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# HRS Documentation Report

## *HRS Epigenetic Clocks – Supplement PACE and Grim2*

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## Table of Contents

I.	Introduction .....	2
A.	Rational .....	2
B.	The HRS Methylation Sample of Respondents .....	2
C.	Collection .....	2
D.	Protocols for DNA Methylation Data .....	2
E.	Subsample Weights.....	3
II.	Individual Clocks.....	4
A.	PACE .....	4
B.	Grim2 .....	5
III.	If You Need to Know More .....	6
A.	HRS Internet Site .....	6
B.	Contact Information.....	6
C.	Citing this Document.....	6
IV.	References .....	7

## I. Introduction

This document describes a data set consisting of values for two epigenetic clocks developed from DNA methylation data derived from the 2016 Health and Retirement Study Venous Blood Study – PACE and Grim2.

The full QC'd HRS 2016 DNA methylation data from which these were constructed are available through NIAGADS (<https://www.niagads.org/>).

### A. Rational

Two additional epigenetic clocks have been constructed using the HRS data, PACE (Belsky 2022) and Grim2 (Lu 2022). This release serves as a supplement to the file including thirteen epigenetic clocks that was released in 2020. Both supplemental clocks were constructed by HRS and also by collaborators at USC to ensure reliability. In addition, in this release we provide epigenetic principal components and cell subsets (identical to those released by NIAGADS) for use as covariates in analyses using the clock data, where desired.

### B. The HRS Methylation Sample of Respondents

DNA methylation assays were done on a subsample (n=4,104) people who participated in the 2016 Venous Blood Study. The sample includes all the participants of the 2016 Healthy Cognitive Aging Project (HCAP) who have provided blood samples, younger participants designated for future HCAP assessments, and a subsample of HCAP non-participants. This subsample fully represents the entire HRS sample. A total of 4,018 samples passed QC. The sample is 58% Female and has a median age of 68.7 years. It is racially diverse: Non Hispanic White (n=2,669, 66.4%), Non Hispanic Black (n=658, 16.4%), Hispanic (n=567, 14.11%), Non Hispanic Other (n=124, 3%). The sample is also socioeconomically diverse. The educational distribution is less than High School (16.8%), High School / GED (52.12%), Some College (5.97%), College + (24.1%), Other (1%).

### C. Collection

The 2016 VBS blood collection was managed by Hooper Holmes Health & Wellness. The phlebotomy service was provided with the names, addresses, and phone numbers of consenting respondents and contacted respondents to set appointments. Collection materials were mailed to the phlebotomists' homes in advance of the scheduled visit. Every attempt was made to schedule the blood draw within 4 weeks of the HRS core interview. Fasting was recommended and preferred but not required. Phlebotomists noted the fasting status of the samples. We collected 50.5 mL of blood in 6 tubes – 1 x 8 mL CPT tube, 3 x 10 mL double gel serum separator tubes (SST), 1 x 10 mL EDTA whole blood tube, and a 2.5 mL PAXgene RNA tube. The SST tubes are centrifuged in the field before being shipped overnight to the CLIA-certified Advanced Research and Diagnostic Laboratory at the University of Minnesota. Tube processing is done within 24 hours of arrival at the lab (within 48 hours of collection). DNA for methylation analysis was done using DNA extracted from the EDTA tube.

More information on the 2016 Venous Blood Study, including details on sampling, consent, and administration, is provided VBS 2016 Data Description.

### D. Protocols for DNA Methylation Data

DNA methylation data are based on assays done using the Infinium Methylation EPIC BeadChip at the University of Minnesota. Samples were randomized across plates by key demographic variables (i.e.

age, cohort, sex, education, race/ethnicity) with 40 pairs of blinded duplicates. Analysis of duplicate samples showed a correlation  $>0.97$  for all CpG sites.

The *minfi* package in R software was used for data preprocessing, and quality control. 3.4% of the methylation probes (n=29,431 out of 866,091) were removed from the final dataset due to suboptimal performance (using a detection P-value threshold of 0.01). Analysis for detection P-value failed samples was done after removal of detection P-value failed probes. Using a 5% cut-off (*minfi*) we remove 58 samples. We also removed sex mismatched samples and any controls (cell lines, blinded duplicates). High quality methylation data is available for 97.9% samples (n=4,018).

Prior to the estimation of the Grim2, missing beta methylation values were imputed with the median beta methylation value of the given probe across all samples.

### E. Subsample Weights

Respondents with at least one valid venous blood result (VBS16VALID) were assigned a VBS weight. The weights were adjusted for the differential probabilities of participation by dividing the HRS 2016 sample weight by the predicted probability of having a valid venous blood result among community-dwelling 2016 HRS respondents born prior to 1960, excluding all members of the LBB cohort. The resulting interim weight was trimmed at the 1st and 99th percentiles and was then post stratified back to the entire 2016 HRS sample born prior to 1960 by age, sex, and race/ethnicity. Two separate respondent-level weights were created for the VBS 2016 Innovative Sub Sample and should be used for analyses of data from that sample. **VBSI16WGTRA should be used for analyses including DNA methylation and epigenetic clocks.** Sample weights can be found in the HRS Tracker data file.

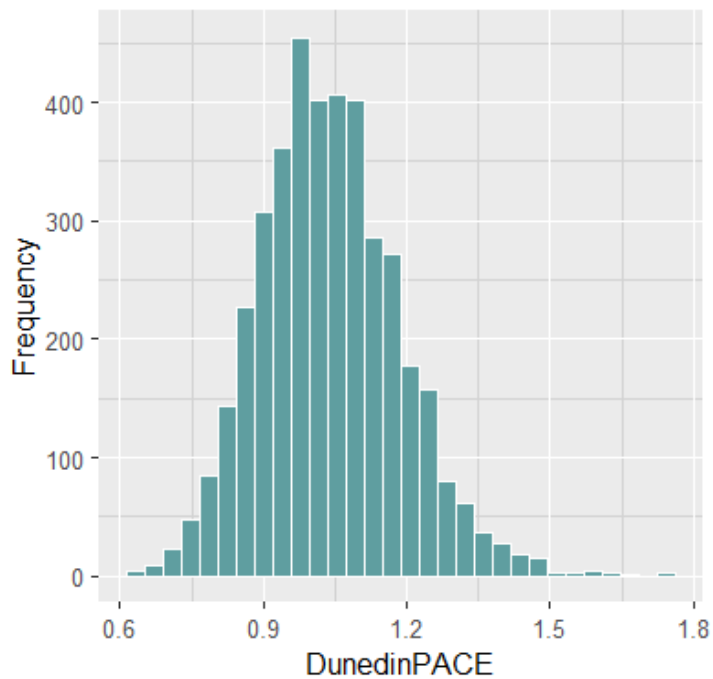
## II. Individual Clocks

### A. PACE

DunedinPACE, the first multi-tissue epigenetic clock, was developed using 817 human blood samples from the Dunedin Study, incorporating 173 CpG sites in order to estimate the DNA methylation pace of aging. They reported high test-retest reliability, and associations with morbidity, disability, and mortality.

HRS PACE details are presented below.

	Sample Size	Min	Max	Range	Median	Mean	SE (mean)
PACE	4018	0.63	1.74	1.11	1.03	1.04	0.002



#### Reference

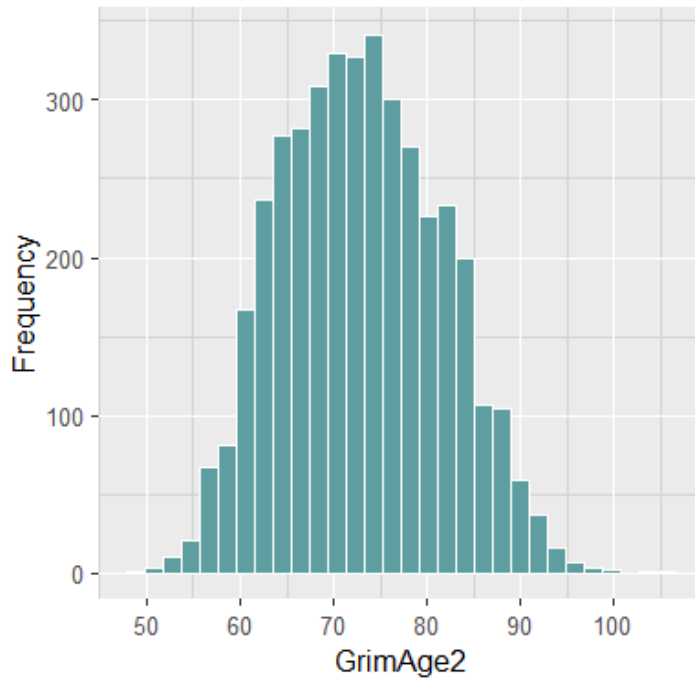
Belsky D.W., Caspi A, Corcoran D.L., et al. (2022). DunedinPACE, a DNA methylation biomarker of the pace of aging. *eLife*, 11:e73420.

## B. Grim2

The GrimAge Version 2 clock is a blood-based age estimator, based on DNA methylation at 1030 CpGs selected from the Illumina EPIC array (Lu 2022). Lu et al. developed this clock based on the whole blood of 1833 humans at ages 59 to 73 from the Framingham Heart Study (FHS). They reported a strong correlation with age for this clock ( $r \sim 0.72$  to  $0.94$ ) and that the age acceleration component strongly predicts time-to-death ( $P=3.6e-167$ ). Both the GrimAge Version 2 score and its sub components are included in the data release file.

HRS Grim2 details are presented below.

	Sample Size	Min	Max	Range	Median	Mean	SE (mean)
Grim2	4018	48.77	105.51	56.74	72.62	72.91	0.13



### Reference

Lu A.T., Binder A.M., Zhang J, et al. (2022). DNA methylation GrimAge version 2. *Aging (Albany NY)*, 14(23), 9484.

### III. If You Need to Know More

This document is intended to serve as a brief overview to the HRS Epigenetic Clock Supplement data product. If you have questions or concerns that are not adequately covered here or on our Web site, or if you have any comments, please contact us. We will do our best to provide answers.

#### A. HRS Internet Site

Health and Retirement Study public release data and additional information about the study are available on the Internet. To access public data or to find out more about restricted data products and procedures, visit the [HRS Web site](#).

#### B. Contact Information

If you need to contact us, you may do so by one of the methods listed below.

Internet: Help Desk at the HRS Web site (<http://hrsonline.isr.umich.edu>)

E-mail: [hqsquestions@umich.edu](mailto:hqsquestions@umich.edu)

Postal Service:

Health and Retirement Study  
The Institute for Social Research  
426 Thompson Street  
Ann Arbor, Michigan 48104

#### C. Citing this Document

Please include the following citation in any research reports, papers, or publications based on these data along with the citation for the reference epigenetic clock:

In text: "The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan."

In references: "Smith T, Crimmins EM, Faul JD. HRS Epigenetic Clocks – Supplement. Ann Arbor, MI: Survey Research Center, Institute for Social Research, University of Michigan; 2025."

## IV. References

Belsky D.W., Caspi A, Corcoran D.L., et al. (2022). DunedinPACE, a DNA methylation biomarker of the pace of aging. *eLife*, 11:e73420.

Crimmins, E., Faul, J., Thyagarajan, B., & Weir, D. (2017). Venous blood collection and assay protocol in the 2016 Health and Retirement Study 2016 Venous Blood Study (VBS). In (pp. 1-73). Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan.

Lu A.T., Binder A.M., Zhang J, et al. (2022). DNA methylation GrimAge version 2. *Aging (Albany NY)*, 14(23), 9484.