try to adjust our lifestyles while we're still healthy," Snyder said.

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