Is there evidence for a limit to human lifespan?

ARISING FROM X. Dong, B. Milholland & J. Vijg *Nature* **538,** 257–259 (2016); doi:10.1038/nature19793

In their Letter, Dong *et al.*[1] claimed to have found evidence for a natural limit to human longevity, based on analysis of yearly maximum reported age at death (MRAD) values over the period 1968–2006 (see figure 2a in ref. 1). After splitting the period into two ranges (1968–1994 and 1995–2006), the authors fitted linear regressions to each group separately and concluded that the MRAD no longer increased significantly after 1995, and instead slightly decreased by 0.28 years each year[1]. There are strong statistical grounds to question the validity of their conclusions, which we illustrate by an analogous treatment of historical data on athletic performance. There is a Reply to this Comment by Dong, X. *et al. Nature* **546,** http://dx.doi.org/10.1038/nature22789 (2017).

Whether or not human lifespan is subject to an intrinsic limit has long been discussed. Current understanding of the biology of ageing points firmly away from any idea that the end of life is itself genetically programmed[2]. Ageing results from progressive accumulation of multiple forms of damage, many of which arise as inevitable by-products of the molecular and cellular processes that underpin living systems. As time goes by, the burden of damage grows and the risk of dying increases. In this sense, the extremes of human longevity resemble the records for physical performance in other spheres, such as sport.

In 1968, Bob Beamon set a male long-jump record that would endure for more than 20 years (see Fig. 1, which is based on records from the Olympics (https://www.olympic.org/olympic-results), and the International Association of Athletics Federations World Championships (https://www.iaaf.org/competitions/iaaf-world-championships)). In 1991, Beamon's record was exceeded by Mike Powell, whose long-jump record still stands. From Fig. 1 it might seem that after the world record in 1991, a decline in long-jump performances set in. If we partition the data in two groups, before and after 1991, and apply linear regression followed by two-tailed statistical testing, an argument is provided for rejecting the null hypothesis that there is no change, thereby pointing to an improvement in performance up to 1991 and deterioration thereafter. But when we apply a similar analysis to the whole of the data since 1960, we find a statistically significant increase in the winning long-jump distances over time.

There is marked similarity between the patterns seen in our Fig. 1 and figure 2a of ref. 1. We make the comparison not because there is any specific reason to pick long-jump records as being intrinsically important among other datasets of a comparable nature, but simply to illustrate the fundamental nature of the statistical reasoning that has been applied, we think questionably, to the MRAD values. It is the analytical principle that matters, not the case to which it has been applied. Just as we should be cautious to accept our first analysis of the long-jump data suggesting a decline, especially when most other athletic sports have shown progressive improvement, we believe that on a question of such perennial interest and importance as human longevity, a more careful approach is called for before claiming evidence of a limit.

First, Dong *et al.*[1] committed a basic statistical error by using the same dataset both to propose the hypothesis that there has been a change in the trends of human longevity occurring around 1995 and also to test it. It is well known that such a procedure leads to a false assessment of statistical significance.

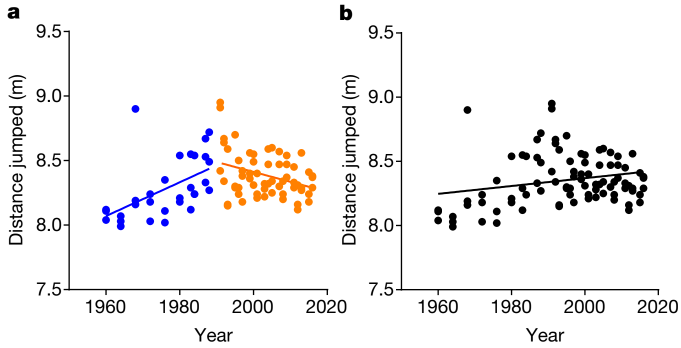

Figure 1 | Distance jumped for gold-, silver-, and bronze-medallists at the Olympics (1960–2016) and the International Association of Athletics Federations World Championships (1983–2015). a, Lines represent the function of linear regression for the period before the current world record (1960–1990) ($y = 0.013x - 17.58$; $P = 0.003$) and after the current world record (1991–2016) ($y = -0.008x + 23.78$; $P = 0.008$). **b**, Line represents the function of a linear regression for the period 1960–2016 ($y = 0.003x + 2.26$; $P = 0.027$).

Second, the idea of a set limit to human longevity is not strongly supported by what is being discovered about the biology of ageing. The continuing increase in human life expectancy that has occurred over recent decades was unforeseen. It provides evidence for greater malleability of human ageing than was originally thought. In the light of this evidence, we suggest the claim that the maximum human lifespan is fixed is improbable a priori, and therefore, even in the absence of statistical error, should be regarded with appropriate caution.

We conclude that it is premature to make inference based on data from 1995–2006, spanning barely a decade, and too soon to know what might be revealed by MRAD values in the decades to come. Improvements in underlying survival probabilities at old age show no deceleration, stall or decline. In technical terms, the authors have committed a statistical 'error of the third kind' by correctly rejecting the null hypothesis of no change but erroneously inferring that there is a limit to, or even a decline in, maximum lifespan, while in reality there is the strong possibility of a continuing increase[3–5].

Data Availability All data are available from the corresponding author upon reasonable request.

Maarten P. Rozing[1,2], Thomas B. L. Kirkwood[1,3] & Rudi G. J. Westendorp[1,2]
[1]Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark.
email: mroz@sund.ku.dk
[2]Department of Public Health, section of Social Medicine, University of Copenhagen, Copenhagen, Denmark.
[3]Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark.

Received 28 October 2016; accepted 31 March 2017.

1. Dong, X., Milholland, B. & Vijg, J. Evidence for a limit to human lifespan. *Nature* **538,** 257–259 (2016).
2. Kowald, A & Kirkwood, T. B. Can aging be programmed? A critical literature review. *Aging Cell* **15,** 986–998 (2016).
3. Kimball, A. W. Errors of the third kind in statistical consulting. *J. Am. Stat. Assoc.* **52,** 133–142 (1957).
4. Kaiser, H. F. Directional statistical decisions. *Psychol. Rev.* **67,** 160–167 (1960).
5. Hopkins, B. Educational research and type III errors. *J. Exp. Educ.* **41,** 31–32 (1973).

Author Contributions M.P.R. performed data analysis, M.P.R., T.B.L.K. and R.G.J.W. wrote the manuscript.

Competing Financial Interests Declared none.

doi:10.1038/nature22788

Dong *et al.* reply

REPLYING TO M. P. Rozing, T. B. L. Kirkwood & R. G. J. Westendorp *Nature* **546,** http://dx.doi.org/10.1038/nature22788 (2017)

In the accompanying Comment[1], Rozing *et al.* provide the interesting analogy of sports performance with ageing to question our finding of a limit to human lifespan[2]. We thank them for giving us the opportunity to clarify several misunderstandings.

First, the long-jump records merely show that, while the occasional athlete may set a new record, there is still a fundamental limit to human performance. As another commentary comparing our findings with the world of sport observed[3], although leading athletes might be able to reduce the world record for the 100-metre sprint by few milliseconds, they will never be able run the same distance in, for example, 5 seconds. Similarly, somebody might jump a few extra centimetres, but they will never span a kilometre in a single leap. Whether that reflects a mechanism that is similar to the process of ageing is unclear, but certainly not supported by any concrete evidence.

The criticism that we use the same dataset both to propose a hypothesis and to test it is simply not true. First, a possible end to the continuous life expectancy increases of older and older cohorts is suggested by our figure 1 (ref. 2), apparently overlooked by Rozing *et al.*[1], who mistakenly believe that survival probabilities at old age show no deceleration. Second, our analysis of the International Database on Longevity (IDL) and the Gerontological Research Group (GRG) database (independent datasets, albeit based in part on the same individuals) is data-driven and generates a model that provides strong evidence for a limit to lifespan (not a decline, as Rozing *et al.*[1] mistakenly infer from our paper). The fact that a significant increase in the maximum reported age at death (MRAD) value is obtained when all data from the 1960s to 2015 are considered is obvious and does not preclude a finding that the MRAD value reaches a plateau in the 1990s. Indeed, the fact that such an increase has been lacking for more than 20 years (not a decade, as Rozing *et al.*[1] state) in spite of the fact that the number of centenarians over that same time period has increased exponentially speaks for itself.

Xiao Dong[1], Brandon Milholland[1] & Jan Vijg[1,2]
[1]Department of Genetics, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
email: jan.vijg@einstein.yu.edu
[2]Department of Ophthalmology & Visual Sciences, Albert Einstein College of Medicine, Bronx, New York 10461, USA.

1. Rozing, M. P., Kirkwood, T. B. L. & Westendorp, R. G. J. Is there evidence for a limit to human lifespan? *Nature* **546,** http://dx.doi.org/10.1038/nature22788 (2017).
2. Dong, X., Milholland, B. & Vijg, J. Evidence for a limit to human lifespan. *Nature* **538,** 257–259 (2016).
3. The limits to human lifespan must be respected. *Nature* **538,** http://dx.doi.org/10.1038/538006a (2016).

doi:10.1038/nature22789