PROGRESS OF RESEARCH ON THE PACE OF AGING AND LITERATURE REVIEW

January 2024 (Terrie E. Moffitt)

Website: https://moffittcaspi.trinity.duke.edu/dunedinpace

DunedinPACE is a biomarker that measures the pace of aging. It is designed to function as a speedometer for aging, offering a single-timepoint measurement of how fast a person is now aging. DunedinPACE is published (Belsky et al. 2022 eLife) and code to compute it in DNA methylation data is available on GitHub, https://github.com/danbelsky/DunedinPACE. The code is also included in BioLearn.

History: The Duke/Dunedin team modelled the Pace of Aging using multiple assessment waves of multiple biomarkers in 2015. We then updated and improved the Pace of Aging in 2021 by adding an additional wave of data. We also realized that few other research teams could adopt the approach, because they lack three or more waves of multiple biomarkers across the whole body. So, we translated the Pace of Aging into a DNAmethylation version that can be derived from one blood draw. We published our paper on the DNAm version in 2020 (Belsky et al eLife 2020) and updated in 2022 (Belsky et al. ELife 2022. We reported how to measure the Pace of Aging using DNAmethylation data, calling the measure DunedinPACE for "**P**ace of **A**ging **C**alculated in the **E**pigenome." We have also translated the Pace of Aging into a brain MRI version that can be derived from one MRI brain scan image, calling the measure DunedinPACNI for "**P**ace of **A**ging **C**alculated in a **N**euro-**I**mage" (report coming in 2024).

Five design advantages distinguish this measure from others:

First, DunedinPACE was derived on a cohort of people who were all born the same year. To date this design feature is unique in the world of aging measures. This is an advantage because DunedinPACE has no *noise* from historical differences in exposure to factors that in multi-age samples alter the participants' body or their epigenome. People who were born earlier or later differ on exposure to things like influenza epidemics, leaded gasoline, vaccines, anti-biotics and anti-inflammatory medications, air-conditioning, indoor plumbing, birth control, fruits and vegetables in winter, years of education, and more. Other bio-age measures derived on people who have different birth years contain some of this exposure noise.

Second, DunedinPACE was derived from 19 biomarkers ascertained longitudinally at ages 26, 32, 38, and 45, comprising 69,715 data points. This longitudinal design tracks true unidirectional decline that is correlated across organ systems as age advances. This is an advantage because DunedinPACE has no *noise* from short term illnesses or infections that could elevate a biomarker temporarily. Other bio-age measures are typically derived from only one cross-section of data and thus contain some noise from spells of sickness.

Third, DunedinPACE was derived in a cohort of healthy adults studied up to age 45. This is an advantage because DunedinPACE has no *noise* from late-life diseases such as diabetes, heart disease, kidney disease, dementia, or cancers, because these diseases have not yet onset in the Dunedin cohort. Other bio-age measures are typically derived from samples in which many of the older members already have chronic diseases that alter their body and epigenome.

Fourth, DunedinPACE was derived in a midlife cohort for which attrition by death has been minimal; under 3%. This is an advantage because of "survivor bias." Other bio-age measures are typically derived from samples in which the many of the older members are missing due to death. In multi-age samples, the youngest participants can be sampled from all people born their year, but the older participants can only be sampled from the subset of those left alive. The fastest agers will have already died, which reduces the potential range of scores on any bioage measure. Thus, in other bio-age measures, the young versus old participants differed from each other on some noise factors that are not aging.

Fifth, DunedinPACE was derived from a pool of DNA methylation probe sites that were pre-selected to have strong test-retest reliability. Unreliable probe sites were excluded from DunedinPACE. Most methylation prob sites are unreliable, which adds noise to DNAm bioage measures. Other bioage measures offset this noise after the fact, by deriving principal factors.

EXPORTING DUNEDINPACE TO THE FIELD: We posted the DunedinPACE algorithm on Github. Since then, to our delight, the research community has embraced the measure. Here are a few of the major recent advances:

1. We first exported our original version published in 2020, called DunedinPoAm, to the NIA-funded Health and Retirement Study (HRS), a large open-access data source for the aging research community. The HRS made the measure publicly available to the field in 2021. We count 26 publications by HRS data users already. More are known to be in the pipeline.

2. We subsequently exported to the HRS our new, improved version published in 2022, called DunedinPACE. To date, the HRS team have been using it and publishing with it (for example, Faul et al. 2023). We expect the HRS to make DunedinPACE public soon for other users.

3. We exported DunedinPACE to NHANES, who will make it publicly available to their users soon. We also exported DunedinPACE to the UK Understanding Society cohort, which will make it public for users. These are large open-access data sources for the research community.

4. We posted the algorithm for DunedinPACE on Github, along with meta-data to help users. We offer tech support, but it is easy to use. (NOTE: as the Illumina company who provides DNAmethylation arrays has updated from their 450k to EPIC1 to **EPIC2**, we have updated the Github algorithm. It automatically works with data created from any of those Illumina platforms.)

5. **52 large epidemiological cohort studies in 15 countries are now using DunedinPACE**, including, in alphabetical order: The Alzheimer disease neuroimaging initiative (ADNI), AHAB, ALSPAC UK, ASPREE Study Australia, Austrian Stroke Prevention Study, BeCOME Germany, Baltimore Longitudinal Study of Aging (BLSA), CALERIE, Canadian longitudinal study on aging (CLSA), CARDIA, Cebu Longitudinal Health and Nutrition Survey (CLHNS Philippines), Child Health and Development Study, Dutch Hunger Winter Study, E-Risk Longitudinal Twin Study UK, FACHS (African American families), FinnTwin, Finnish Twin Study on Aging FITSA, Framingham Offspring Cohort, Fragile Families, Future of Families and Child Wellbeing (FFCW), Generation Scotland, German Socioeconomic Panel Study (SOEP-Gene), Grady Trauma Project, HANDLE (NIA's intramural study), Health and Retirement Study (HRS), KORA (Cooperative Health Research in the Region Augsburg study), Leiden Longevity Study, Lothian Birth cohort, Melbourne Collaborative Cohort Study Australia, MESA, MIDUS, National Heart, Lung, and Blood Institute Growth and Health Study (NGHS, 1992), NHANES, Normative Aging Study, Northern Finland 1966 birth cohort, Norwegian MOBA, Penn State Child Health Study,

REWARD Study in Wisconsin, Rotterdam Study, Sister Study, SOEPG Germany, Strong Heart Study of Native American Indians, Swedish Adoption/Twin Study of Aging, Swiss Family Study, Taiwanese Biobank, The Texas Twin Study, TILDA Ireland, Thinking and Living with Cancer (TLC) Study, UK Household Longitudinal Study, UK Understanding Society, Veterans Administration Post-Deployment Mental Health Study (PDMH), Women's Health Initiative, plus others.

STUDIES VALIDATING DUNEDINPACE AS A USEFUL MEASURE OF WHOLE-BODY AGING:

6. **Other research teams have already published 124 reports** of new findings from these data sets since 2021 (these reports are not from our team).

7. **We ourselves have published 24 reports** with findings using our measures of the pace of aging. As an example, we reported that faster DunedinPACE distinguishes long-term cannabis users from recreational users in the Dunedin cohort (Meier et al. 2022, *Lancet Healthy Longevity*). As another example, people with more education have slower DunedinPACE, after controls for genetic confounds (Sugden et al. 2023, *J of Gerontology*).

8. **Replication and robustness.** Our publications have generally replicated findings by using one or more of the data sets that now include DunedinPACE; we often report multi-study publications. Our paper announcing DunedinPACE reported validation in 5 data sets (Belsky et al 2022, *eLife*). As another example, we reported that faster DunedinPACE distinguishes Alzheimer dementia patients in **2 cohorts,** ADNI and the Framingham Heart Study (Sugden et al. 2022, *Neurology).* We also reported that people with more education have slower DunedinPACE, after controls for genetic confounds, in **5 cohorts** (Sugden et al. 2023, *J of Gerontology*). Other replication papers show that DunedinPACE relates to MRI-measured brain structure in **3 cohorts** (Whitman et al. 2023 *Neurobiology of Aging*) and to schizophrenia in **5 case-control studies** (Caspi et al. 2023 *Biological Psychiatry*).

9. **Comparison to clocks:** Overall, findings have shown that DunedinPACE routinely outperforms the Horvath, Hannum, and PhenoAGE clocks, and typically performs on par with the GrimAGE clock. DunedinPACE outperformed the GrimAGE clock on some analyses of cognitive decline and Alzheimers dementia, but this comparison is early days yet.

10. **Ethnic ancestry:** DunedinPACE was originally trained on white New Zealanders, but it is being reported on groups of other ancestries. Yin (2023) reported in the Taiwanese Biobank that DunedinPACE is faster in **Han Chinese** who have multimorbid physical illnesses. Boyer et al (2023) reported DunedinPACE findings in **Native American Indians**. Overall, published findings in **African Americans** are looking similar to those in Whites, as shown in the FACHS, HANDLE, Future of Families and Child Wellbeing (FFCW), MIDUS, National Heart, Lung, and Blood Institute Growth and Health Study (NGHS 1992), and HRS data sets, as well as the Veterans Administration Post-Deployment Mental Health Study (PDMH), which is 50% African American. Krieger et al. studied DunedinPoAm in Black, Hispanic, and white ethnicity with respect to racialized and economic injustice in MESA. One report from HRS found that DunedinPACE did not serve as a mediator variable as well in Black males as it did in White males (Avila-Rieger et al. 2022).

11. **Children:** DunedinPACE was originally trained on people age 45, but overall, published findings show DunedinPACE is relevant for studies of children and adolescents: E-Risk,

ALSPAC, FinnTwin, PennState Child Health Study, Texas Twins, Quebec Longitudinal Study of Child Development, Future of Families and Child Wellbeing (FFCW), and others. More data are needed to understand interpretation of scores in children. (NOTE: some child studies used buccal/saliva as the source of DNA, whereas DunedinPACE was trained on venous blood as the source of DNA.)

12. **Older adults:** DunedinPACE was trained on people age 45, but it is proving relevant for studies of older adults: BLSA, Framingham, HANDLE, HRS, MESA, NAS, TILDA, UK Understanding Society, Finnish Twin Study on Aging FITSA, Canadian longitudinal study on aging CLSA, 1958 British Birth cohort, Lothian birth Cohorts, Swedish Adoption/Twin Study of Aging, Rotterdam Study, Leiden Longevity Study, Women's Health Initiative, and others.

13. **Predicting endpoints:** Faster DunedinPACE has been shown to statistically predict endpoint indicators including functional and cognitive decline, frailty, disease multimorbidity, and mortality (age at death) in AHAB, BLSA, Framingham, Generation Scotland, HANDLE, HRS, Melbourne Collaborative Cohort Study, MESA, NAM, UK Understanding Society, FITSA, Taiwanese Biobank, Rotterdam Study, Leiden Longevity Study, Lothian birth cohort, Women's Health Initiative, and others.

14. **Predicting diagnosed dementia:** Faster DunedinPACE has been reported to predict ADRD and Mild Cognitive Impairment in ADNI and Framingham (Sugden et al, 2022), and cognitive decline (Elliot et al. 2021; Reed et al. 2022). Another study did not find this (Schäfer Hackenhaar, et al. 2023).

15. **Risk factors for fast aging:** DunedinPACE has been shown to be accelerated in people who experienced psycho-social adversity and deprivation in ALSPAC, BLSA (Baltimore Longitudinal Study of Aging), E-Risk Longitudinal Twin Study UK, FACHS (African American families study), Future of Families and Child Wellbeing (FFCW), Generation Scotland, HANDLE (NIA's intramural study), HRS, MESA, NHANES, Normative Aging Study, the Sister Study, Swiss Family Study, The Texas Twin Study, TILDA (Ireland), UK Understanding Society, Canadian longitudinal study on aging (CLSA), Grady Trauma Project, Taiwanese Biobank, Veterans Administration Post-Deployment Mental Health Study, and five schizophrenia case-control studies, plus other studies.

16. **Sensitivity of DunedinPACE to detecting short-term change:** DunedinPACE has been reported to slow in response to lifestyle changes that beneficially affect aging biology in FACHS and CALERIE. DunedinPACE has also slowed after successful treatment for insomnia. DunedinPACE was sensitive to a drug intervention in ClockBASE. It has been shown to speed up under conditions of stress in FACHS, and under conditions of bio-stress in three clinical datasets reported by Gladyshev et al. 2023. This set of findings is important because it shows that DunedinPACE can be sensitive to detecting change, and that it can be repeated as a before-after measure on a time-span of weeks to quantify short-term change in the pace of biological aging. But this is early days and much more research is needed to confirm.

17. Idan Shalev reports that most epigenetic sites are unstable, except those in Dunedin PACE (and in PC clocks). https://www.tandfonline.com/doi/full/10.1080/15592294.2023.2230686

18. **Clockbase:** Many studies that have derived DunedinPACE have joined ClockBASE, an open access computational biology data repository: http://gladyshevlab.org:3838/ClockBase/.

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19. **Biolearn** **https://bio-learn.github.io/**, is an open source library to help with calculating any composite biomarker of aging on any molecular data. This library will standardize all the public biomarker formulations, including the collection of epigenetic clocks standardized by Morgan Levine/Albert Higgins-Chen's (methylCIPHER) and Vadim Gladyshev's (ClockBase) groups as well as the blood biomarkers standardized by Daniel Belsky's group (BioAge). At the same time, Biolearn will harmonize public and private molecular datasets commonly used for biomarker validation. Biolearn is scientifically and financially supported by Biomarkers of Aging Consortium and Methuselah Foundation.

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20. **TruDiagnostic report** (Licensed Feb 2021).

https://drive.google.com/file/d/1ZXdQhc8io9InMypjbr6C-Ml1BC-hPugy/view

21. Everything Epigenetics podcast by Hannah Went:
https://everythingepigenetics.com/episode/dr-terrie-moffitt-how-fast-are-you-aging-really-dunedinpace/

22. **Bryan Johnson's Blueprint** for slowing aging and **Rejuvenation Olympics** lederboard features DunedinPACE.
https://www.lifespan.io/news/bryan-johnsons-race-against-time/
https://blueprint.bryanjohnson.co/
https://rejuvenationolympics.com/

TIME magazine feature story on Bryan Johnson.
https://time.com/6315607/bryan-johnsons-quest-for-immortality/

***Men's Health* tested three aging tests, including DunedinPACE.**
https://www.aol.com/lifestyle/fast-am-really-aging-took-191900851.html

23. **Youtube: LifeNoggin video**: *Body secrets*

https://www.youtube.com/watch?v=kcxdSt-wYsM

24. Application in geroprotection clinical trials:
https://www.newsobserver.com/press-releases/article277627968.html
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The name of the dataset is below each citation.

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Gerontological Society of America Symposium 2023: Causal Effects of Early-Life Adversity and Mid/Late-Life Behavioral Intervention on the Pace of Biological Aging

Thursday, November 9, 2023
Chair: Daniel Belsky, PhD, Columbia University
Discussant: Luigi Ferrucci, MD, PhD, National Institute on Aging
Individual Symposium Abstract First Author: Daniel Belsky, PhD, Columbia University
Individual Symposium Abstract First Author: Judith Carroll, PhD, University of California, Los Angeles
Individual Symposium Abstract First Author: Lauren Schmitz, PhD, University of Wisconsin-Madison
Individual Symposium Abstract First Author: Mengling Cheng, PhD candidate, Swiss Centre of Expertise in Life Course Research

Epigenetic clocks have taken gerontology by storm. With the advent of 2nd and 3rd generation epigenetic clocks, including GrimAge and DunedinPACE, the field now has genomic biomarkers of aging that exhibit strong and consistent associations with aging-related morbidity and mortality. But the causes of variation in these powerful indices of aging-related biological changes remain poorly understood. In this symposium, we present four studies at the vanguard of research to elucidate causal drivers of 2nd and 3rd generation epigenetic clocks drawn from four disciplines. From life-course epidemiology, we present a natural-experiment study of the long-term impact of in-utero famine exposure. From economics, we present a quasi-natural experiment study of long-term impacts of early-life exposure to the Great Depression. From psychology, we present results from a randomized controlled trial (RCT) of cognitive behavioral

therapy (CBT) for insomnia in older adults. And from geroscience, we present results from an RCT of long-term calorie restriction in healthy, non-obese adults (CALERIE). These studies report novel and important findings that suggest early-life adversity acts to accelerate the pace of biological aging –and— that it may be possible to slow the pace of biological aging in mid- and later-life through behavioral intervention. They also illustrate study designs and methods that can help move the field forward as costs for measurement of epigenetic clocks fall, enabling their introduction into many more cohort and intervention studies.

Brief description:

DunedinPACE is a biomarker that measures the human pace of aging. It is designed to function as a speedometer for aging, offering a single-timepoint measurement of how fast a person is now aging. Co-inventors are Daniel Belsky (of Columbia University), Terrie Moffitt, Avshalom Caspi, and Karen Sugden (of Duke University), and David Corcoran (of UNC Chapel Hill). DunedinPACE is published (Belsky et al. 2022 eLife) and code to compute it in DNA methylation data is available on GitHub. The code is also included in BioLearn. Code is appropriate for EPIC2 DNAm datasets. Dunedin PACE has now been validated in more than 50 large cohorts, including older adults and children, in more than 15 countries, and more than 5 ethnic ancestry groups. Five design advantages distinguish this measure from others: First, DunedinPACE was derived on a cohort of people who were all born the same year; it has no noise from differences in historical exposures that in multi-age samples alter the participants' bodies or their epigenomes. Second, DunedinPACE was derived from 19 multi-organ biomarkers ascertained longitudinally at ages 26, 32, 38, and 45, comprising 69,715 data points; it has no noise from short term sicknesses that could elevate a biomarker temporarily. Third, DunedinPACE was derived in a cohort of healthy adults studied up to age 45; it has no noise from late-life chronic diseases such as diabetes, heart disease, kidney disease, dementia, or cancer (or medications), because these diseases have not yet onset in the Dunedin cohort. Fourth, DunedinPACE was derived in a midlife cohort for which attrition by death has been under 3%; it has no noise from "survivor bias" in which the fastest aging older participants aren't studied because they already died. Fifth, DunedinPACE was derived from a pool of DNA methylation probe sites that were pre-selected to have strong test-retest reliability, yielding reliability over .90 for DunedinPACE. More than 150 publications have reported DunedinPACE.