NTU Singapore scientists find link between excess visceral fat and cognitive performance in Asians

Scientists from the Lee Kong Chian School of Medicine (LKCMedicine) at Nanyang Technological University, Singapore (NTU Singapore) have found that Asians with an excess amount of visceral fat tend to have a poorer ability to think, learn, and remember.

This finding is based on an analysis of the health data of close to 9,000 multi-ethnic Singaporeans and permanent residents collected for the Health for Life in Singapore (HELIOS) study between 2018 and 2021.

The scientists found that an increase in the type of fat wrapped around the internal organs – known as visceral fat – is associated with poorer performance in cognitive tests of memory, executive function, processing speed, and attention.

When the scientists conducted a deeper dive into the relationship between body fat and cognition, using statistical analysis of genetic data from global databases, they found that a higher body mass index (BMI) and BMI-adjusted waist-to-hip ratio were also linked to a fall in cognitive performance.

These findings, published in the April edition of the medical journal The Lancet Regional Health – Western Pacific, highlight the impact that preventing obesity could have on maintaining cognitive function, said the scientists.

NTU LKCMedicine’s Professor John Chambers, senior author of the study and HELIOS study’s lead investigator, said: "With dementia expected to afflict 78 million people in 2030, and 139 million people by 2050[1], understanding and addressing the determinants of cognitive function is a major public health priority."
“Through our Asian population health study, we observed a link between visceral fat and poorer cognitive performance, which was subsequently confirmed with a statistical analysis of global genetic data. These findings raise the possibility that the prevention and control of obesity in Asian populations could play a critical role in maintaining cognitive function and protecting against the future risk of dementia.”

The study supports one of the goals outlined in NTU 2025, the University's five-year strategic plan, to respond to the needs and challenges of healthy living and ageing, one of humanity's grand challenges.

It was led by NTU LKCMedicine scientists, some of whom hold joint appointments at Singapore’s National Healthcare Group, in collaboration with scientists at Imperial College London (See Notes to Editor below for the full list of study authors).

Observations from a population cohort study

While earlier studies have shown that metabolic disorders could be risk factors for cognitive decline, scientists have been less certain that body fat is a risk factor for it.

Most of these earlier studies were performed in western populations of older individuals, leaving out Asians, who make up 60 per cent of the world’s population and whose health and disease are determined by a different combination of factors.

To assess the link between body fat and cognitive function in an Asian population, the scientists studied the health data of 8,769 participants living in Singapore of Chinese, Malay, or South-Asian ethnicity recruited for the Health for Life in Singapore (HELIOS) study.

The HELIOS study, which began in 2018, is a population-cohort study led by NTU LKCMedicine and carried out in partnership with the National Healthcare Group and Imperial College London.
Evaluation of HELIOS data revealed that three parameters are consistently associated with a lower cognitive performance: reduced high-density lipoprotein (or 'good' cholesterol), increased visceral fat mass index (a measure of visceral fat mass relative to body mass), and increased waist-to-hip ratio.

In contrast, parameters such as triglyceride levels (fat content in blood), blood pressure and glycaemic indices showed no association with cognitive performance.

Sockets That Spin Slide Switch

Establishing a biological link between body fat and cognition

To form a clearer picture of the link between body fat and cognitive function, the scientists turned to Mendelian randomisation, a statistical approach that makes use of small snippets of genes that vary from person to person.

Through large-scale genetic studies – also known as genome-wide association studies – scientists have associated many of these snippets with specific health behaviours and risks. Such genetic variants are present in humans at birth at random and are not altered by the environment or a person's upbringing. Any difference observed in the health outcomes can be attributed to the presence or absence of specific genetic variants.

Dr Theresa Mina, NTU LKCMedicine Dean's Postdoctoral Fellow and lead author of the study, explained: "Some people may have more visceral fat than others due to genetic reasons. If we can show that these people are more likely to experience reduced cognitive function, that would give us evidence that visceral fat is more directly related to cognitive ageing, and not because of lifestyle or environmental factors."

To carry out their Mendelian randomisation analysis, the NTU LKCMedicine team used data acquired from a number of genome-wide association studies conducted on various populations, focusing on genetic variants that predict visceral fat and body mass index (BMI).

They found that genetic variants predicting excess visceral fat, elevated BMI, and increased BMI-adjusted waist-to-hip ratio are related to reduced cognitive performance.

Following these findings, the NTU LKCMedicine scientists are now looking at how excess visceral fat across Asian ethnicities contributes to traits related to one's metabolism, such as insulin resistance, that are a result of a combination of factors, including genes, lifestyle, and the environment. An example of a metabolic trait is insulin resistance.
The scientists are also trying to understand the impact of metabolic traits on specific areas of cognition.

Notes to Editor:

Paper titled "Adiposity impacts cognitive function in Asian populations: an epidemiological and Mendelian Randomization study" published online in *The Lancet Regional Health – Western Pacific*, and in Volume 33, 100710, April 2023

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About Nanyang Technological University, Singapore

A research-intensive public university, Nanyang Technological University, Singapore (NTU Singapore) has 33,000 undergraduate and postgraduate students in its Engineering, Business, Science, Medicine, Humanities, Arts, & Social Sciences, an
NTU is also home to world-renowned autonomous institutes – the National Institute of Education, S Rajaratnam School of International Studies, Earth Observatory of Singapore, and Singapore Centre for Environmental Life Sciences Engineering – and various leading research centres such as the Nanyang Environment & Water Research Institute (NEWRI) and Energy Research Institute @ NTU (ERI@N).

Under the NTU Smart Campus vision, the University harnesses the power of digital technology and tech-enabled solutions to support better learning and living experiences, the discovery of new knowledge, and the sustainability of resources.

Ranked amongst the world’s top universities, the University’s main campus is also frequently listed among the world’s most beautiful. Known for its sustainability, over 95% of its building projects are certified Green Mark Platinum. Apart from its main campus, NTU also has a medical campus in Novena, Singapore’s healthcare district.

For more information, visit www.ntu.edu.sg

How does an embryo develop? How do children grow, wounds heal or cancer spread? All of this has to do with the growth of body tissue. One of the major research interests of ETH Professor Viola Vogel and her senior assistant Mario C. Benn is to understand this growth in detail. In their quest, they have departed from well-trodden research paths. For a long time, biology was about studying cells and the biochemistry of the metabolic processes within them, often regardless of their natural environment. Vogel and Benn, by contrast, are focusing on the extracellular matrix (ECM), a fibrous structure that surrounds body cells. This matrix is produced by the cells themselves and is a major component of all tissue.

Credit: Benn MC et al. Science Advances, March 2023; image enhanced

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There are many different interactions between body cells and this fibrous matrix. In recent years, research has increasingly shown that not all of these interactions are exclusively biochemical. In fact, some are mechanical or physical. For example, cells are capable of sensing mechanical stimuli from this extracellular matrix.

Together with their team of researchers, Vogel and Benn have now been able to replicate tissue growth in vitro and study this process in detail. "Our results underline the importance of the interactions between cells and the extracellular matrix," Benn says. In time, he hopes to make medical use of these findings – to prevent wound-healing disorders, for example, or in the therapy of cancer and connective-tissue diseases.

**Cell transformation**

Their study focused on two cell types: fibroblasts and myofibroblasts. Each of them is important for human tissue functionality, and each one can change into the other. Fibroblasts are found in the connective tissue of our organs, where they ensure that the extracellular matrix is continuously renewed and ensures healthy cell function.

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Three-dimensional matrix

Some things are known about the biochemical processes that take place when myofibroblasts revert to fibroblasts. Yet little research has been done to explain how the ECM influences this cellular transformation. "With conventional cell-culture methods, the cells grow flat across the culture dish. This leads to the formation of an unnaturally planar ECM," Vogel explains. "And anyway, research up to now has generally ignored the ECM. But studying cells without the extracellular matrix is a bit like studying the behaviour of spiders without their web." The method used by Vogel and Benn is quite different. It was originally developed at the Max Planck Institute of Colloids and Interfaces in Potsdam and has now been refined by the ETH scientists. They use a silicone scaffold, coated with specific proteins, that has microscopic triangular-shaped clefts and sits in a tissue culture medium. Over a two-week period, new tissue forms in these clefts, together with a more natural ECM. Growth begins at the apex, progressively filling the cleft as the tissue grows.

The researchers observed how myofibroblasts are always located precisely at the growth front – i.e., in the area of the tissue that is being newly formed. They were also able to show how myofibroblasts in this area form new ECM – initially in a provisional and then in a more stable form – before converting back into fibroblasts. "The processes are similar to those that take place in human subcutaneous tissue during the late phase of wound healing," Benn says.

The researchers were also able to show that rapidly changing ECM is one of the triggers for the reversion of myofibroblasts to fibroblasts. Moreover, this reversion is promoted when a certain type of ECM fibre – fibronectin – changes from a stretched to a relaxed state. It seems likely that similar interactive processes occur during wound healing.

The researchers then purposely interfered with the cell transition using various agents that change the composition or structure of the extracellular matrix. In this way, they were able to replicate what occurs with pathologies such as fibrosis or cancer – namely, that instead of reverting to fibroblasts as in healthy tissue, the myofibroblasts are stabilised by the extracellular matrix.

Future mechano-medicine

The researchers hope that such miniature tissue cultures will help them decipher further details of the interaction between human cells and their extracellular matrix. This will not only avoid animal testing, which otherwise is often necessary in biomedical research; it is also a method that in future could be used to test candidate substances during drug development. "These applications and research questions are low-hanging fruit," Benn explains. "If we can understand how myofibroblasts and fibroblasts change into one another, and control that process, then we can also make major progress with conditions such as wound-healing disorders, fibrosis and cancer."

Benn and Vogel also refer to a future field called mechano-medicine. This term describes the medical application of findings from the field of mechanobiology: the study of how cells can sense and process mechanical signals. In other words, mechano-medicine aims to apply the insights gained from mechanobiology to medical practice.
In time, the researchers hope to use mechano-medicine in the development of new diagnostic methods for the early detection of fibrotic tissue. “With many conditions, including pulmonary fibrosis, successful treatment depends on early detection,” Benn says. Current screening methods are unable to detect myofibroblasts in lung tissue with any great accuracy. Benn now hopes that further study of the extracellular matrix will reveal biomarkers that enable earlier and easier detection of fibrosis and similar connective-tissue diseases.

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