Mortality Data Suggests that Men do age faster than women

Authors

Peter Lenart^{1,2}, Daniela Kuruczova^{1,2}, Julie Bienertová-Vašků^{1, 2}

¹Department of Pathological Physiology, Faculty of Medicine, Masaryk University, Kamenice 5, building A18, 625 00, Brno, Czech Republic

²*Research Centre for Toxic Compounds in the Environment, Faculty of Science, Masaryk University, Kamenice 5, building A29, 625 00, Brno, Czech Republic*

Abstract:

Women on average live longer than men, which seems to suggest that women also age slower than men. However, the potential difference in pace of aging between sexes is a relatively controversial topic, and both positions "women age slower" and "women and men age at the same pace" have found some support. We thus employ mathematical methods previously established in model organisms to compare the pace of aging between the sexes using freely available mortality data from 13 countries. Our results support hypothesis that men age faster than women.

Introduction:

The life expectancies of men and women are widely recognized as being different: women worldwide live longer than men. This logically leads to the question whether women also age slower than men. Both "yes" and "no" answers have found some support ^{1–3}. The classical argument against the notion that women age slower is the fact that men experience higher

mortality rates at almost every age, i.e. that the reason for their shorter lifespan is that men are the less "robust" sex and as such exhibit higher background mortality^{1,3}. On the other hand, researchers suggesting that women indeed age slower than men note that this line of reasoning may not be altogether valid since men die from different causes at different ages ². Interestingly both of these views fail to answer the existence of the mortality–morbidity paradox, in other words why women live longer but are sicker than men^{3–5}. Regardless of theoretical arguments, aging is defined as an age-dependent increase in mortality ^{2,6,7} and therefore, the pace of aging of men and women may be empirically calculated using available mortality data. In this article, we present the results of an analysis of mortality data which suggests that men do age faster than women.

One method of quantifying aging relies on calculating the rate at which mortality increases with age⁸. The relationship between human age and mortality is usually modeled using a predefined distribution which explicitly defines the relationship between age and mortality rate. Distributions most commonly used for this purpose include Gompertz or its extension Gompertz–Makeham, Weibull and logistic⁹. The choice of a specific distribution depends on the purpose of its use: the best fitting model is often desired when a prediction is sought while a different model may be more suitable for the interpretation of parameter values^{10,11}. Since our objective was to test the difference between the pace of mortality rate increase in men and women, the Gompertz model¹² was selected as well-suited for this purpose. It is appropriate for accommodating human mortality data approximately between 30 and 80 years of age^{11,13} and also offers a means for comparing mortality rate increase by means of mortality rate doubling time (MRDT), a parameter commonly used as an estimate of the rate of aging^{14,15}. Its disadvantage, i.e. the inability to distinguish between intrinsic and extrinsic mortality rate,

however this should be to some extend compensated by the fact that the chosen interval of 30 to 60 years of age is influenced mainly by intrinsic causes¹¹. Furthermore, the Gompertz model may also be easily transformed and estimated as a linear model, which offers straightforward statistical tools for testing the difference between men and women. We have further employed Gompertz-Makeham model to verify results of Gompertz model and help us in interpretation of results.

In this study we used mortality data obtained from the Human Mortality Database¹⁶ to calculate MRDTs by Gompertz model for male and female populations in 13 developed countries. Furthermore, for each country, we also tested whether a statistically significant difference is to be found between the sexes in slopes of lines obtained by the log-linear Gompertz mortality rate model. Mortality rates may be affected by a great variety of external influences unrelated to aging. One extreme example of such external influences was undoubtedly the Second World War (WWII) which dramatically altered mortality rates both directly by the deaths of millions of soldiers and civilians and indirectly by the late effects of injuries, starvation, psychological trauma, etc. Accordingly, mortality rates during the early life of a cohort are known to influence its mortality rates later in life¹⁷. Because most countries in the Human Mortality Database were more or less heavily involved in WWII, we thoroughly analyzed mortality patterns only in people born at least 8 years after the end of this conflict. We calculated MRDTs for cohorts of people born from 1950 to 1954 using their mortality rates in periods starting in 1980 to 1984 to the newest available data in the Human Mortality Database. In other words, investigated mortality rates were from periods starting with their 30th birthday and ending with the end of records.

Methods

Mortality rate data were acquired from <u>www.mortality.org</u> on 12 July 2017. The Human Mortality Database (HMD) contained data about mortality rates for 39 sovereign countries and several others smaller areas and populations. In our analysis we focused on 13 developed, western (plus Japan), stable countries with population exceeding 8 million. Analysed countries are: Australia, Belgium, Canada, France, Italy, Japan, Netherlands, Portugal, Sweden, Switzerland, United Kingdom, United States of America and West Germany.

The Gompertz model

The Gompertz model^{12,14} of exponential hazard growth was used to model the relationship between age and mortality rate. The basic form of the Gompertz model is

$$h(t) = ae^{bt}$$

where *a* and *b* are constants, *t* is time (in our case age), and h(t) is the hazard (mortality) rate. Using the logarithmic transformation, a simple linear model is obtained

$$\log h(t) = +b t.$$

where log(a) signifies the intercept (overall shift of the line in the direction of the y-axis) and *b* expresses the slope of the line. MRDT is subsequently calculated from the slope as

$$MRDT = \frac{\log(2)}{b}$$

and expresses the time it takes for the mortality rate to double.

The Gompertz-Makeham model is a natural extension of the Gompertz model obtained by adding a constant¹⁸:

$$h(t) = c + ae^{bt}.$$

The constant c expresses the part of mortality, that does not depend on age. Focusing only on the age-dependent part of the equation, the mortality rate doubling time can be obtained in the same manner as in the Gompertz model, using the value of parameter b.

The above-described models were fitted on data for each individual country using an age interval beginning at 30 years of age. A separate model was fitted using male and female data in order to obtain parameters for both populations. Due to exponential nature of models, numerical fitting using non-linear least squares was used. Both models accurately fit human mortality dynamics roughly between 30 and 80^{11,13}, which was subsequently confirmed during exploratory analysis of the data from HMD.

Results:

The Gompertz model:

MRDTs calculated for people born in 1954 is longer for males in 10 out of 13 countries (Table 1). However, the possibility of longer male MRDTs is inconsistent with MRDTs calculated for 1953, 1952, 1951 and 1950 cohorts. Males borne in 1953 have longer MRDTs in 8 of 13 countries but those born in 1952 only in 6 of 13. Furthermore, males born in 1951 and 1950 have longer MRDTs only in 8 and 7 countries respectively. Results of the Gompertz model thus suggest that MRDTs are same for males and females.

Table 1. MRDTs calculated by Gompertz model										
Country	Male MRDT 1950	Female MRDT 1950	Male MRDT 1951	Female MRDT 1951	Male MRDT 1952	Female MRDT 1952	Male MRDT 1953	Female MRDT 1953	Male MRDT 1954	Female MRDT 1954
Australia	9.81	9.36	10.03	9.07	10.42	10.19	10.27	10.02	11.10	10.04
Belgium	9.58	10.57	9.91	9.97	9.54	9.59	9.60	10.27	9.88	9.66
Canada ⁽²⁰¹¹⁾	9.63	8.82	9.73	8.93	10.07	9.00	10.44	9.10	10.64	8.65
France	11.41	11.32	11.44	11.13	11.13	11.23	11.30	11.11	11.26	11.17
Italy ⁽²⁰¹²⁾	9.41	9.69	9.69	9.67	9.72	9.67	9.88	9.49	10.11	9.65
Japan	9.20	10.94	9.18	10.84	9.16	10.59	9.18	10.56	9.10	10.56
Netherlands	9.07	9.25	9.31	9.16	9.08	9.09	8.84	9.05	9.18	9.44
Portugal	11.45	12.39	11.55	12.90	11.82	12.76	11.86	13.75	12.47	13.00
Sweden	9.63	9.02	9.68	9.17	9.59	9.70	9.97	9.97	10.53	9.35
Switzerland	10.54	10.32	10.64	10.42	10.17	9.72	11.01	9.57	10.99	10.45
United Kingdom (2013)	9.19	9.10	9.08	9.11	9.39	8.90	9.34	9.25	9.32	9.20
USA	10.65	9.27	10.67	9.25	10.72	9.20	10.73	9.25	10.95	9.33
Western Germany	9.28	9.52	9.39	9.61	9.25	9.42	9.15	9.55	9.43	9.25

Table 1: Summary of MRDTs calculated by Gompertz model for men and women in 13 analyzed countries.

 Years listed in brackets (upper indices in the Country column) indicate the last year with mortality rates

 recorded in the Human Mortality Database. In case no number is included, mortality rates were last recorded in

 2014.

Gompertz-Makeham

Contrary to the results of Gompertz model, the MRDTs calculated by the Gompertz-Makeham model for 1950-1954 cohorts are consistently different between sexes

bioRxiv preprint doi: https://doi.org/10.1101/179846; this version posted March 21, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

(Table 2). MRDTs for 1954 as well as 1953 cohorts are longer for women in all 13 countries. This trend is further evident in all remaining cohorts. MRTDs for 1952, 1951 and 1950 cohorts are higher for females in 12,11 and 10 of 13 countries respectively.

	Ta	able 2 MI	RDTs cale	culated by	Gomper	rtz-Make	ham mod	el		
Country	Male MRDT 1950	Female MRDT 1950	Male MRDT 1951	Female MRDT 1951	Male MRDT 1952	Female MRDT 1952	Male MRDT 1953	Female MRDT 1953	Male MRDT 1954	Female MRDT 1954
Australia	7.94	9.26	7.71	8.14	7.55	11.33	7.48	10.55	7.31	9.64
Belgium	9.38	13.91	9.44	9.85	8.94	9.52	9.11	12.15	8.59	9.58
Canada ⁽²⁰¹¹⁾	8.29	8.20	7.60	8.43	7.64	9.75	8.02	9.72	7.33	8.34
France	14.02	12.49	13.89	12.64	12.12	12.62	12.78	13.24	11.95	14.76
Italy ⁽²⁰¹²⁾	8.99	9.91	8.79	9.75	8.62	9.99	8.61	9.53	8.19	9.66
Japan	10.02	12.67	9.93	12.10	9.67	11.58	9.55	11.53	9.84	12.60
Netherlands	9.51	10.41	10.36	10.85	10.04	10.59	8.38	10.94	9.74	11.92
Portugal	11.54	17.78	11.21	12.18	12.22	13.08	12.63	20.12	14.11	21.37
Sweden	7.57	9.03	8.17	8.55	7.17	9.46	7.46	11.50	7.94	8.30
Switzerland	9.60	11.22	10.31	10.15	8.13	8.87	8.24	9.11	7.46	8.95
United Kingdom (2013)	10.19	10.07	9.88	10.17	10.61	9.58	10.52	10.82	10.12	10.44
USA	9.48	9.73	9.29	9.73	9.58	9.94	9.04	9.79	8.58	10.06
Western Germany	9.18	9.48	9.21	9.95	8.92	9.68	8.64	10.58	9.29	9.74

Table 2: Summary of MRDTs calculated by Gompertz-Makeham model for men and women in 13 analyzed countries. Years listed in brackets (upper indices in the Country column) indicate the last year with mortality rates recorded in the Human Mortality Database. In case no number is included, mortality rates were last recorded in 2014.

The opposing results of the Gompertz and Gompertz-Makeham models are most likely caused by different parametrization rather than different curve shape (Fig. 1). When the age-independent parameter c is not included like in the Gompertz model, the value of the other two parameters

changes accordingly in order to provide best-fitting curve. If a roughly same mortality curve is described by the Gompertz and Gomperz-Makeham model, following applies: the growing c value of the Gompertz-Makeham corresponds to a decreasing b value in the Gompertz model and thus a increasing MRDT. We have found that the age-independent parameter c is universally higher in males (Table 3) which explains the different results of Gompertz and Gompertz-Makeham models.

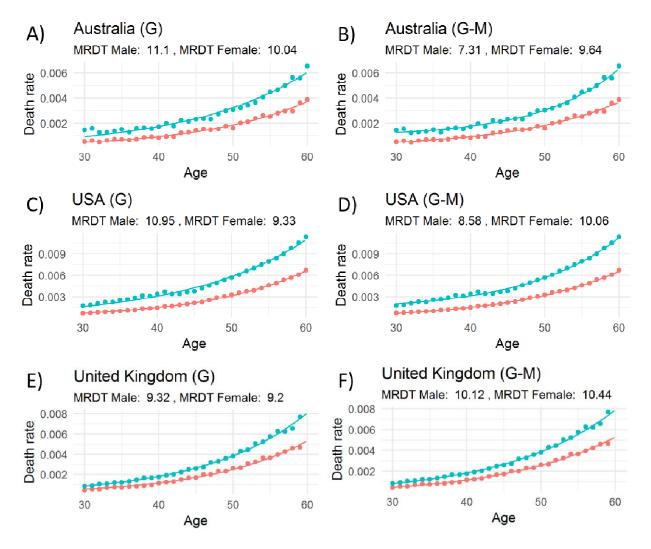


Figure 1: Comparison between curve shapes for Gompertz (G) and Gompertz makeham (G-M) in three representative countries.

Table 5 parameter c of Gomp	ertz-makenam mode	l lor 1954 conort
Country	Male C	Female C
Australia	0.00096	0.00009
Belgium	0.00047	-0.00003
Canada ⁽²⁰¹¹⁾	0.00081	0.00008
France	-0.00037	-0.00071
Italy ⁽²⁰¹²⁾	0.00051	-0.00002
Japan	-0.00030	-0.00031
Netherlands	-0.00017	-0.00065
Portugal	-0.00076	-0.00115
Sweden	0.00069	0.00016
Switzerland	0.00091	0.00018
United Kingdom ⁽²⁰¹³⁾	-0.00024	-0.00033
USA	0.00108	-0.00020
Western Germany	0.00002	-0.00007

Table 3 parameter c of Gompertz-Makeham Model for 1954 cohort

Table 3: Summary of parameter c of Gompertz-Makeham model for men and women in 13 analyzed countries. Years listed in brackets (upper indices in the Country column) indicate the last year with mortality rates recorded in the Human Mortality Database. In case no number is included, mortality rates were last recorded in 2014.

Discussion

In this study, we have investigated mortality data to test whether men age faster than women, as was previously suggested by several authors^{2,19–21}. Interestingly, our calculations of MRDTs using Gompertz model do not show any consistent difference in pace of aging between sexes while results of Gompertz-Makeham model strongly suggests that men age faster than women. The diference between results of Gompertz and Gompertz-Makeham model may be explained by the fact that Gompertz-Makeham unlike Gompertz model, includes an age-

bioRxiv preprint doi: https://doi.org/10.1101/179846; this version posted March 21, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

independent parameter c which is almost universally higher in men. Furthemore, this also implies that Gompertz-Makeham model is beter suited to compare aging between sexes. Thus, overal our results suport hypothesis that men age faster than women.

The potential weakness of our work is that our analysis of mortality data does not distinguish between intrinsic and extrinsic sources of mortality. There is a great body of literature focusing on partitioning mortality to intrinsic and extrinsic mortality^{22,23}. Partitioning of mortality remains the gold standard which can in some situations undoubtedly bring an important insight into the aging process. However, partitioning mortality to intrinsic and extrinsic is highly superficial, and the assumption that intrinsic sources of mortality are caused by aging while the extrinsic sources of mortality are caused by the environment and are thus constant over age is simply wrong²⁴. Accordingly, even Bruce A. Carnes and S. Jay Olshansky arguably the two most influential authors studying mortality partitions sharply disagree with such naive assumption. This is probably best documented by the fact that both of them are among authors of a paper which clearly states ,,It is difficult to envision a cause of death for humans or any other species, either intrinsic or extrinsic, that does not exhibit age-dependence."²². In other words, biologically, older individuals have a higher risk of death from both intrinsic and extrinsic sources. Thus we believe that for our purpose using total mortality to compare the pace of aging should be sufficient or even preferable to using only intrinsic mortality.

Overall, our results indicate that men age faster than women. This may have a far-reaching implications for aging research as well as medicine.

Code availability

Code is available at <u>http://www.math.muni.cz/~xkuruczovad/Gompertz_calc.R</u> or upon request.

References:

- 1. Austad, S. N. Why women live longer than men: Sex differences in longevity. *Gend. Med.* **3**, 79–92 (2006).
- 2. Blagosklonny, M. V. Why men age faster but reproduce longer than women: mTOR and evolutionary perspectives. *Aging* **2**, 265–273 (2010).
- Austad, S. N. & Fischer, K. E. Sex Differences in Lifespan. *Cell Metab.* 23, 1022–1033 (2016).
- 4. Vaupel, J. W. Biodemography of human ageing. Nature 464, 536–542 (2010).
- Oksuzyan, A., Juel, K., Vaupel, J. W. & Christensen, K. Men: good health and high mortality. Sex differences in health and aging. *Aging Clin. Exp. Res.* 20, 91–102 (2008).
- 6. Kirkwood, T. B. L. & Austad, S. N. Why do we age? *Nature* **408**, 233–238 (2000).
- Lenart, P. & Bienertová-Vašků, J. Keeping up with the Red Queen: the pace of aging as an adaptation. *Biogerontology* 18, 693–709 (2017).
- Pletcher, S. D., Khazaeli, A. A. & Curtsinger, J. W. Why do life spans differ? Partitioning mean longevity differences in terms of age-specific mortality parameters. *J. Gerontol. A. Biol. Sci. Med. Sci.* 55, B381-389 (2000).
- Pham, H. Mortality Modeling Perspectives. in *Recent Advances in Reliability and Quality in Design* 509–516 (Springer, London, 2008). doi:10.1007/978-1-84800-113-8_25
- Ricklefs, R. E. & Scheuerlein, A. Biological Implications of the Weibull and Gompertz Models of Aging. *J. Gerontol. Ser. A* 57, B69–B76 (2002).
- Nash, F. R. Reliability Assessments: Concepts, Models, and Case Studies. (CRC Press, 2016).

- Gompertz, B. On the Nature of the Function Expressive of the Law of Human Mortality, and on a New Mode of Determining the Value of Life Contingencies. *Philos. Trans. R. Soc. Lond.* 115, 513–583 (1825).
- 13. Easton, D. M. & Hirsch, H. R. For prediction of elder survival by a Gompertz model, number dead is preferable to number alive. *Age* **30**, 311–317 (2008).
- de Magalhães, J. P., Cabral, J. A. S. & Magalhães, D. The Influence of Genes on the Aging Process of Mice. *Genetics* 169, 265–274 (2005).
- de Magalhães, J. P., Costa, J. & Church, G. M. An Analysis of the Relationship Between Metabolism, Developmental Schedules, and Longevity Using Phylogenetic Independent Contrasts. J. Gerontol. A. Biol. Sci. Med. Sci. 62, 149–160 (2007).
- Human Mortality Database. Available at: http://www.mortality.org/. (Accessed: 30th June 2017)
- 17. Beltrán-Sánchez, H., Crimmins, E. M. & Finch, C. E. Early Cohort Mortality Predicts the Cohort Rate of Aging: an Historical Analysis. *J. Dev. Orig. Health Dis.* **3**, 380–386 (2012).
- Pletcher. Model fitting and hypothesis testing for age-specific mortality data. *J. Evol. Biol.* 12, 430–439 (1999).
- Barrett, E. L. B. & Richardson, D. S. Sex differences in telomeres and lifespan. *Aging Cell* 10, 913–921 (2011).
- 20. Phillip, J. M. *et al.* Biophysical and biomolecular determination of cellular age in humans. *Nat. Biomed. Eng.* **1**, 0093 (2017).
- Kolovou, G. D., Kolovou, V. & Mavrogeni, S. We Are Ageing. *BioMed Research International* (2014). doi:10.1155/2014/808307

- 22. Carnes, B. A., Holden, L. R., Olshansky, S. J., Witten, M. T. & Siegel, J. S. Mortality Partitions and their Relevance to Research on Senescence. *Biogerontology* **7**, 183–198 (2006).
- 23. Olshansky, S. J. & Carnes, B. A. Ever since Gompertz. *Demography* 34, 1–15 (1997).
- 24. Koopman, J. J. E., Wensink, M. J., Rozing, M. P., van Bodegom, D. & Westendorp, R.
 - G. J. Intrinsic and extrinsic mortality reunited. *Exp. Gerontol.* 67, 48–53 (2015).

Acknowledgements

The project was supported by the CETOCOEN PLUS (CZ.02.1.01/0.0/0.0/15_003/0000469) project of the Czech Ministry of Education, Youth and Sports. The project was also supported by the RECETOX Research Infrastructure (LM2015051 and CZ.02.1.01/0.0/0.0/16_013/0001761). Furthermore, Peter Lenart received support from the Brno Ph.D. Talent. We want to thank an anonymous reviewer who showed us we were wrong.

Authors' contributions

P. L. formulated the research problem, chose data sources and interpreted the results. D. K. analysed the data and J. B. V supervised the project. All authors co-wrote the manuscript.