Many possible maximum lifespan trajectories

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

The recent Letter by Dong *et al.*[1] analysed demographic trends to claim that there is a biological limit to maximum human lifespan (approximately 115 years). Although this claim is not novel—Antero-Jacquemin *et al.* also identified a biological 'barrier' at 115 years[2]—the methodology that the authors used is. Here we show that the analysis presented by Dong *et al.*[1] does not allow the distinction between the hypothesis that maximum human lifespan is approximately 115 years and the null hypothesis that maximum lifespan will continue to increase. There is a Reply to this Comment by Dong, X. *et al. Nature* **546,** http://dx.doi.org/10.1038/nature22787 (2017).

The central difficulty with this exercise is accurately extrapolating onwards from a limited, noisy set of data. The authors' claim that maximum lifespan has reached a plateau[1] is depicted graphically in Fig. 1a (in black, with, in red, the International Database on Longevity (IDL; http://www.supercentenarians.org/) data that are presented in figure 2a of ref. 1). This figure also depicts different trajectories that maximum lifespan could follow over time if the null hypothesis (that maximum lifespan will continue to increase) were true, with maximum lifespans continuing to increase to an eventual future plateau (dark grey) or indefinitely (light grey). These projected trajectories were simulated using parameter values derived from fitting the models to the IDL data (with random scatter; see Methods and Fig. 2a). Note that all three models appear equally consistent with the known maximum lifespan data used (Fig. 1a, b, in red).

How the authors differentiated between these possibilities is important. Their claim[1] rests on their identification of a plateau in the ages of maximum lifespan beginning around 1995 and close to 1997, which is the year that Jeanne Calment, a supercentenarian with the longest confirmed human lifespan on record, died. Dong *et al.*[1] then separated the data into two groups, 1968–1994 and 1995–2006, and modelled each group using linear regression. While the first partition shows a trend for increasing maximum lifespan ($R^2 = 0.46$), the second partition does not ($R^2 = 0.12$, with a trend to decrease over time). It is this latter partition upon which their conclusions are largely based. This is problematic, because, even within a dataset showing an overall trend for an increase with time, normal variability can generate apparent plateaus and even temporary decreases over small intervals. For example, Fig. 1b shows linear regressions performed over 10-year intervals (with lines expanded outwards a further 5 years for clarity) for the IDL data and the simulated continuous linear growth model from Fig. 1a. Note the presence of several periods during which lifespan seems to be stable or is even decreasing, despite the clear upwards trend.

Furthermore, the authors do not describe how they identified the lifespan plateau[1], nor the partition site, indicating that these were products of casual visual inspection. This is a critical point for the validity of their argument because even slight changes to the assumptions that they made can notably alter the results of their analysis, with markedly different outcomes. Here we analyse the critical effects of the assumptions made by Dong *et al*[1].

First, the assumption that the dataset should be partitioned. By fitting a linear model to the dataset using the ordinary least squares method, without artificially dividing the dataset in two, we reveal a long-term increasing trend (Fig. 2a, blue line; $R^2 = 0.29$, Pearson's correlation $P = 0.0013$, suggestive of a long-term positive association between time and maximum lifespan). Alternatively, if we hypothesize that growth is nonlinear, a three-parameter function describing logarithmic growth up to a defined plateau (see Methods) should model the claims made by Dong *et al.*[1] However, this model provides only a marginally improved fit ($R^2 = 0.30$; Fig. 2a, black dashed line; essentially superimposed on the linear regression line), and the fitting does not support claims that

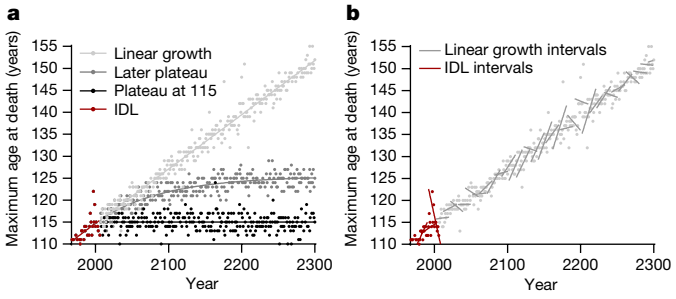

Figure 1 | Multiple future trajectories for maximum lifespan are compatible with current trends. a, Maximum ages at death from the International Database on Longevity (IDL, in red) as reported by Dong *et al.*[1], and simulated future maximum lifespans based upon the authors' conclusion that maximum human lifespan is approximately 115 years (black), or, alternatively, that maximum lifespan will continue to increase in the short-term but eventually plateau (dark grey), or that it will continue to increase linearly indefinitely (light grey). **b**, Maximum lifespans from the IDL (red) and simulated by the continuous linear growth model (grey, as above), divided into 10-year intervals and analysed by linear regression (lines are extended outwards an additional 5 years for clarity). This shows that short-term trends may not be representative of those for the full interval.

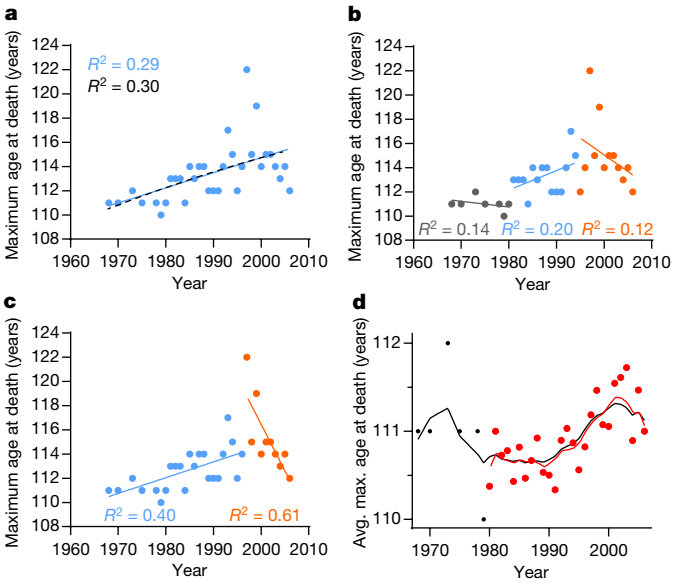

Figure 2 | Alternative approaches for analysing maximum lifespans from the IDL can lead to notably different conclusions. a, Non-partitioned linear or nonlinear regression both indicate a continuing increase in maximum lifespan. **b**, Linear regression with multiple partitions reveals apparent plateaus in both the first and last third of the analysed period. **c**, Linear regression with the partition point shifted just two years (1994–1996) shows a strong decrease, rather than a plateau, in maximum lifespan. **d**, For average supercentenarian age at death, exclusion of the pre-1980 UK-only data yields a different long-term pattern.

maximum lifespan has reached a plateau, instead predicting an eventual plateau of approximately 125 years (as shown in Fig. 1a).

Second, the assumption that there is only one plateau. Dong *et al.*[1] correctly noted that maximum observed lifespans did not tend to increase over the final 11 years of the analysed period. However, the same is true for the first 12 years (1968–1980) (Fig. 2b, $R^2 = 0.14$). If the authors had conducted their analysis in 1980, they would have erroneously concluded that there was a maximum possible lifespan of approximately 111 years. It is not clear what justification Dong *et al.*[1] give for the latter plateau not being equally ephemeral.

The third assumption made by Dong *et al.*[1] is that the correct year to partition the data is 1994. If the partition date is moved two years, from 1994 to 1996, it no longer shows a lifespan plateau. Instead, there is a very pronounced decrease in maximum lifespan over time ($R^2 = 0.61$, $P = 0.008$ or $R^2 = 0.51$, $P = 0.03$ if the 122-year-old Jeanne Calment is excluded as an outlier) (Fig. 2c). This would be an interesting finding. However, many scientists would probably view it as an artefact of the unnecessary truncation of a complex dataset. Of those who do accept it, most would attribute it to environmental effects (such as subtle changes in medical practice) or some artefact of the dataset composition (see below), rather than being representative of an underlying principle of biology. If the period of 1997–2006 is not informative about the mechanisms of ageing, then there is no reason why 1995–2006 should be any different.

Dong *et al.*[1] expand upon their supercentenarian analysis in their figure 2b and 2c. Figure 2b of ref. 1 shows that inclusion of the second to fifth highest ages of death does not change the underlying pattern, and the authors claim that all series showed the same pattern as the maximum reported age at death. It is therefore susceptible to the same criticisms that we made above. Figure 2c of ref. 1 shows the average ages of supercentenarian death over time, in contrast to figure 2a and 2b of ref. 1, which show only the maximum. As the authors point out, it does not show a clear trend for an increase over the time period analysed (reproduced in Fig. 2d, black). However, this argument is compromised by the asynchronous addition of the four analysed countries into the IDL[3]. Notably, the pre-1980 period consists only of data from the United Kingdom, including only 7 entries—that is, less than one supercentenarian per year, compared to an average of 19.6 per year for the remainder of the dataset. Exclusion of this time period gives a very different pattern, suggesting that there is no change over the 1980–1990 interval, followed by an increase (Fig. 2d, red). It is possible that the step-wise appearance of the graph may be related to the asynchronous addition of additional countries to the dataset (United States in 1980, France in 1987 and Japan in 1996), which further complicates interpretation. Great care is needed when pooling data from different sources. In this case, these countries have different population sizes, healthcare systems, and genetic compositions. The later introduction of a new population could give the appearance of (or hide) a shift in the trendline that, in reality, may only be an artefact of varying lifespan distributions between countries. A proper analysis of maximum lifespans would need to take this into account in some way.

In conclusion, the analyses described by Dong *et al.*[1] do not permit us to predict the trajectory that maximum lifespans will follow in the future, and hence provide no support for their central claim that the maximum lifespan of humans is "fixed and subject to natural constraints". This is largely a product of the limited data available for analysis, owing to the challenges inherent in collecting and verifying the lifespans of extremely long-lived individuals[3].

Methods

For modelling, we used a standard linear model ($y = mx + b$) and a three-parameter model allowing for logarithmic growth (rate K) up to a plateau of Y_{max}:

$$y = Y_0 + (Y_{max} - Y_0)(1 - e^{(-Kx)})$$

Future trajectories were simulated using parameter values determined by fitting the above models to the IDL data (see Fig. 2a), except for the 115-year plateau, which was projected as a straight line with slope 0 and intercept 115. Scatter was simulated as Gaussian-distributed random error (95% at 1.5 standard deviations and 5% at 5 standard deviations), rounded to the year. Prism 6.07 (GraphPad Software) was used for all regressions, simulations and graphing.

Data availability. All data are available from the corresponding authors upon reasonable request.

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Dong *et al.* reply

REPLYING TO B. G. Hughes & S. Hekimi *Nature* **546,** http://dx.doi.org/10.1038/nature22786 (2017)

In the accompanying Comment[1], Hughes and Hekimi disagree with our finding of a limit to human lifespan[2]. Although we thank them for alerting us to the work of Anerto-Jaquemin *et al.*[3], who also reported a limit of around 115 years, we disagree with the arguments presented by Hughes and Hekimi[1] and remain confident in our results.

We feel that the scenarios that Hughes and Hekimi[1] present in their figure 1a, although imaginative, are not informative. They argue that their three different models (which they extrapolate until the year 2300) are not statistically differentiable based on the data available from the International Database on Longevity (IDL; http://www.supercentenarians.org/). The statistical power to differentiate two models is determined by the ratio of the signal to noise. Thus, it is possible to make any set of models undifferentiable simply by adding enough noise. We do not know how Hughes and Hekimi[1] decided that the maximum reported age at death (MRAD) follows a Gaussian distribution with such high variance (95% at 1.5 standard deviations and 5% at 5 standard deviations). In our original Letter[2], we used a data-driven approach to identify the trend in the MRAD by analysing

actual data rather than arbitrary simulations; although Hughes and Hekimi[1] criticize us for visually inspecting our data, graphing data in order to evaluate the choice of model has long been acknowledged as a useful and important technique by statisticians[4]. We think that the MRAD trend that we found is unlikely to be the result of fluctuations. Indeed, figure 1b of Hughes and Hekimi[1] inadvertently highlights this: the deviation from the increasing trajectory since 1995 in the real data clearly stands out as much larger than any of the deviations in the simulated data.

Despite the appearance of an MRAD increase over the entire trajectory of the IDL data in the linear model presented by Hughes and Hekimi[1] (figure 2a; assumption 1), further analysis of the model residuals reveals that the data support an increase only in early years, but no longer from about 1995 ($P = 0.043$ for the absence of a further increase after 1995; one-sided test for correlation using Spearman's rho on the model residuals).

In assumption 2 (figure 2b of ref. 1), there is a lack of a linear correlation between calendar years and MRAD in all three of the intervals, as indicated by the small R^2 values (≤ 0.2). In addition, there is much less support for a 7-year plateau of MRAD at 111 years starting in 1973 than for such a plateau between 1995 and 2015 (data from the IDL plus the Gerontological Research Group; GRG), a 20-year period without an increase in the MRAD. This is in sharp contrast with the period between 1969 and 1995, which shows an uninterrupted increase in MRAD. Moreover, the 122-year record of Jeanne Calment from 1997 (assuming that this is not based on a clerical error) is still the maximum as of the most recent data (19 years later in the GRG, or 10 years in the IDL), the 119-year record at 1999 is still the second-highest, and the 117-year record is still the third-highest since 1993. The endurance of these records, combined with the better fit of our model, make the evidence supporting a plateau at 115 years very strong.

In their figure 2c, Hughes and Hekimi[1] claim that shifting the breakpoint may produce a spurious decline in the MRAD. We suspect that the post-breakpoint decline in both our[2] and their[1] analyses merely reflects a regression to the mean after the exceptional case of Jeanne Calment and not a long-term trend of decline. When we conducted additional analyses with more recent data from the GRG (see extended data figure 6 of ref. 2), we found that the decline was not significant ($P = 0.7$).

It is unclear to us why Hughes and Hekimi[1] think that the second to the fifth highest reported ages at death are "susceptible to the same criticisms". Instead, adding the second to the fifth highest reported age at death clearly provides a more robust set of observations than the MRAD alone.

Finally, Hughes and Hekimi[1] speculate that the increase after 1990 of the average age at death of supercentenarians is possibly related to the asynchronous addition of the four analysed countries into the IDL dataset (figure 2d of ref. 1). However, note that although the average age at death of supercentenarians over the entire course of the database fluctuated under these conditions, it tended to remain at around 111 years, as shown in both figure 2d of ref. 1 and our figure 2c (from ref. 2). We agree that cohort size should be evaluated for its contribution to the average age at death of supercentenarians as well as the MRAD. However, despite some 20 years of a rapidly increasing centenarian population, we have not seen a corresponding increase in the MRAD in either the IDL or GRG databases since 1995, as evidenced by our figure 2 and extended data figure 6 (ref. 2).

Taken together, and in the absence of solid statistical underpinning of various possible future scenarios, we feel that our interpretation of the data as pointing towards a limit to human lifespan of about 115 years remains valid.

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