
Weight-bearing exercise can help to stave off the age-related loss of skeletal muscle.

YOSHIKAZU TSUNO/AFP/GETTY IMAGES

AGEING

# Lifting the burden of old age

*The loss of muscle and strength that accompanies ageing can be debilitating. But is the inevitable process actually a disease that could be treated?*

**BY LIAM DREW**

At the time of Queen Victoria's accession to the British throne in 1837, the longest life expectancy for women in the world's most developed countries was roughly 45 years. By 2015, it had increased to almost 87 — a gain of more than 2 years a decade.

Much of this improvement is the result of profoundly lower rates of child mortality. But something else has also changed: old people are living for longer. "Since 1950, there has been enormous progress in bringing down death rates for people in their sixties and seventies and eighties," says James Vaupel, who studies ageing and the structure of populations at the Max Planck Institute for Demographic Research in Rostock, Germany.

The size of the elderly population worldwide is unprecedented, and the oldest of this group are the fastest growing segment of society. In 2000, 71 million people were over the age of 80, according to the United Nations Department of Economic and Social Affairs. By 2030, that number will have increased to almost 202 million people, and by 2050, to 434 million.

This demographic shift poses profound questions as to the ability of medicine to meet the health needs of the oldest strata of society. "The paradigm of medicine has been curing, so the main issue has been mortality," says Alfonso Cruz-Jentoft, a specialist in geriatric medicine at the University Hospital Ramón y Cajal in Madrid. He thinks that needs to change. As people age, he explains, "function becomes more important than mortality". In other words, maintaining the ability to live independently may trump the need to prolong life for the very elderly. "The most meaningful definition of health is can you take care of yourself," says Vaupel.

Few conditions are more central to the erosion of elderly people's independence than sarcopenia — an age-related loss of skeletal muscle mass and function. Progressive loss of such muscle can prevent a person from leaving their home, climbing stairs or even rising from their chair. These failures in daily living, as well as the falls that are associated with muscle weakness, are among the leading causes of admission to nursing homes and hospitalization among the elderly.

Recognition of sarcopenia as a condition of considerable concern for public health is, however, a fairly recent development. "We physicians all know about renal insufficiency and heart failure and respiratory failure," says Cruz-Jentoft, "but we'd never thought about muscle failure." It was only in 2016, when sarcopenia was officially recognized by the

World Health Organization's International Classification of Diseases, that doctors could formally diagnose people with the condition.

Even in the light of these positive steps, sarcopenia remains a condition with neither an agreed on definition nor an effective treatment. As the average age of the world's population increases, researchers are working on both. "We know we're an increasingly ageing population," says Elaine Dennison, an epidemiologist who works on sarcopenia at the University of Southampton, UK. "One of the challenges for us is how to make sure that those added years are quality years."

## IN ALL BUT NAME

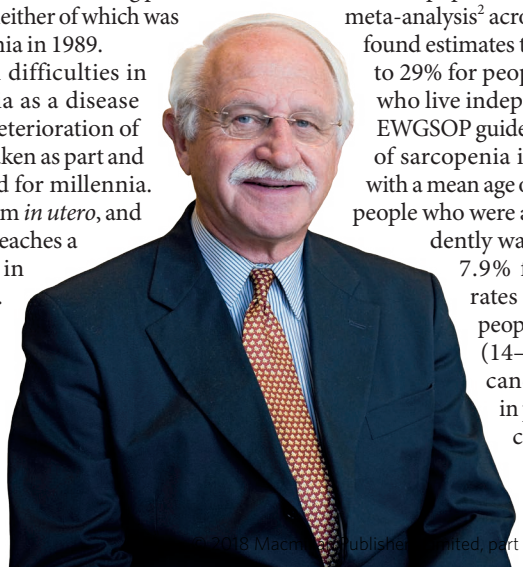
Sarcopenia's emergence as a clinical concern can be traced to a specific event. In 1988, Irwin Rosenberg, the then-director of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts, attended a scientific meeting on health in older people in Albuquerque, New Mexico, after which he was asked to write up his notes[1]. In these, Rosenberg called attention to a point that clearly had been neglected, given that it touched so many aspects of health. "No decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass," he wrote. "Why have we not given it more attention?"

In answer to himself, and somewhat tongue-in-cheek, he offered: "Perhaps it needs a name derived from the Greek. I'll suggest a couple: sarcomalacia or sarcopenia."

Although the term sarcomalacia sank without trace, within a year, sarcopenia — meaning a loss or poverty of flesh — was the subject of a call for grant proposals by the US National Institutes of Health. "It was a pick-up of almost dizzying speed," Rosenberg says.

If the 27 years between the coinage of the term sarcopenia and recognition of the condition by the World Health Organization feels less dizzying, it is probably because establishing a disease category takes time. Before the medical community can develop treatments and prevention strategies, robust diagnostic criteria and the underlying disease-causing processes must be defined — neither of which was in place for sarcopenia in 1989.

One of the main difficulties in defining sarcopenia as a disease is that a degree of deterioration of the body has been taken as part and parcel of getting old for millennia. Muscle begins to form *in utero*, and then grows until it reaches a peak mass, usually in a person's late 20s. From then on, there is continual loss.



**Irwin Rosenberg coined the term sarcopenia.**

TUFTS UNIVERSITY PHOTO

Although slow at first, with age the process quickens until, in some people, it reaches a level that impinges on daily life.

The stereotypical profile of the gain and subsequent reduction of muscle mass across a person's life echoes the life course of many tissues, and it presents a challenge to sarcopenia researchers: if all people can expect some natural loss, how severe must the loss be before it is considered a disease?

The European Working Group on Sarcopenia in Older People (EWGSOP) — a consortium, led by Cruz-Jentoft, of representatives from four major European science bodies working on ageing — was set up in 2009 to precisely define sarcopenia, facilitating basic and clinical research into the disease. EWGSOP published its initial guidelines for describing and diagnosing the condition in 2010, and similar groups in the United States (the International Working Group on Sarcopenia in 2011) and Asia (the Asian Working Group for Sarcopenia in 2014) have also produced recommendations. The goal of these collaborations was to come up with quantifiable metrics that would enable doctors to "decide who has sarcopenia and who does not", says Roger Fielding, a physiologist and colleague of Rosenberg at Tufts, who co-led the US effort.

The working groups agreed that sarcopenia should be defined not solely by muscle loss, but also by a measure of muscular function. To that end, they all recommended that an assessment of grip strength and gait speed should be part of the diagnostic procedure. However, when attempting to define cut-off points for speed and strength, below which a person can be said to have the condition, the three groups diverged — not drastically, but enough to prevent the adoption of a standard definition (see 'Crossing the threshold').

This has been problematic, says Dennison. "You need the definition to be able to do good studies, to look at the extent of the problem. And regarding treatment, you have to have hard end points to trials," she says. Estimates of the prevalence of sarcopenia have varied considerably, depending on both the definition used and the population surveyed — a 2014 meta-analysis[2] across several countries found estimates that ranged from 1% to 29% for people aged 60 or older who live independently. Using the EWGSOP guidelines, the prevalence of sarcopenia in a UK population with a mean age of 67 and comprising people who were able to live independently was 4.6% for men and 7.9% for women[3]. Such rates are much higher in people in residential care[2] (14–33%), in those with cancer[3] (15–50%) and in patients in intensive-care units[4] (60–70%). When developing diagnostic parameters, many specialists in sarcopenia draw analogies with the recognition of osteoporosis as a disease in the 1980s. Similarly to muscle mass, bone density decreases with age from a peak value attained in a person's 20s, and tends to decline steeply in women after the menopause. However, to robustly demarcate osteoporosis as a medical condition, a cut-off needed to be set. This was done by plotting bone density against the risk of fracture, which rises as the density falls — slowly at first, but then increasingly dramatically. A density value at which the fracture risk was viewed to be unacceptably high was then picked. "It isn't that something magical happens when you hit that threshold," says Dennison. But the threshold is tied to real-life outcomes — in the same way that the blood-pressure values used to define hypertension are linked to an elevated rate of adverse cardiovascular events. In both cases, crossing the threshold is a cue for medical intervention.

*"It may be that muscle is setting the pace of ageing of other tissues."*

The quest to find a concrete link between muscle decline and real-life outcomes took a considerable step forward in 2012, according to Fielding, when epidemiologists involved in the US Foundation for the National Institutes of Health Sarcopenia Project presented a review of medical data gathered from more than 26,000 elderly people. They had set out to determine which clinically measurable parameters — be it degree of muscle loss or decline in physical performance — were most strongly linked to real-life outcomes such as slow walking or being unable to rise from a chair unaided. Such analyses are feeding into ongoing attempts to develop an internationally accepted definition of sarcopenia, and further guidelines are expected, including a revision from EWGSOP in late 2018.

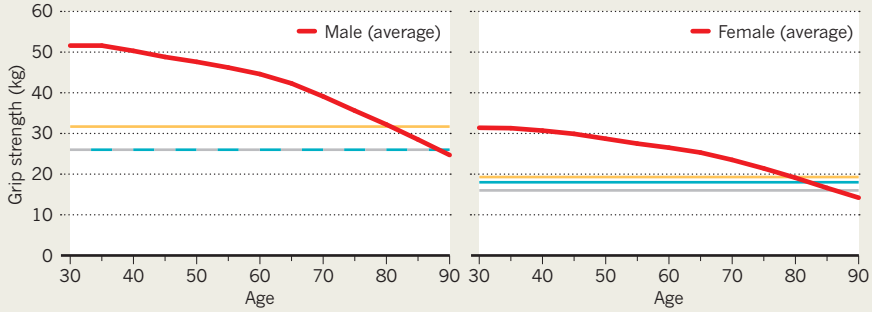
However, agreeing on a disease threshold is unlikely to end the question of how to define muscle health in ageing. "Usually with new diseases, you start with the sickest patients," says Cruz-Jentoft, "before you move to intermediate ones." As the field of sarcopenia evolves, the threshold could fall or an 'at-risk' category could emerge — similar revisions have occurred, for example, for both hypertension and diabetes. Such progression will be shaped by a greater understanding of the underlying biology and the risk factors of sarcopenia, as well as — most importantly — the development of effective treatments. "A fundamental requirement of screening or early identification of a disease process," Rosenberg says, "is that you have something to offer."

## HALTING SARCOPENIA

Sarcopenia does not have an unambiguous biological hallmark. There is no single process that is responsible for the demise of muscle

## CROSSING THE THRESHOLD

A person's grip strength begins to decline at around the age of 30, with an acceleration in his or her 60s. Working groups established to define sarcopenia do not agree fully on the point at which low strength should be considered a feature of the disease. But by the age of 85, most people's strength will fall below a clinical threshold for sarcopenia. However, not all people with such a strength will meet the full criteria for the disease.




SOURCES: DODDS, R. M. *ET AL. PLOS ONE* **9,** E113637 (2014) (GRIP STRENGTH); DENNISON, E. M., SAYER, A. A. & COOPER. C. *NATURE REV. RHEUMATOL.* **13,** 340–347 (2017) (THRESHOLDS).

fibres with age. Factors that contribute to the development of sarcopenia include hormonal changes (in particular, falling levels of testosterone, oestrogen or growth hormone), loss of the neurons that stimulate the muscle, an infiltration of fat into muscle, insulin resistance, physical inactivity, a vitamin D deficiency and not eating enough protein. And it's probable that the relative contribution from each varies between individuals.

Researchers who hope to prevent sarcopenia are looking for areas in which changes in lifestyle can make a difference. Trials investigating the use of weight or resistance training have yielded positive results, but aerobic activities alone have little impact. This has been demonstrated by numerous small- and medium-sized clinical trials, and resistance training is now being investigated further in combination with nutritional intervention in a large multicentre European trial.

Diet is another prominent modifiable factor. In particular, accumulating evidence indicates that eating too little protein can contribute to muscle loss. In 2013, a review led by the European Geriatric Medicine Society suggested an increase in the recommended amount of protein that people aged over 65 should consume, and advocated that older people who were ill should consume more protein still.

One group at particular risk of developing sarcopenia is older people who undergo long periods of inactivity as a result of, for example, serious illness or the need for sustained bed rest. Fielding advocates for making muscle rehabilitation an intrinsic part of managing the recovery from such an episode.

Other processes that lead to muscle loss seem to be intrinsic consequences of ageing, which require pharmacological intervention. Small biotechnology firms and large pharmaceutical companies alike have been active in this area of research for a decade, developing an array of compounds that act through various mechanisms. Drugs that increase the sensitivity of the androgen receptor for the hormone testosterone have shown promise in phase II clinical trials. (However, simply administering testosterone to boost muscle mass causes a number of adverse side effects.) Researchers are also targeting a molecule called myostatin — one of hundreds of signalling molecules, known as myokines, that are released from muscle. Feedback from myostatin inhibits muscle growth, and drugs that block it have produced promising results in phase II trials.

Yet drug development is still at an early stage. These compounds bid to increase muscle mass and to stimulate muscle growth, but it's unclear whether this is the best approach to improving muscle function in ageing bodies. "The right target and the right mechanism of action is probably still unknown," says Fielding. He emphasizes that research into the processes underlying muscle decline in extreme old age remains immature because, until recently, people used to die earlier in life from other diseases, meaning such processes "weren't even in the wheelhouse of things to investigate".

One idea in its infancy is that treating sarcopenia could have broad anti-ageing effects. After myokines are released from muscle, they enter the bloodstream and regulate the activity of many organ systems. Fabio Demontis, who studies ageing at St Jude Children's Research Hospital in Memphis, Tennessee, is investigating whether changes in the levels of myokines released, owing to muscle ageing and inactivity, can affect the health of other tissues.

Demontis conducts his work in the fruit fly *Drosophila*, for which an arsenal of genetic tools enables researchers to perform experiments that are impossible in mammals at present. He is able to flick a genetic switch selectively in the muscles of these insects to slow muscle-fibre ageing — and has found that this action slows ageing in other tissues of the fly as well. "It may be," he says, "that muscle is setting the pace of ageing of other tissues — and potentially of the whole organism."

Demontis is trying to find out whether the widespread effects of muscle ageing that he sees in flies are found in species throughout the animal kingdom. "Anything that helps with these devastating age-related conditions is very important," he says, echoing the views of clinicians. "If you are able to delay disease onset for ten years, that's a big deal."

### HOW TO TREAT AGEING

Rosenberg attributes the interest in muscle ageing that followed him naming sarcopenia to one main thing: "We take disease seriously, whereas we view processes of ageing as simply being natural."

David Gems, who studies the biology of ageing at University College London, thinks that there is nothing benign about senescence. He sees the myriad changes that occur throughout the body after the age of about 30, and that accelerate with age, as precursors to the outright diseases of old age. "I don't see how the idea that they're somehow non-pathological can stand up to rational analysis," he says. Convention, he argues, plays a large part in shaping what is viewed as normal in medicine.

But such views are fluid, and in the emergence of sarcopenia, both Gems and Rosenberg see a parallel with Alzheimer's disease. Gems says that when he was growing up in the 1970s, dementia was seen as a normal cognitive decline that came with age. "It was seen as nature taking its course," he says. "Granny's just having a second childhood, she's a little bit gaga."

But around the same time, neurologists revisited German psychiatrist Alois Alzheimer's work from the early twentieth century and reconceptualized dementia. Suddenly, stark cognitive decline — regardless of when it started — came to be viewed as a disease that might be halted. Rosenberg says that this led to "a meteoric rise, not only in interest, but in research funding and diagnosis". What constituted normal ageing for one generation had been redefined as an illness for the next.

When Rosenberg coined the term sarcopenia, he described it as "an opportunity". Although dementia has remained the most stubborn of foes, it's hoped that by focusing research on muscle ageing, the quality of life of people in their later years can be improved considerably. ■

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