PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Examining mortality risk and rate of aging among Polish Olympic athletes: A survival follow-up from 1924 to 2012
AUTHORS	Lin, Yuhui; Gajewski, Antoni; Poznańska, Anna

VERSION 1 - REVIEW

REVIEWER	Hans Degens School of Healthcare Science Neuromuscular and Skeletal Ageing Research Group Manchester Metropolitan University John Dalton Building; Chester Street Manchester M1 5GD United Kingdom
REVIEW RETURNED	19-Jan-2016

GENERAL COMMENTS	This is an interesting paper addressing the question whether elite athletes show decelerated ageing and a lower mortality risk. It is concluded that physical training in youth should be promoted. While I in principle agree with this suggestion, it is not a conclusion that can be drawn from this analysis for several reasons. 1) It is not necessarily the case that the Olympic athletes already trained in their youth and 2) it is very likely that the athletes maintained an active lifestyle long after the Olympic games; this off course can also have a significant impact on survival. So, temper the conclusion somewhat along the lines of 'Elite athletic performance decelerates ageing and decreases mortality risk. It will probably help the readability of the manuscript if a native English speaker checked it. Minor comments: Can the authors inform the reader where they got their survival data from for the athletes? In table 1 the age at death for Cohort II is an underestimate of course. Can you maybe add a column for Cohort 2 indicating the average age of the 784 that are still alive? In table 2 explain what the a, b and y reflect, as a table or graph one should be able to read as a stand-alone, without reference to the text. The parameter b was lower in the athletes in cohort I, but higher in the athletes than the general population in cohort II it appears in Table 2; is this correct?

REVIEWER	Michael J Joyner, MD Mayo Clinic USA
REVIEW RETURNED	19-Jan-2016

GENERAL COMMENTS	Papers related to mortality and longevity of elite athletic cohorts have been analyzed and published in many journals. Based on these prior studies, the results of this paper show the expected differences in longevity/survival. In this context the paper suffers from the inherent limitations of almost all such analysis: 1) Were the athletes healthier throughout life, including when very young? 2) What was their lifetime pattern of physical activity? 3) Did smoking rates differ? 4) Did endurance athletes differ from non-endurance athletes? 5) Did the athletes have increased social status as the aged? Since the paper offers no new insights on these topics, I think it might be better for an epidemiology or actuarial journal.

REVIEWER	Masaru Teramoto University of Utah, USA
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	This study has the potential to make a contribution to research on exercise epidemiology. The research topic is interesting to readers, and the research question and aim of the study are clearly stated. The data analysis was performed appropriately, and the manuscript is well written. I have a few comments listed below, and addressing these aspects would strengthen the paper. Strengths & Limitations -> Please discuss how unobserved heterogeneity could have influenced the analysis of your study. Introduction -> Please add explanations of "aging d(log(u(x)))/dx" in the Introduction, so that readers who are not familiar with this definition and equation can better understand the term. Page 14, Lines 243-245, "In addition, ... multifactorial risk assessment." -> Please add the reference(s) to support this statement. Page 15, Lines 268-270, "This results further suggest ... achieve a deceleration in the rate of aging." -> This part, to me, is a bit overstated, as your study does not exactly provide the results to support this statement. Please revise (weaken) the sentence a bit.

REVIEWER	Alejandro Lucia Universidad Europea, Madrid, Spain
REVIEW RETURNED	31-Jan-2016

GENERAL COMMENTS	The study is timely and addresses an important topic.

	1. The Ms would benefit from a thorough linguistic revision by a native English speaker. 2. Importantly, I was really surprised by the fact that the authors have totally ignored important references in the field that should be cited in the revised Ms, particularly (and among others): Marijon et al Eur Heart J Garatachea el al (meta-analysis in Mayo Clinic Proceedings 2014 Sep;89(9):1195-200. Pls cite this one and the main studies that were analyzed in it (such as the Marijon et al paper) Finally the stats approach is beyond my understanding (at least to some extent) but I do like the idea of addressing the question of 'rate of aging' (not just mortality/longevity). There is recent controversy in the literature regarding the somehow 'toxic' effects of 'over exercise' (particularly at the cardiac level -pls see O'Keeefe et al hypotheses). Thus, the present findings are nice. I would be quite nice (if this was possible here or in future studies) to perform sub-analyses for cardiac-mortality risk and cardiac related rate of aging.

VERSION 1 – AUTHOR RESPONSE

Prof. Hans Degens
I) To fine tune the sentence in the conclusion section
Agree to a certain extent on the points to be made in the conclusion section.
However, in order to qualify for the Olympic games, athletes must have qualified or competed in their sports at the national level. Their median age at recruitment for the Olympic games Cohort I: 26 and Cohort II: 24. The athletes must have received some professional training before their age of debut or age at recruitment at the Olympic games. Ages below 30 is considerably young adulthood.

To address the comment, the following sentence has been revised. At lines 174 to 179, 'All parameter estimates were obtained using the Maximum Likelihood Estimation (MLE); where age at debut as left-truncation and vital status as right censoring for each recruited athlete were introduced during the survival analysis (Supplementary Equation S3). Age at debut shall hereafter be known as age at recruitment, and athletes were assumed to have received professional training in their sports expertise prior to their debut at the Olympic Games.'
II) To include the mean age at last survival follow-up for Cohort II survivors
Refer to the revised article: line 199 to 200, we have included it in the text rather than in Table 1.

III) Higher b in Cohort I athletes than Cohort II general population and athletes
From the maximum likelihood estimation (MLE), Cohort I athletes experienced a slightly higher rate of aging than Cohort II. It should be considered very, very similar; difference of 0.002.

Cohort II general population has to be interpreted with good sensibility and care. A reliable and more sophisticated mathematical model to adjust for medical improvements in life-tables across years and birth cohorts has yet to be introduced. To account for medical improvements during life-table analyses, there are still strong correlations in the parameters during MLE.

A possibility to disentangle the parameters is to impose very strong assumptions, and we reckon that such approach deficits the purpose of running a simple and comprehensive survival model. We are very certain that Cohort II has its research interests and findings from Cohort II population deserve a separate discussion.

The Cohort I estimates of athletes and the general population are good for comparison as the general population did not experience continuous mortality progress; refer to supplementary materials, Figure S2. Medical improvements among the athletes should have been adjusted for during the event-history analysis.

IV) Origin of the data and the survival profiles
Refer to lines 181 to 195 of the revised manuscript.

V) To include what the parameters a, b, γ reflect in table and graph.
The following text is included: 'Parameters: a represents the magnitude of the hazard or risk of mortality; b represents the rate of aging; γ represents unobserved heterogeneity.'

Prof. Michael J Joyner

I) Missing heterogeneity or better known as covariates in this study
Please also refer to revisions made in Strengths & Limitations page 3 line 40, and Introduction page lines 84 to 88.

There is definitely an interest to analyze endurance and non-endurance athletes, and other socioeconomic interests that may be beneficial for athletes' longevity. However, those covariates are not available in this study. Our study has shown the possibility to obtain reliable age-specific mortality trajectories by implementing heterogeneity that has not been observed, and that frequent physical activity does decelerate the rate of aging and lower mortality risk. In the article, we have defined the difference between rate of aging and risk for mortality. The revised article, Methods section: Gompertzian b, lines 139 to 156; Supplementary materials: Equation S1 and S3.

There are many population studies that contain mortality profile of each individual. One of the earliest population study was originated from parish, where gender, birth and death records of each family member were recorded by the priest, and with no additional covariate. There may be some historic records on infectious diseases and extreme weather conditions, but those events are usually not too non-selective on which individuals to die first, e.g. smallpox. The Polish Olympic athletes study is one example where behavioral covariates (e.g. smoking) was not recorded and due to the small sample size to further categorized the athletes into subgroups will make it impossible to infer any mortality trajectory. These were the predominant motivations to implement unobserved heterogeneity also known as frailty in the survival model. For the application of present prospective longitudinal studies, it can be done and the analysis is much easier with observed heterogeneity or covariates.

Despite the inclusion of right censoring during survival analysis, it is often anticipated that more occurring deaths provide a better representation of the risk exposure on population dynamics. Professional athletes as we know are more likely to experience a longer life-expectancy, and hence a longer time is required for them to expire in the population. If there's an elite athlete population study with a good follow-up of fifty to sixty years, Lin would like to analyze it and to see if the conclusion may differ from this study.

Lin had also worked on longitudinal data studies with covariates and, the estimates from the following scenarios were obtained and compared:
1) the common survival analysis that takes into account of covariates or observed heterogeneity;
2) the frailty survival analysis that accounts for unobserved heterogeneity;
3) survival analysis to account for both observed and unobserved heterogeneity.

The hazard estimates obtained from the aforementioned three scenarios were not affected with the use of their respective models. The Gompertz frailty model is a stable parametric model for normal human population and the model has been verified many times by demographers and epidemiologists with expertise in mathematics. Yashin et. al, Aalen et al., etc.

Prof. Masaru Teramoto

I) How would unobserved heterogeneity affect the estimates?
Refer to the revised article; Strengths and Limitations, p.3 (lines 43 to 46)

II) For readers: What is d(log(u(x)))/dx in this study?

Refer to the revised article; lines 139 to 156

III) Additional references included in revised manuscript
23. Aalen OO. Heterogeneity in survival analysis. Stat Med. 1988;7:1121–37.
24. Gerber Y, Myers V, Goldbourt U, Benyamini Y, Scheinowitz M, Drory Y. Long-term trajectory of leisure time physical activity and survival after first myocardial infarction: a population-based cohort study. Eur J Epidemiol. 26:109–16.
25. Yashin AI, Arbeev KG, Akushevich I, Kulminski A, Akushevich L, Ukraintseva SV. Model of hidden heterogeneity in longitudinal data. Theor Popul Biol. 2008;73(1):1–10.

IV) Rephrase page 15; ll.268 to 270
Rephrased, Refer to revised article lines 341 to 343: The age-specific mortality trajectories of Cohort I elite athletes also suggest frequent exercise can decelerate the rate of aging by 1% with an achievement of three-fold risk reduction in mortality.

Prof. Alejandro Lucia
I) Additional references to be included, Refer to revised manuscript
11. Gajewski A, Poznańska A. Mortality of top athletes, actors and clergy in Poland: 1924 - 2000 follow-up study of the long term effect of physical activity. Eur J Epidemiol. 2008;23(5):335–40.
12. Teramoto M, Bungum TJ. Mortality and longevity of elite athletes. J Sci Med Sport. 2010 Jul 1;13(4):410–6.
13. Garatachea N, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Emanuele E, et al. Elite Athletes Live Longer Than the General Population: A Meta-Analysis. Mayo Clin Proc. 2014 Aug;89(9):1195–200.

We have also considered to include SMR, however, presenting results of the SMR will deviate the focus of the paper; the rate of aging and age-specific mortality trajectories. When hazard ratio for exposure of interest is lower than the reference group, the SMR will surely be <1. The hazard ratio and mortality estimates give a better overview of the population. We have had a thorough read of the French Cyclist paper which offers some good information on SMRs and causes of death, and we reckon that the information and statistical approaches are not relevant enough to be included in the study. The other paper by Garatachea et al, is a meta-analysis paper, and the finding happens to support our current finding.

As it seems that it is a common interest in epidemiology and biostatistics to use SMRs for observed and expected mortality, we, the authors, agreed to include a short paragraph to explain on SMRs and hazard ratios. Refer to the revised article, line 270 to 276.

II) Cardiac-related rate of aging
Harvard Alumni Health Study may have sufficient data points to perform a study related to the findings

in this analysis. However, we are not sure if they are making further plans to conduct follow-up study. There are other longitudinal studies for cardiac-related rate of aging, but they may not present cardiac-related mortality trajectories of professional athletes, e.g. Framingham Heart Study.

The Polish Olympic athletes dataset may current permit the analysis of overall SMR only. We have tried to gather data concerning causes of death – we have about 50% of them and expectedly, the external causes are over-represented among them. Information about fatal accident of a popular athlete (active or former) is always mentioned in press, whereas the typical obituaries do not contain the cause of death.

VERSION 2 – REVIEW

REVIEWER	Hans Degens School of Healthcare Science Manchester Metropolitan University John Dalton Building; Chester Street Manchester M1 5GD United Kingdom
REVIEW RETURNED	01-Mar-2016

GENERAL COMMENTS	I recommend to have someone check the English to improve the readability of the manuscript. Maybe you do not need to speak so much about the 'rate of ageing' but rather 'the rate of mortality' as that is what you assess e.g. on page 39 line 146.

REVIEWER	Masaru Teramoto University of Utah, U.S.A.
REVIEW RETURNED	03-Mar-2016

GENERAL COMMENTS	The authors have addressed here the aspects that were unclear to me in the first manuscript. I believe that the paper is now qualified for publication in BMJ Open.

VERSION 2 – AUTHOR RESPONSE

Prof. Hans Degens,

Thank you for reviewing the article. We have consulted native English speakers and researchers who are not too familiar with the application of parametric frailty models in human populations. We try to accommodate by improving the explanation of each sentence written in the article. However, it is essential to keep in mind that they have some strong fundamental backgrounds in statistics and mathematics.

We have also changed some parts of the article to an active voice which may help the lines to flow better and rephrased the sentences as required. It is quite possible that most readers will require to read the article more than once, and might learn something new every time they were to read it.

We try to limit the number of linguistic expressions for the same inference; such as mortality profile or survival profile. In such case, we decide to use the term survival profile as it has been a preferred choice among epidemiological and medical studies. We have to use the term selection for mortality rather than selection for survival, because the algorithm of the MLE represents the selection for mortality, not for survival.

The rate of aging or ageing, is the rate of change in mortality. Age-specific mortality rate shows $\mu(x)$, and the rate of change in mortality, is the increment per unit of time, i.e. x = age; $d(\log(\mu(x)))/dx$, refer to the article. It is the rate of aging.

Prof Masaru Teramoto,

Thank you for reviewing the article. Though the concept and logic are straightforward, we have to provide some clarity for researchers or clinicians who are not familiar with parametric frailty models and its applications in longitudinal studies. Some insertions of phrases or a sentence can help them to comprehend the rationale behind each step of the research.