Exercise at consistent times could realign body clock for better skeletal health and performance, scientists suggest

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Consistent daily patterns of exercise and rest can synchronize the local body clocks associated with joints and spine with the brain clock, potentially helping individuals to maintain skeletal health, improve athletic performance and avoid injury, research by University of Manchester scientists has argued.

Though the study, published in *Nature Communications*, involved mice, the scientists suggest there is a high probability human cartilage and intervertebral disks—which have very similar physiological properties -will respond in a comparable way.

It also helps to contextualize an observation posed 300 years ago by a Reverend Mr. Wasse, rector of Aynho in Northamptonshire, to a Dr. Mead, concerning the difference in the height of a human body, between morning and night.

In the letter published by the Royal Society, the Reverend cited his observations of soldiers discharged from the army for being too short, arguing we are over half an inch taller after a good night's sleep.

Daily rhythms in mammalian behavior and physiology are generated by a circadian system which tunes into environmental cues such as light and feeding.

Scientists have long known that misalignment between the central body clock in the brain and other organs which have their own body clock—can increase the risk of pathology and diseases such as diabetes and cardiovascular disease.

However until now, very little was understood about the relationship between the clocks in joint cartilage—which has no nerve or blood supply—and the brain.

Professor Qing-Jun Meng, a senior author and body clock expert from The University of Manchester said, "Not only have we identified that misalignment between cartilage and intervertebral disk clocks and our central clock in the brain can occur through exercising at an inappropriate time, we have found the mechanism by which this happens and that skeletal clocks can resynchronize to daily patterns of physical activity.

"Our earlier work discovered internal body clocks in intervertebral disks and cartilage that dampen with aging. Importantly, healthy cartilage and intervertebral disks have no nerves and no blood supply, so until now it was not clear how their internal clocks synchronize with the brain."

Professor Judith Hoyland, another senior author and spine/intervertebral disk expert from The University of Manchester said, "Among the many health challenges, the age-related musculoskeletal decline—and its adverse consequences -is a major burden to individuals.

"Loss of bone density, degraded articular cartilage and degeneration of the intervertebral disks are primary features of the aging skeleton, all of which can contribute to pain and loss of mobility.

"Importantly, we have identified a new clock mechanism underlying skeletal aging, which could have far-reaching impacts on understanding frailty and designing more efficient treatment timing of exercise and physiotherapy to maintain good skeletal health and mobility."

Dr. Michal Dudek, lead author from The University of Manchester said, "While we are standing and moving around during the day, water is pressed out of intervertebral disks in our spine as well as the cartilage in hips and knees, making us slightly shorter by the end of the day—just as the Reverend Mr. Wasse identified 300 years ago.

"But what he didn't know was that this causes increase in osmolarity of the tissue because the same amount of minerals is now dissolved in less water so the actual concentration increases. Cells sense this change in osmolarity and synchronize the clocks within these skeletal tissues."

"The water comes back at night when we rest and osmolarity decreases, though this direction of change had no effect on the clock.

The scientists examined the mice who were given daily exercise on a treadmill during their resting time to show what happened to the clocks in the cartilage, intervertebral disk and the brain.

They confirmed the findings by compressing mouse intervertebral disks or cartilage explants in the lab or exposing them to higher osmolarity culture medium within a normal physiological range. Both resulted in a similar clock synchronizing effect.

Professor Qing-Jun Meng said, "We have in effect identified a new mechanism to understand how our body clocks align to the external environment.

"The clocks have evolved to prepare you for predictable rhythmic changes in the environment.

"Our results showed that physical activities in the morning, associated with daily patterns of sleep/wake cycle, convey timing information from the light-sensitive central clock in the brain to the weight bearing skeletal tissues. In effect it's telling your skeletal system it's time to wake up.

"But when this alignment is uncoupled with the brain, then like in other organs and tissues it can result in adverse impacts on your physical health.

"If you are constantly changing the time you exercise, you may be more prone to this desynchronization.

"However, if you change when you exercise, but then maintain that regime for some time, we show that your body clocks will eventually re-align with each other and you will adapt to it."

He added, "So, for example, frequently switching time zones to compete in sports events- a facet of the life of the international athlete for example, may undermine athletic performance and could make individuals more prone to injury.

"And our work showed that clocks in skeletal tissues of older animals remain responsive to daily patterns of exercise. As such, walking groups organized for older people could be more beneficial for their health if they happen at a similar time every day."

Lucy Donaldson, Director of Research & Health Intelligence at Versus Arthritis, said, "We already know that exercise is one of the best ways to reduce the pain and impact of arthritis, and this very early research shows that exercising at certain times of day might bring added benefits for people with arthritis.

"The daily 24-hour cycle that our bodies follow, such as our internal temperature dropping when we sleep and our blood pressure rising at certain times of day, is known as our circadian rhythm. There are processes inside our body which keep this rhythm going, known as 'clocks,' which are all linked to our central body clock in the brain.

"This early research in mice explores a link between the local clocks in joint cartilage and the central body clock in the brain, which the results suggest contribute to how quickly our bones and cartilage deteriorate over time. The findings show that when these clocks go out of sync, our

bones and cartilage deteriorate faster, but when they're aligned, the process is slowed down. Exercising at certain times of day helps to keep the clocks in sync and so could slow the progression of arthritis.

"This is an important discovery because it could help us to develop more targeted treatments for musculoskeletal conditions such as arthritis using exercise and physical activity."

More information: Michal Dudek et al, Mechanical loading and hyperosmolarity as a daily resetting cue for skeletal circadian clocks, *Nature Communications* (2023). DOI: 10.1038/s41467-023-42056-1

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