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RESEARCH ARTICLE

The dynamic upper limit of human lifespan [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

We respond to claims by Dong *et al.* that human lifespan is limited below 125 years. Using the log-linear increase in mortality rates with age to predict the upper limits of human survival we find, in contrast to Dong *et al.*, that the limit to human lifespan is historically flexible and increasing. This discrepancy can be explained by Dong *et al.*'s use of data with variable sample sizes, age-biased rounding errors, and $\log(0)$ instead of $\log(1)$ values in linear regressions. Addressing these issues eliminates the proposed 125-year upper limit to human lifespan.

Keywords

lifespan, human lifespan, contradictory findings, ageing, life history, refutation

This article is included in the **Preclinical Reproducibility and Robustness** gateway.

Open Peer Review

Approval Status ? ✓ ?

	1	2	3
version 2 (revision) 09 Jun 2017			? view
version 1 26 Apr 2017	? view	✓ view	

1. **Jean-Michel Gaillard**, University of Lyon, Villeurbanne, France
2. **Michael R. Rose**, University of California, Irvine, Irvine, USA
Laurence D Mueller, University of California, Irvine, USA
3. **James Vaupel**, University of Southern Denmark, Odense, Denmark
José Manuel Aburto , University of Southern Denmark, Odense, Denmark

Any reports and responses or comments on the article can be found at the end of the article.

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Recent findings by Dong *et al.*¹ suggested fixed upper limits to the human life span. Using the same data, we replicated their analysis to obtain an entirely different result: the upper limit of human life is rapidly increasing.

Dong *et al.* conclude that the maximum reported age at death (MRAD) is limited to 125 years in humans¹ and that lifespan increases above age 110 are highly unlikely, due to the reduced rate of increase in life expectancy at advanced ages.

We repeated Dong *et al.*'s¹ analysis using identical data (SI). Replicating these findings requires the inclusion of rounding errors, treating zero-rounded values as log(1) and the incorrect pooling of populations.

The Human Mortality Database (HMD) data provide both the age-specific probability of survival (q_x) and the survival rates of a hypothetical cohort of 100,000 individuals (l_x). However, l_x survival rates are rounded off to the nearest integer value.

The magnitude and frequency of l_x rounding errors increases as the probability of survival approaches 1 in 100,000. These rounding errors mask variation in survival rates at advanced ages: over half of l_x survival data are rounded to zero above age 90 (Figure 1b).

Dong *et al.* appear to have used these rounded-off survival data in their models¹ and incorrectly treated log(0) values as log(1) in log-linear regressions (Figure 1a–d; SI).

Figure 1. Rate of change in late-life survival for the French population 1816–2014. (a) Figure modified after Dong *et al.* Figure 1b, showing rounded survival data (red points), rounded survival data with log(0)=log(1) (black points), the resulting linear regression in Dong *et al.* (solid red line) and observed survival data (pink points). (b) Rounding errors in survival data (box-whisker plots; 95% CI) and the proportion of survival data rounded to zero in males (blue line) and females (red line). (c) Survival data from (a) with rounding errors removed, showing variation outside the 1900–1990 period (vertical dotted lines). (d) The rate of change in late-life mortality since 1900 with (dotted lines) and without (solid lines) rounding errors (after Dong *et al.* Figure 1c).

These errors have considerable impact. Re-calculating cohort survival from raw data or excluding zero-rounded figures eliminates the proposed decline in old-age survival gains (Figure 1d; SI).

Likewise, recalculating these data removed their proposed limits to the age of greatest survival gain (SI), which in 15% of cases were the result of the artificial 110-year age limit placed on HMD data².

We also found that variation in the probability of death was masked by date censoring¹. Major non-linear shifts in old-age survival occur outside the 1900-1990 period used by Dong *et al.* (Figure 1c). Why these data were excluded from this regression, but included elsewhere, is unclear.

Evidence based on observed survival above age 110 appears to support a late-life deceleration in survival gains¹. For the period 1960–2005 Dong *et al.* present data¹ from 4 of the 15 countries in the International Database on Longevity³ (IDL). In their pooled sample of these countries, there is a non-significant ($p=0.3$) reduction in MRAD between 1995 and 2006 (Figure 2a).

The declining MRAD reported by Dong *et al.*¹ arises from the use of falling sample sizes. According to the Gerontology Research Group (GRG), 62% of validated supercentenarians alive in 2007 resided in France and the USA. However, these countries are not surveyed³ by the IDL after 2003 (Figure 2a). The proposed post-1995 decline in MRAD results from this dramatic fall in sample size.

Viewed individually, all four countries have an upward trend in the mean reported age at death (RAD; Figure 2b) of supercentenarians (SI) and the top 5 ranked RADs (Figure 2c). All four countries achieved record lifespans since 1995, as did 80% of the

countries in the IDL. Without the pooling of IDL data used by Dong *et al.* there is no evidence for a plateau in late-life survival gains.

We attempted to reproduce Dong *et al.*'s supporting analysis of GRG records. The text and Extended Data Figure 6 of Dong *et al.* do not match annual MRAD records from 1972 as stated¹. However, they do match deaths of the world's oldest person titleholders from 1955 (GRG Table C, Revision 9) with all deaths in May and June removed (SI).

Actual MRAD data from the GRG support a significant decline in the top-ranked age at death since 1995 ($r = -0.47$; $p = 0.03$, $MSE = 3.2$). However, this trend is not significant if only Jeanne Calment is removed ($p = 0.9$). Linear models fit to lower-ranked RADs have an order of magnitude better fit, and all indicate an increase in maximum lifespan since 1995 ($N = 64$; SI).

Collectively, these data indicate an ongoing rebound of upper lifespan limits since 1950, with a progressive increase in observed upper limit of human life. To estimate theoretical limits, we developed a simple approximation of the upper limit of human life.

Mortality rates double with age in human populations (Figure 3a and b). Log-linear models fit to this rate-increase closely approximate the observed age-specific probability of death⁴. These models also provide a simple method of predicting upper limits to human life span that is independent of population size.

We fit log-linear models to age-specific mortality rates from the HMD data used by Dong *et al.*¹, and used these models to predict the age at which the probability of death intercepts one. This maximum survivable age (MSA) provides a simple, conservative estimate of the upper limit of human life (Figure 3c).

Figure 2. Maximum reported age at death of supercentenarians. (a) Reproduction of Dong *et al.* Figure 2a, including 95% CI for increasing ($p<0.0001$) and falling ($p=0.3$) maximum recorded age at death (MRAD), showing data biased by the addition and removal (up and down arrows) of populations. (b) Locally weighted smoothed splines of MRAD in Japan (green), the USA (red), the UK (dark blue) and France (purple). (c) Locally weighted trends of MRAD in the USA across the oldest 5 reported ages at death (red, orange, green, blue and purple lines show rank 1–5 respectively).

Figure 3. Observed and projected variation in the maximum survivable age (MSA). (a) In humans, the probability of death q at age x (q_x ; red line) increases at an approximately log-linear rate with age (black lines; 95% CI), shown here for the birth cohort of Jeanne Calment (d.122.5 years; circle). Projection of this log-linear increase to $\log(q) = 0$ provides the MSA, the upper limit of human survival, shown here for (b) observed and projected global populations⁵ and (c) 40 historic HMD populations 1751–2014.

Log-linear models closely approximate the observed probability of death in HMD populations for both period and cohort life tables (median $R^2 = 0.99$; 4501 population-years). These models predict an MSA exceeding 125 years within observed historic periods (Figure 3b and c; SI).

Furthermore, period data indicate that MSA is steadily increasing from a historic low c.1956 (Figure 3b and c) and that the MRAD is

expected to rise over the next century. This result is supported by trends in global mortality data from the United Nations⁵, sampled across 194 nations (Figure 3b).

This analysis provides an estimate of human lifespan limits that is conservatively low. Log-linear mortality models assume no late-life deceleration in mortality rates⁶, which, if present, would increase the upper limits of human lifespan⁷. In addition, these models are

fit to population rates and cannot provide an estimate of individual variation in the rate of mortality acceleration.

Given historical flexibility in lifespan limits and the possibility of late-life mortality deceleration in humans⁸, these models should, however, be treated with caution.

A claim might be made for a general, higher 130-year bound to the human lifespan. However, an even higher limit is possible and should not be ruled out simply because it exceeds observed historical limits.

Methods

Life table data were downloaded from the United Nations⁵ (UN) and the Human Mortality Database (HMD) and lifespan records from the International Database on Longevity (IDL) and the Gerontology Research Group (GRG).

Least squared linear models were fit to life table data on the log-transformed age-specific probability of death (q_x), and projected to $q_x=1$ to predict the maximum survivable age in each population (Figure 1b and c; SI). Maximum lifespan within GRG and IDL data was annually aggregated and fit by locally weighted smoothed splines⁹ (Figure 3b and c).

We reproduced the analysis of Dong *et al.* in R version¹⁰ 3.2.1 (SI), using the code in [Supplementary File 1](#).

An earlier version of this article can be found on bioRxiv (doi: [10.1101/124800](https://doi.org/10.1101/124800)).

Data availability

The authors declare that all data are available within the paper and its [supplementary material](#).

Author contributions

S.J.N. wrote the analysis and code, and reproduced Dong *et al.*'s analysis. S.J.N. and S.E. developed the analysis, methods and statistical design, and co-wrote the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Supplementary material

Supplementary File 1: Supplementary information guide. The supplementary information supplied here constitutes two sections of integrated code in the R statistical language:

1. R code required to calculate the maximum survivable age or MSA from both public data and the human mortality data used by Dong *et al.*, and required to reproduce our findings in full.
2. R code required to reproduce Dong *et al.*¹ with original errors, often including several error-corrected or partially corrected versions.

Both sections are wrapped in the same script, and require several package dependencies and datasets outlined in the annotated code.

[Click here to access the data.](#)

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Open Peer Review

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Reviewer Report 30 May 2017

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Laurence D Mueller

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Evidently the Dong et al. *Nature* article¹ made some major, though elementary, mistakes: (a) an incorrect rounding procedure; and (b) choosing data from an historical period (1900-1990) that generally fit a limited lifespan expectation, while neglecting to consider other data. Newman and Eastaugh² correct the rounding error and look at human cohort data from a broader range of historical dates. However, they fit log-linear Gompertz models to the data, though doing so is questionable as they themselves admit, if in fact human mortality rates plateau³. It is often the case that extrapolating regression models beyond the range used to fit them is fraught with danger.

Of most interest for us was whether the fundamental concept of inferring a species-wide maximum lifespan from one or even many cohorts of demographic data is cogent at all. With that in mind, we used mortality data from a twenty-cohort study of *Drosophila melanogaster* that we and our colleagues recently published⁴. Specifically, we used "A-type" populations to predict sex-specific "maximum lifespans" for populations of "C-type" populations. Each of the ten pairs of A and C type populations share a common ancestral population in our laboratory, though they have since evolutionarily diverged.

We took the initial sample size of, say, cohort CO-i, sex-j (N_{ij}), and then computed the age at which the probability of survival in the matching ACO-i, sex-j cohort is $\leq 1/(10 \cdot N_{ij})$. We plotted the maximum lifespans predicted from the 20 "A" sex-specific cohorts versus the observed maximum lifespan in the 20 corresponding "C" cohorts (see Figure 1) using a double plateau Gompertz model⁴. If the concept of species-wide maximum longevity were cogent, we would expect all the observed maximum lifespans to be near or well below the $y=x$ line. In fact, most are well above that line, and show no correlation with the predicted values. Effectively, the maximum lifespan estimation procedure is not generally reliable. In the case of the example that we give here, the maximum lifespan was altered by substantial genetic changes caused by natural selection.

We have long used experimental evolution to reconfigure the onset and end of periods of aging in carefully handled cohorts, as illustrated in publications 3 and 4. We do not regard maximum lifespans as characteristic of entire species, however they might be defined demographically. Rather, we view them as phenotypes that depend on both genotype and environment even in so-called “wild-type” populations, like most components of life history, as the extensive evolutionary literature on life history and aging has long suggested. More importantly, in cohorts that show a cessation of aging³ we doubt that the concept of maximum lifespan has any biological cogency.

Figure 1. The predicted maximum lifespan based on 10 A-type populations⁴ and the observed maximum lifespan in 10 C-type populations:

<https://f1000researchdata.s3.amazonaws.com/supplementary/11438/8c2e3298-9ed0-4ac5-8b85-ce62336a9bbb.png>

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Aging; Evolution of demography

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 08 Jun 2017

Saul Newman, Australian National University, Acton, Australia

We wish to thank MRR and LDM for their review. We agree with the ideas expressed, particularly with the risk of extrapolating log-linear models and the potential for improving estimates of lifespan limits using alternate models of old age survival.

There is little about maximum human lifespan or lifespan limits can be concluded with certainty. Therefore, our focus was on implementing the simplest available methods. The appended figure S2 supported the rationale for our use of log-linear models for projecting lifespan limits.

This figure reproduces the plot presented by MRR and LDM for *Drosophila* using human data. It plots the upper observed lifespan (MRAD) of individuals in the GRG against their calculated lifespan limit.

We could match 331 validated maximum lifespan observations to a historical gender-pooled MSA estimate. Of these, 330 approached but do not exceed their predicted limit. The only exception was Jeanne Calment, who outlived the gender-pooled MSA limit by 3 years but fell short of the female-cohort limit shown in Figure 3a. Unlike *Drosophila*, these calculated limits seem to fit reasonably well with MRAD.

However, there are many problems involved in human data that do not affect *Drosophila*. Human populations are not directly observable past their maximum age, individual variation in mortality acceleration is unknown, and ascertainment and validation problems abound.

Therefore, we still consider these projection methods, the GRG and IDL data, and much of the discussion of MRAD, problematic.

Finally, we agree that in species with a cessation of ageing or negative senescence there will be an unbounded, finite maximum lifespan with intrinsic limit. By extension, if there were a complete cessation of ageing in humans at extreme old ages there would be no intrinsic limit, but many probabilistic constraints, to human lifespan.

Competing Interests: The authors disclose no competing interests

Reader Comment 28 Jun 2017

Xiao Dong, Brandon Milholland and Jan Vijg, Albert Einstein College of Medicine, USA

In their review, Rose and Mueller briefly express their approval of Newman and Eastaale's paper before moving on to a lengthier discussion of their own experiments with *Drosophila*. As to the first point, we believe that even a cursory examination of our work and the

material produced by Newman and Eastaer will show that the accusations of errors are themselves erroneous; see our comment for an in-depth critique. As for the results in fruitflies, Rose and Mueller's findings are potentially very interesting, but their immediate relevance to humans is unclear. If as Rose and Mueller say "extrapolating regression models...is fraught with danger" extrapolating from flies to humans must be similarly fraught.

Xiao Dong, Brandon Milholland and Jan Vijg

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 May 2017

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Jean-Michel Gaillard

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This manuscript challenges the recent findings by Dong *et al.* that human lifespan has an upper limit and proposes that human lifespan is rapidly increasing. While I am quite convinced by all the problems the authors identified in the analysis performed by Dong *et al.* and by the maximum survivable age of about 125 years the authors estimated for humans, I am not convinced at all by the claim that maximum reported age at death is expected to rise over the next century. In particular, I do not understand the rationale of removing Jeanne Calment from the analysis. This data point has been validated. Contrary to the authors' interpretation, the mere existence of a lifespan of 122 observed 20 years ago without being even approached since then seems to indicate that some saturation in the maximal age at death is occurring. It is required to estimate the probability of not observing older ages at death for 20 years under different scenarios of increasing trends in maximal age at death.

Detailed comments:

p. 3 second column 3rd paragraph l. 1: Remove "significant"

p. 3 second column 3rd paragraph l. 1: Should be "Calment", not "Clament"!

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biodemography

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 06 Jun 2017

Saul Newman, Australian National University, Acton, Australia

We thank J-MG for these comments, and welcome the opportunity to clarify our analysis and expand our rationale for this study.

We wish to clarify that our projected increase in MRAD over the coming century is not based on IDL or GRG lifespan data, and these projections do not require either removal or inclusion of Jeanne Calment. Rather, these projections are based on theoretical lifespan limits calculated using HMD and WHO life table data, including the WHO population projections through 2100.

Our statement that “period data indicate that MSA is steadily increasing from a historic low c.1956 (Figure 3b and c) and that the MRAD is expected to rise over the next century” is based on observed HMD and WHO data for the “historic low” in 1956 and on WHO population projections over 2015-2100 for the ‘steady rise’. We can see that we did not make this distinction sufficiently clear and we have amended the text to make it clearer.

The rationale for removing Jeanne Calment from the regression of observed trends was to demonstrate her singular effect on recent MRAD trends. Jeanne Calment is a remarkable statistical outlier from historic trends in both Dong *et al.* and our linear models, with a Cook’s distance of 1.97 (Cook, 1982).

A large Cook’s distance is not necessarily grounds for ignoring a well-validated data point.

Our finding that the inferred decline in MRAD is eliminated by removal of one outlier demonstrates that the inference is tenuous rather than invalid.

We find it notable that such broad conclusions on lifespan limits depend on the status of a single data point. We agree that the 20-year streak set by Jeanne Calment is remarkable, and we consider it valid. However, we disagree that this indicates a saturation of old-age survival.

Jeanne Calment's record-holding streak is not unprecedented in length. Mary Kelly held the overall lifespan record for 17 years from 1964 to 1981. Gert Adrians-Boomgaard held the male lifespan record for 68 years. Mathew Beard broke this record, and held it for another 21.9 years (1985-2007). Like Jeanne Calment, Mathew Beard exceeded the next-lowest record by three years for this period.

We consider that these record-holding streaks do not reflect saturation of the MRAD, but the uncertain ascertainment and stochastic nature of lifespan records. Therefore, we suggest Jeanne Calment's survival reflects a rare statistical event where survival has approached the calculated upper limit of lifespan in her cohort. We think this event is a result of stochastic variation, and is biasing the projection of short-term trends. The simulated removal of Jeanne Calment was intended to indicate this.

More broadly, we feel that too much emphasis is placed on this single data point. Jeanne Calment's predecessor Carrie White held a well-verified claim to the world's oldest and then second-oldest woman for 24 years, before the claim was recognised as a clerical error in 2012 and retracted.

In the unlikely event that Jeanne Calment's lifespan claim is also false, demographers would be depending on conclusions about lifespan limits from a single, false data point that is an outlier from the aggregate trend across 1626 other supercentenarians in the GRG (see figure S1).

Furthermore, a declining or flat trend in lifespan limits is inconsistent with our analysis of 3.3 billion lifespan records in 194 nations. We maintain that statistical trends in data for billions of deaths should not be ignored in favour of a single data point in 1997.

Finally, we accept our spelling error for Jeanne Calment's name. Yet we do not understand the request to remove the word 'significantly' from the text: the negative trend was significant ($p=0.03$).

Competing Interests: The authors have no competing interests.

Reader Comment 28 Jun 2017

Xiao Dong, Brandon Milholland and Jan Vijg, Albert Einstein College of Medicine, USA

Gaillard is correct to express reservations about this paper: the "problems" that Newman and Eastaig claim to have identified do not actually reflect the contents of our paper; see

our comment for more detail. Gaillard is “not convinced at all by the claim that maximum reported age at death is expected to rise over the next century” and neither are we. As our correctly conducted analysis shows, the MRAD is likely to remain stagnant in the future.

Xiao Dong, Brandon Milholland and Jan Vijg

Competing Interests: No competing interests were disclosed.

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