June 2, 2020

Dear Editor,

My co-authors and I are pleased to submit our manuscript entitled “Parity is not associated with multiple measures of biological age: Evidence from NHANES 1999-2010” to be considered for publication in *Scientific Reports*.

Individuals of the same chronological age differ in their rate of age-related physical and cognitive decline. Understanding the factors that contribute to this variation – referred to as ‘biological age’ – is a major public health concern. In women, number of pregnancies and live births have been linked to increased risks of cardiovascular disease, type II diabetes, reproductive cancers, and all-cause mortality2. Gravidity and parity have also been linked measures of cellular aging such as telomere length and epigenetic age3. It is unknown, however, whether widely used clinic-based measures of biological age can be used to study the impact of reproduction on biological aging in women.

Using a large (n = 2,669) nationally-representative sample of US women, we tested for associations between parity and three recently-validated, clinic-based measures of biological age (Levine Method, homeostatic dysregulation, and Klemera-Doubal Method biological age). These measures capture biological aging and decline across range of physiological processes and complement prior work on cellular aging. Controlling for important age-related covariates and looking at both pre- and post-menopausal women, we did not find any evidence for an association between parity for any of the measures of biological age. Associations between time since last birth and biological age were also not significant. Our results suggest that unlike cellular-based measures of biological age, validated clinic-based measures of biological age do not reflect either acute or chronic effects of parity.

Understanding the factors that drive variation in the rate of biological deterioration or repair, known as ‘biological age,’ is of significant public health concern. In women, reproduction entails significant investment and changes across a range of physiological systems. These costs, referred to as ‘costs of reproduction’, may manifest as relationships between parity and cardiovascular disease mortality1, all-cause mortality2, and cellular markers of accelerated aging such as telomere length and DNA methylation patterns3. It is unknown, however, whether parity is associated with previously-validated, clinic-based measures of biological age that predict functional decline and disease, but measure fundamentally different physiological processes than cellular-based measures of biological age.

We tested whether parity was associated with accelerated biological aging using three previously-validated clinic-based measures of biological age (Levine Method, homeostatic dysregulation, and Klemera-Doubal Method biological age) in a nationally-representative sample of women in the US (*n* = 2,669) recruited as part of the National Health and Nutrition Examination Survey. When controlling for covariates related to biological age, we found no significant associations between parity and biological age across all biological age measures in both pre- and post-menopausal women. Associations between time since last birth and biological age were also not significant. Our results suggest that unlike cellular-based measures of biological age, validated clinic-based measures of biological age do not reflect either acute or chronic effects of parity.

We believe our findings will be of general scientific interest, and of interest to those whose work focuses on reproductive epidemiology, evolutionary biology, reproductive physiology, and geroscience. We further believe readers of *Scientific Reports* will find this research of interest because of recent papers published in the journal that served as the impetus for our study.

Thank you in advance for your consideration of our article, and we look forward to hearing from you.

Sincerely,

Talia Shirazi, MA

Department of Anthropology

Pennsylvania State University

421 Carpenter Building

University Park, PA 16802

[tus37@psu.edu](mailto:tus37@psu.edu)

1. Lv, H., Wu, H., Yin, J., Qian, J. & Ge, J. Parity and Cardiovascular Disease Mortality: a Dose-Response Meta- Analysis of Cohort Studies. *Sci. Rep.* **5:13411**, 1–9 (2015).

2. Zeng, Y. *et al.* Parity and All-cause Mortality in Women and Men: A Dose-Response Meta-Analysis of Cohort Studies. *Sci. Rep.* **6:19351**, 1–11 (2016).

3. Ryan, C. P. *et al.* Reproduction predicts shorter telomeres and epigenetic age acceleration among young adult women. *Sci. Rep.* 1–9 (2018). doi:10.1038/s41598-018-29486-4

**Suggested Reviewers**

Grazyna Jasienska

Professor, Department of Environmental Health

Jagiellonian University Medical College

[jasienska@post.harvard.edu](mailto:jasienska@post.harvard.edu)

Daniel Belsky

Professor, Mailman School of Public Health

Columbia University

[db3275@cumc.columbia.edu](mailto:db3275@cumc.columbia.edu)

Rebecca Sear

Professor, Department of Population Health

London School of Hygiene & Tropical Medicine

[rebecca.sear@lshtm.ac.uk](mailto:rebecca.sear@lshtm.ac.uk)

Anna Ziomkiewicz

Researcher, Department of Anthropology

Polish Academy of Sciences

[anna.ziomkiewicz-wichary@hirszfeld.pl](mailto://anna.ziomkiewicz-wichary@hirszfeld.pl)

Daniel Parker

Medical Instructor, Department of Medicine

Duke University

[daniel.parker@duke.edu](mailto:daniel.parker@duke.edu)