

Artículo de revista:

Acosta, Enrique (2022) "Global Estimates of Excess Deaths from COVID-19." *Nature*, 613: 31-33, December (ISSN: 1476-4687)
<https://doi.org/10.1038/d41586-022-04138-w>.

These side effects include sarcopenia – an age-associated decline in skeletal muscle mass and function that occurs as ageing skeletal muscle becomes replaced by fat and fibrotic tissue, pointing to an inability of the muscle to repair itself⁴. By contrast, healthy young skeletal muscle has a remarkable regenerative capacity, even after injury. Moiseeva *et al.* set out to investigate how the presence of senescent cells might underlie skeletal muscle's diminishing ability to regenerate with age in mice.

The first challenge was to selectively isolate senescent cells from muscle tissue. The enzyme senescence-associated β -galactosidase (SA- β -gal) is highly active in senescent cells. The authors collected muscle tissue that had previously been damaged, and treated it with a fluorogenic substrate that fluoresces when cleaved by SA- β -gal. This enabled them to separate fluorescent senescent cells from other cells using a well-established approach called fluorescence-activated cell sorting. The group observed many more senescent cells in ageing tissue than in young tissue after injury. They also used their cell-labelling strategy to identify and study the positions of the cells in the injured tissue *in vivo*.

Tissue regeneration requires both stem cells and surrounding 'niche' cells, which can influence the behaviour of the stem cells. Moiseeva and colleagues examined gene expression and chromatin (the DNA–protein complex in which genetic material is packaged in the nucleus) in the senescent cell populations from young and old animals. They found that senescent cells – even those from young animals – make up part of the niche and have inflammation-promoting characteristics, which are associated with age-related declines in health (Fig. 1). The authors showed that several different cell types give rise to senescent cells, including skeletal muscle stem cells, myeloid cells and fibro-adipogenic cells, the last of which can promote inflammation, fat deposition and fibrosis in ageing animals⁵.

The group's discovery that senescent-cell numbers increased drastically after damage highlights a mechanism that might explain why some older people are more affected by ageing processes than others – if they have had an injury, more senescent cells might be present in their muscles. In line with this idea, geriatric mouse muscle that had been injured and so harboured senescent cells was less able to induce force than was uninjured geriatric tissue, even after the injury had repaired. However, the strength of the muscle was improved by giving the animals dasatinib and quercetin, drugs that can kill senescent cells. This shows that removal of senescent cells can improve muscle function.

Moiseeva *et al.* found that removal of senescent cells also improved muscle repair in younger animals. This finding was somewhat surprising, because senescence is not usually

associated with younger animals (or people). The result therefore suggests that strategies to remove senescent cells might also help younger people to recover from muscle injury.

To explore the mechanism by which senescent cells block muscle regeneration, the group further profiled gene expression in the cells, and found a decrease in expression of genes related to the function of energy-producing organelles called mitochondria, and an increase in inflammatory genes, among other changes. In particular, interferon-stimulated genes (which are associated with inflammation) are upregulated in both ageing and senescence. Moreover, the authors found changes in collagen production, which have previously been linked to fibrosis⁶. Fibrosis interferes with regeneration by creating the equivalent of scar tissue, instead of competent normal tissue. In the case of skeletal muscle, fibrotic tissue forms instead of muscle fibres, thus impinging on muscle function.

Together, Moiseeva and colleagues' findings indicate that senescent cells trigger inflammation and block regeneration throughout the animal's life, and in particular seem to be responsible for many of the detrimental

changes found in aged skeletal muscle. The changes in gene expression observed by the authors have also been shown to occur in the cells of aged tissue in general⁶, indicating that age-induced changes might be driven by senescent cells. It was not previously known that senescence might be the main driver of age-related gene changes. The work therefore gives fresh rationale to the strategy of seeking treatments that selectively remove senescent cells to combat age-related muscle weakness.

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The author declares no competing interests.

This article was published online on 21 December 2022.

Epidemiology

Global estimates of excess deaths from COVID-19

Enrique Acosta

Estimating the number of deaths attributable to COVID-19 around the world is a complex task – as highlighted by one attempt to measure global excess mortality in 2020 and 2021. See p.130

Knowing how COVID-19 affects global mortality rates is crucial if we are to understand the factors that govern its spread and severity, and to be able to evaluate the effectiveness of government responses to the pandemic. In May, a team of researchers led by the World Health Organization (WHO) and the United Nations Department of Economic and Social Affairs published the first results from their attempt to estimate global, COVID-19-related death rates. On page 130, Msemburi *et al.*¹ present these estimates in more detail.

Many deaths from COVID-19 went undetected in official reports from 2020 and 2021, because of limited testing capacity and misclassification of causes of death. This lack of data makes it challenging to quantify the mortality toll of short-term events, such as wars and natural disasters, as well as pandemics. For this reason, excess mortality – defined

as the difference between all observed and expected deaths in a given period – is considered the gold-standard approach for estimating the mortality toll of short-term events^{2,3}. But it is hard to find a universally effective way to measure excess mortality^{4,5}, because there are substantial variations in underlying mortality trends and data availability across populations.

Msemburi and colleagues set out to estimate excess deaths from COVID-19 for every country in the world. The authors report that there were between 13.2 million and 16.6 million more deaths than expected in 2020 and 2021. This death toll was between 2.4 and 3.1 times higher than the officially reported number of COVID-19-related deaths. Four out of five excess deaths occurred in middle-income countries (Fig. 1), with some of the worst affected in Latin America. In both

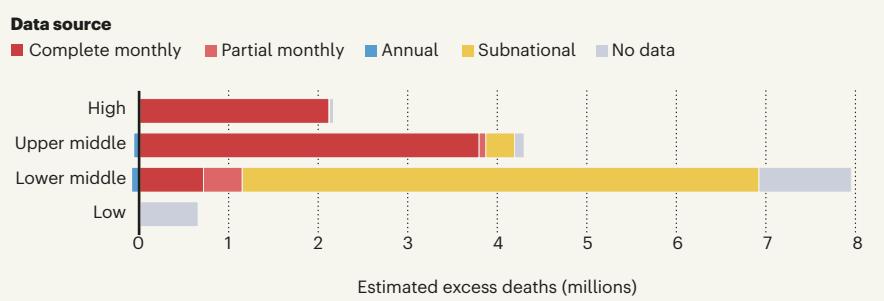


Figure 1 | Country income level and estimated excess deaths from COVID-19. Msemburi *et al.*¹ estimated the number of excess deaths that occurred in every country in the world in 2020 and 2021. Here, countries are grouped according to their income level (high, upper middle and so on). The authors made their estimates using monthly, country-level data on the total number of deaths where available. However, they had to make estimates of excess deaths from incomplete data for most countries. For some, data were available for only certain months or as annual data. More problematically, in many countries, data were available on only a subnational level, or not at all. Globally, half of the estimated excess deaths came from these countries, with this proportion varying hugely by the country's income level. The authors' estimates involved subtracting negative excess (where there were fewer than expected deaths) from positive excess, meaning that for some subgroups (such as annual upper middle and lower middle), the overall number of deaths is negative. (Figure generated using data from Supplementary Tables 5–13 of ref. 1.)

years combined, the observed mortality in Peru was double the expected level, and it was between 41% and 51% higher than expected in Mexico, Bolivia and Ecuador. Low-income countries had fewer deaths, mostly because they account for only 9% of the global population, and have younger populations, on average, than do higher-income countries. Compared with the published data, Msemburi *et al.* present more-detailed methods and more-refined estimates, by adjusting the way in which underlying mortality trends were forecast for several countries⁶.

However, the authors' estimates must be interpreted with extreme caution. This is because only 37% of countries had complete data for the number of people who died from any cause in each month of 2020 and 2021 – an essential figure for accurately calculating excess mortality. There were no data at all for 43% of countries; 2% of countries had data for only some regions; 5% had only annual data; and 13% had incomplete monthly series. The availability of data is heavily correlated with income. For example, only 2% of European countries had no data for 2020, whereas for African countries this figure was 87%.

As a result, the authors had to make some problematic inferences. First, for countries that lacked data in some regions, they had to scale death counts from subnational to national levels. This assumes a constant share of deaths between regions before and during the pandemic. But the spread, timing and severity of COVID-19 within countries was far from uniform^{7,8}.

Second, the researchers had to infer the number of expected and excess deaths in countries with no mortality data (mostly low-income countries) by extrapolating patterns from those with more-complete data

(mostly high-income countries that have robust health-care systems). The researchers adjusted the patterns seen across the latter group to make estimates for the former using country-specific proxies for socio-economic conditions, the intensity of the pandemic, each country's susceptibility to COVID-19 and its capacity to respond to the crisis. As such, half of global excess deaths were estimated without data on mortality, or by using data from subnational regions (Fig. 1).

There are other factors to consider when interpreting Msemburi and colleagues' findings, including 'avoided' and 'displaced' mortality. The former refers to expected deaths that did not occur – for instance, influenza-related deaths that were avoided in 2020 and 2021, owing to changes in people's behaviour and social-isolation measures⁹. The latter refers to deaths of frail or sick people that were expected to occur during the observation period, but were brought forward by COVID-19, producing a temporary surplus in mortality followed by a deficit, and consequently ignored when calculating cumulative excess deaths.

Msemburi *et al.* did not adjust for these factors, because they aimed to identify all changes in mortality during the pandemic. Nevertheless, adjusting estimates for these numbers is essential if the goal is to understand COVID-19 fatality better. There are already models available that can adjust for influenza-related avoided mortality¹⁰, and new approaches have been proposed for use in the context of the COVID-19 pandemic¹¹. For displaced mortality, partial adjustments can be made by excluding mortality deficits when computing the cumulative number of excess deaths over the months of the observation period. (The adjustment is only partial because COVID-19 deaths that occur during periods of

overall deficit remain uncounted.)

Although the inferences made by Msemburi and colleagues are not ideal, there is no obvious alternative. However speculative these estimates, most are surely closer to the truth than are officially reported numbers of deaths from COVID-19. To rely on confirmed deaths would imply that the pandemic spared low-income and lower-middle-income countries – vulnerable populations that have limited capacity for testing and response. This assumption is highly implausible, and even irresponsible.

Nonetheless, the complexity of the task is apparent from the fact that similar attempts to estimate the effect of the pandemic on global mortality have given different results. For the same period, the University of Washington's Institute for Health Metrics and Evaluation in Seattle¹² estimated 18.2 million excess deaths, and *The Economist* magazine estimated 16 million (see go.nature.com/3uykedp). This makes the WHO estimate the most conservative of the three. Compared with these other studies, the approach adopted by Msemburi *et al.* is simpler, and their estimation of uncertainties is more rigorous.

A sensible next step for Msemburi and colleagues – and one currently under way (see go.nature.com/3vhmybu) – is to include information on age in their data. The risk of COVID-19 death increases with age¹³. Because the authors calculated excess mortality for entire populations, any difference between countries is affected by variations in their age compositions. There have been some attempts to rank countries' response to the pandemic (including one in the current study) by estimated overall death toll, but without data on age, any assessments of differences in pandemic severity or the effectiveness of responses will be biased.

Finally, the complexity of estimating the effect of the pandemic on global mortality underscores the urgent need to build robust, centralized systems that allow for real-time monitoring of global mortality. The construction of such systems will require considerable global efforts to strengthen civil registration and crucial statistics systems worldwide, especially in low- and middle-income countries. But, once built, they will serve as an essential early warning for future pandemics and health crises.

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The author declares no competing interests.
This article was published online on 14 December 2022.

Materials science

Electric switch found for a superconductor

Kenji Yasuda

Ferroelectricity has been found in a superconducting compound. Strong coupling between these two properties enables ferroelectric control of the superconductivity, which could prove useful for quantum devices. See p.48

When some materials are cooled, their electrons flow without friction. This is a property known as superconductivity, which makes them lose their electrical resistance at ultralow temperatures. Superconductivity is particularly promising for the development of quantum devices, and the ability to switch between a superconductor and a normal metal adds an extra functionality to such devices – information storage. On page 48, Jindal *et al.*¹ report that the superconductivity of ultrathin sheets of the semimetallic compound molybdenum ditelluride (MoTe_2) coexists with another property, called ferroelectricity, that can be used to switch the material's superconductivity on and off.

In some crystals, the arrangement of atoms separates positive and negative charges in a way that generates a macroscopic electrical polarization. Materials in which the direction

of this polarization can be switched by an external electric field are known as ferroelectrics. Superconductivity and ferroelectricity are thought to be mutually exclusive, because the electrons in a superconductor pair up to conduct electricity extremely well, and this high conductivity should cancel the electrical polarization². But Jindal *et al.* show that these properties can coexist in bilayer MoTe_2 (Fig. 1).

The authors do so by combining two previous discoveries. In 2018, it was shown that the electrical polarization of bilayer and trilayer tungsten ditelluride (WTe_2) could be switched with an external electric field³. This ferroelectric metal belongs to a broad group called van der Waals materials, which have layered crystal structures that can be thinned down to atomic thickness through mechanical exfoliation. It is this layered structure that enables the coexistence of metallic

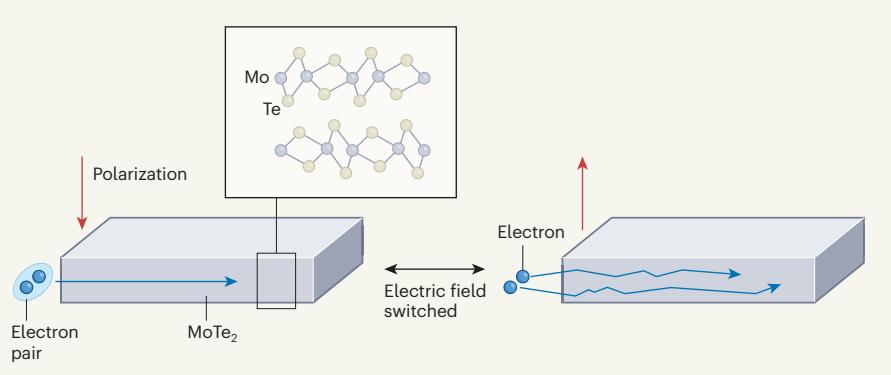


Figure 1 | Switching superconductivity on and off. Jindal *et al.*¹ show that two layers of molybdenum ditelluride (MoTe_2) exhibit coexisting properties: superconductivity (in which electrical resistance is zero and electrons move without friction in pairs) and ferroelectricity (in which an external electric field can switch a material's electrical polarization). In the authors' MoTe_2 device, an external field can be changed to switch the electrical polarization, turning the superconductor into a normal metal (in which electrons encounter friction) and back again.

From the archive

How kangaroo rats avoid eating too much salt, and searching for trout

50 years ago

The harsh environment of the desert poses many problems, such as [that] of ... obtaining enough food and water, to animals like the kangaroo rats ... in the deserts of western North America. The possibility of obtaining food and water from such plants as can survive there is confounded by the fact that one of the adaptations shown by desert plants such as the saltbush (*Atriplex*) is to have a layer of salt-filled tissue at the surface of their leaves. This seems to help the salt–water balance of the plants but would make them dangerous eating for most animals because of the high concentration of salt. In one species of kangaroo rat, *Dipodomys microps*, this particular difficulty has been partially solved ... G. J. Kenagy reports ... that this species has broad, chisel-shaped lower incisors ... [that] enable it to strip off the salty outer layers of the leaves and obtain the inner portions ... which are relatively salt-free. *D. microps* holds a saltbush leaf in its forefeet and draws it over its lower teeth about ten times, so shaving off the outer layers of one side. It then turns the leaf over and does the same thing to the other side.

From *Nature* 5 January 1973

150 years ago

Some months ago I inquired through the columns of the *Field* newspaper if any sportsman, fisherman, or naturalist would oblige me by replying to the following queries respecting the rarer *Salmonidae* of Great Britain. Firstly, whether *Salmo ferox* (the great lake trout) had ever been taken in any lake in Wales, and, secondly, whether any of the Gwiniad tribe (*Coregoni*) ... or any of the Chars (*Salmo salvelinus*) have ever been taken in any lake which is not a glacial lake ... ? The only reply with respect to the first query ... establish[ed] the fact that [*Salmo ferox*] still lingers in North Wales. To the second question I have received no reply. Is it possible that I may be more fortunate among the many naturalists and geologists who take *Nature*?

From *Nature* 2 January 1873

