23\_mepigen\_clocks+exposure\_table 2 shell\_draft3e\_0424.doc (ver: 04/24/23)

NK table shell: 11/14/21

CT edit: 11/18/21, 11/22/21, 12/09/21, 12/10/21, 01/04/22, 01/11/22, 04/20/23

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2. Chronological age, epigenetic clock and accelerated aging data and epigenetic assay covariates: *My Body My Story* study (MBMS; Boston, MA, 2008-2010; ages 35-64 years) and Multi-Ethnic Study of Atherosclerosis (MESA; 6 US sites, Exam 5 epigenetic subsample, 2010-2012; ages 55-94 years).** | | | | | | | | | | | | |
|  | **Chronological age, epigenetic clocks and measures of accelerated aginga: mean (SD [standard deviation])** | | | | | | | | | | | |
| **Variable** | **My Body My Story (MBMS) (N = 293)** | | | **Multi-Ethnic Study of Atherosclerosis (MESA, Exam 5) (N = 1262)b** | | | | | | | | |
|  | **Total (all US-born)** | **Black non-Hispanic** | **White non-Hispanic** | **Total** | **US-born** | | | | **Not US-born** | | | |
|  |  |  |  | **Total: US-born** | **Black non-Hispanic** | **White non-Hispanic** | **Hispanic** | **Total: not US-born** | **Black non-Hispanic** | **White non-Hispanic** | **Hispanic** |
| **Total: N** | 293 | 224 | 69 | 1262 | 975 | 229 | 555 | 191 | 287 | 41 | 35 | 211 |
| **Chronological age: mean (SD)** | 49.0 (7.9) | 49.0 (7.8) | 48.7 (8.3) | 69.6 (9.4) | 70.0 (9.3) | 71.0 (8.9) | 70.1 (9.5) | 68.4 (8.9) | 68.2 (9.6) | 64.4 (7.8) | 71.3 (9.4) | 68.4 (9.7) |
| **Raw estimates: mean (SD)** |  |  |  |  |  |  |  |  |  |  |  |  |
| **1st Generation** |  |  |  |  |  |  |  |  |  |  |  |  |
| **-- Age estimator** |  |  |  |  |  |  |  |  |  |  |  |  |
| Hannumc | 42.01 (6.96) | 41.66 (6.78) | 43.13 (7.44) | 72.93 (8.65) | 73.43 (8.51) | 72.26 (8.00) | 74.27 (8.62) | 72.39 (8.53) | 71.21 (8.92) | 66.88 (7.72) | 75.10 (7.81) | 71.41 (9.00) |
| Horvathc | 50.04 (7.82) | 50.23 (7.49) | 49.41 (8.82) | 63.82 (8.72) | 64.39 (8.62) | 64.58 (8.14) | 65.13 (8.43) | 62.03 (9.34) | 61.85 (8.78) | 58.36 (6.43) | 65.15 (7.98) | 61.98 (9.09) |
| Zhang (age) | 48.85 (7.84) | 48.62 (7.52) | 49.60 (8.83) | 70.70 (7.89) | 71.22 (7.74) | 70.89 (7.31) | 71.92 (7.92) | 69.58 (7.47) | 68.94 (8.18) | 64.51 (7.32) | 72.35 (6.75) | 69.24 (8.22) |
| **-- Mitotic age** |  |  |  |  |  |  |  |  |  |  |  |  |
| MiAgec | 807.91 (136.97) | 820.59 (143.34) | 766.72 (104.52) | 735.45 (92.96) | 734.38 (92.53) | 770.84 (101.45) | 718.46 (81.05) | 736.97 (100.17) | 739.08 (94.47) | 744.22 (99.01) | 709.83 (105.16) | 742.94 (91.29) |
| EpiTocc | 0.06 (0.01) | 0.06 (0.02) | 0.06 (0.01) | 0.09 (0.01) | 0.09 (0.01) | 0.09 (0.01) | 0.09 (0.00) | 0.09 (0.01) | 0.09 (0.01) | 0.09 (0.01) | 0.09 (0.00) | 0.09 (0.01) |
| **-- Telomere length** |  |  |  |  |  |  |  |  |  |  |  |  |
| DNAmTL | -0.87 (0.25) | -0.84 (0.25) | -0.96 (0.24) | -1.12 (0.23) | -1.14 (0.22) | -1.02 (0.19) | -1.19 (0.21) | -1.14 (0.23) | -1.07 (0.23) | -0.90 (0.21) | -1.20 (0.20) | -1.08 (0.22) |
| **2nd Generation** |  |  |  |  |  |  |  |  |  |  |  |  |
| **-- Age estimator** |  |  |  |  |  |  |  |  |  |  |  |  |
| Phenoage | 41.82 (8.10) | 42.13 (7.93) | 40.80 (8.62) | 71.77 (9.29) | 72.16 (9.24) | 72.52 (9.12) | 72.30 (9.21) | 71.35 (9.48) | 70.41 (9.35) | 67.39 (7.97) | 73.99 (8.15) | 70.41 (9.61) |
| DunedinPoAm (pace of aging) | 1.13 (0.09) | 1.14 (0.09) | 1.10 (0.10) | 1.06 (0.08) | 1.06 (0.08) | 1.10 (0.08) | 1.05 (0.07) | 1.06 (0.07) | 1.05 (0.07) | 1.08 (0.07) | 1.06 (0.08) | 1.05 (0.07) |
| **-- Mortality predictor** |  |  |  |  |  |  |  |  |  |  |  |  |
| Zhang (mortality) c | -1.15 (0.43) | -1.15 (0.44) | -1.18 (0.43) | -1.90 (0.36) | -1.86 (0.35) | -1.88 (0.38) | -1.84 (0.33) | -1.92 (0.36) | -2.00 (0.37) | -2.19 (0.39) | -1.85 (0.42) | -1.99 (0.34) |
| GrimAge | 54.49 (7.18) | 54.77 (6.96) | 53.56 (7.82) | 79.37 (8.13) | 79.84 (8.05) | 81.52 (7.64) | 79.52 (8.04) | 78.73 (8.29) | 77.81 (8.22) | 74.60 (6.65) | 80.58 (7.55) | 77.97 (8.43) |
| **Accelerated aging estimators (detrended for age): mean (SD)** |  |  |  |  |  |  |  |  |  |  |  |  |
| **1st Generation** |  |  |  |  |  |  |  |  |  |  |  |  |
| **-- Age estimator** |  |  |  |  |  |  |  |  |  |  |  |  |
| Hannumc | 0.00 (4.95) | -0.39 (4.59) | 1.26 (5.84) | 0.00 (4.74) | 0.19 (4.78) | -1.74 (4.97) | 0.94 (4.44) | 0.34 (4.91) | -0.66 (4.53) | -2.08 (4.49) | 0.81 (4.53) | -0.63 (4.48) |
| Horvathc | 0.00 (6.21) | 0.15 (5.85) | -0.50 (7.27) | 0.00 (5.43) | 0.29 (5.43) | -0.25 (5.20) | 0.93 (5.00) | -0.96 (6.53) | -0.97 (5.33) | -1.70 (5.16) | 0.05 (4.69) | -1.00 (5.46) |
| Zhang (age) | 0.00 (4.78) | -0.28 (4.27) | 0.92 (6.12) | 0.00 (3.17) | 0.21 (3.11) | -0.89 (3.08) | 0.82 (3.01) | -0.24 (2.99) | -0.71 (3.30) | -2.22 (3.98) | 0.29 (2.53) | -0.58 (3.18) |
| **-- Mitotic age** |  |  |  |  |  |  |  |  |  |  |  |  |
| MiAgec | 0.00 (134.77) | 12.48 (140.50) | -40.52 (105.25) | 0.00 (91.95) | -1.66 (91.39) | 33.35 (100.97) | -17.76 (80.36) | 3.17 (97.43) | 5.62 (93.75) | 16.28 (101.05) | -28.19 (104.68) | 9.16 (89.59) |
| EpiTocc | 0.00 (0.01) | 0.00 (0.02) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.01) |
| **-- Telomere length** |  |  |  |  |  |  |  |  |  |  |  |  |
| DNAmTL | 0.00 (0.23) | 0.03 (0.23) | -0.09 (0.21) | 0.00 (0.19) | -0.01 (0.19) | 0.12 (0.16) | -0.06 (0.17) | -0.03 (0.20) | 0.04 (0.19) | 0.15 (0.16) | -0.06 (0.16) | 0.03 (0.19) |
| **2nd Generation** |  |  |  |  |  |  |  |  |  |  |  |  |
| **-- Age estimator** |  |  |  |  |  |  |  |  |  |  |  |  |
| Phenoage | 0.00 (6.68) | 0.28 (6.37) | -0.89 (7.57) | 0.00 (5.91) | 0.09 (5.96) | -0.31 (6.29) | 0.13 (5.86) | 0.45 (5.83) | -0.31 (5.77) | -0.44 (6.34) | 0.87 (5.14) | -0.48 (5.76) |
| DunedinPoAm | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **-- Mortality predictor** |  |  |  |  |  |  |  |  |  |  |  |  |
| Zhang (mortality) c | 0.00 (0.43) | 0.01 (0.44) | -0.03 (0.43) | 0.00 (0.35) | 0.03 (0.35) | 0.00 (0.38) | 0.05 (0.33) | -0.01 (0.35) | -0.09 (0.35) | -0.24 (0.37) | 0.02 (0.42) | -0.09 (0.32) |
| GrimAge | 0.00 (4.81) | 0.24 (4.71) | -0.79 (5.07) | 0.00 (4.14) | 0.16 (4.23) | 1.10 (4.55) | -0.24 (4.10) | 0.20 (4.04) | -0.55 (3.75) | -0.93 (3.01) | -0.12 (4.70) | -0.54 (3.71) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Predicted cell type proportion estimates: mean (SD)d** |  |  |  |  |  |  |  |  |  |  |  |  |
| B cell | 0.07 (0.02) | 0.08 (0.02) | 0.06 (0.01) | 0.03 (0.03) | 0.03 (0.02) | 0.04 (0.03) | 0.03 (0.02) | 0.03 (0.02) | 0.04 (0.03) | 0.04 (0.04) | 0.03 (0.02) | 0.04 (0.03) |
| CD4T | 0.17 (0.05) | 0.17 (0.05) | 0.15 (0.04) | 0.03 (0.02) | 0.03 (0.02) | 0.04 (0.02) | 0.03 (0.03) | 0.03 (0.01) | 0.03 (0.02) | 0.04 (0.02) | 0.03 (0.01) | 0.03 (0.02) |
| CD8T | 0.00 (0.01) | 0.01 (0.02) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.00) |
| Eosinophil | 0.01 (0.02) | 0.01 (0.02) | 0.00 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) |
| Monocyte | 0.12 (0.02) | 0.12 (0.02) | 0.12 (0.02) | 0.91 (0.04) | 0.91 (0.04) | 0.90 (0.05) | 0.91 (0.04) | 0.92 (0.04) | 0.91 (0.04) | 0.90 (0.05) | 0.91 (0.03) | 0.91 (0.05) |
| Neutrophil | 0.57 (0.10) | 0.55 (0.10) | 0.62 (0.08) | 0.00 (0.00) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.01) | 0.00 (0.01) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) |
| Natural Killer | 0.10 (0.04) | 0.11 (0.04) | 0.09 (0.04) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.01) | 0.01 (0.02) |
| a The raw data are the values of the epigenetic clocks, not detrended for age. Accelerated aging is detrended for age and refers to the residuals when epigenetic age is regressed on chronological age for each of the MBMS and MESA populations; an accelerated aging value greater than 0 indicates the participant’s epigenetic clock value exceeded the predicted epigenetic clock value for that participant given their chronological age.  b MBMS inclusion criteria were that all participants had to self-identify as being US-born and being either Black non-Hispanic or white non-Hispanic; MESA did not have these nativity restrictions, and in the Exam 5 epigenetic subsample, 77.1% were US-born and 22.7% were born outside of the US.  c These clocks contain CpG sites which are not available on the EPIC array, consequently their values in MBMS will be based on the available subset of clock CpG sites.  d Cell type proportions for blood samples were estimated from DNA methylation levels measured in the samples and in purified cell types [ref1, ref2]. In MESA, samples were purified using flow cytometry to contain >90% monocytes [ref3], consistent with our estimates showing 91% monocyte content on average.  [ref1] Houseman, E. A. et al. DNA methylation arrays as surrogate measures of cell mixture distribution. *BMC Bioinformatics* 13, 86 (2012).  [ref2] Reinius, L. E. et al. Differential DNA methylation in purified human blood cells: implications for cell lineage and studies on disease susceptibility. *PLoS ONE* 7, e41361 (2012).  [ref3] Reynolds LM, Taylor JR, Ding J, et al. Age-related variations in the methylome associated with gene expression in human monocytes and T cells. *Nat Commun*. 2014;5:5366. Published 2014 Nov 18. doi:10.1038/ncomms6366 | | | | | | | | | | | | |

CITATIONS FOR CLOCKS

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| --- | --- |
| **Horvath** | Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol.* 2013;14(10):R115. doi: 10.1186/gb-2013-14-10-r115. Erratum in: *Genome Biol.* 2015;16:96. PMID: 24138928; PMCID: PMC4015143. |
| **Hannum** | Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y, Deconde R, Chen M, Rajapakse I, Friend S, Ideker T, Zhang K. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell.* 2013 Jan 24;49(2):359-367. doi: 10.1016/j.molcel.2012.10.016. Epub 2012 Nov 21. PMID: 23177740; PMCID: PMC3780611. |
| **EpiToc (Yang)** | Yang Z, Wong A, Kuh D, Paul DS, Rakyan VK, Leslie RD, Zheng SC, Widschwendter M, Beck S, Teschendorff AE. Correlation of an epigenetic mitotic clock with cancer risk. *Genome Biol.* 2016 Oct 3;17(1):205. doi: 10.1186/s13059-016-1064-3. PMID: 27716309; PMCID: PMC5046977. |
| **Zhang (2019)** | Zhang Q, Vallerga CL, Walker RM, Lin T, Henders AK, Montgomery GW, He J, Fan D, Fowdar J, Kennedy M, Pitcher T, Pearson J, Halliday G, Kwok JB, Hickie I, Lewis S, Anderson T, Silburn PA, Mellick GD, Harris SE, Redmond P, Murray AD, Porteous DJ, Haley CS, Evans KL, McIntosh AM, Yang J, Gratten J, Marioni RE, Wray NR, Deary IJ, McRae AF, Visscher PM. Improved precision of epigenetic clock estimates across tissues and its implication for biological ageing. *Genome Med*. 2019 Aug 23;11(1):54. doi: 10.1186/s13073-019-0667-1. PMID: 31443728; PMCID: PMC6708158. |
| **MiAge(Youn and Wang)** | Youn A, Wang S. The MiAge Calculator: a DNA methylation-based mitotic age calculator of human tissue types. *Epigenetics*. 2018;13(2):192-206. doi: 10.1080/15592294.2017.1389361. Epub 2018 Feb 6. PMID: 29160179; PMCID: PMC5873367. |
| **DNAmTL (Lu)** | Lu AT, Seeboth A, Tsai PC, Sun D, Quach A, Reiner AP, Kooperberg C, Ferrucci L, Hou L, Baccarelli AA, Li Y, Harris SE, Corley J, Taylor A, Deary IJ, Stewart JD, Whitsel EA, Assimes TL, Chen W, Li S, Mangino M, Bell JT, Wilson JG, Aviv A, Marioni RE, Raj K, Horvath S. DNA methylation-based estimator of telomere length. *Aging* (Albany NY). 2019 Aug 18;11(16):5895-5923. doi: 10.18632/aging.102173. Epub 2019 Aug 18. PMID: 31422385; PMCID: PMC6738410. |
| **Zhang mortality** | Zhang Y, Wilson R, Heiss J, Breitling LP, Saum KU, Schöttker B, Holleczek B, Waldenberger M, Peters A, Brenner H. DNA methylation signatures in peripheral blood strongly predict all-cause mortality. *Nat Commun.* 2017 Mar 17;8:14617. doi: 10.1038/ncomms14617. PMID: 28303888; PMCID: PMC5357865. |
| **PhenoAge (Levine)** | Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, Hou L, Baccarelli AA, Stewart JD, Li Y, Whitsel EA, Wilson JG, Reiner AP, Aviv A, Lohman K, Liu Y, Ferrucci L, Horvath S. An epigenetic biomarker of aging for lifespan and healthspan. *Aging* (Albany NY). 2018 Apr 18;10(4):573-591. doi: 10.18632/aging.101414. PMID: 29676998; PMCID: PMC5940111. |
| **DunedinPoAm** | Belsky DW, Caspi A, Arseneault L, Baccarelli A, Corcoran DL, Gao X, Hannon E, Harrington HL, Rasmussen LJ, Houts R, Huffman K, Kraus WE, Kwon D, Mill J, Pieper CF, Prinz JA, Poulton R, Schwartz J, Sugden K, Vokonas P, Williams BS, Moffitt TE. Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. *Elife*. 2020 May 5;9:e54870. doi: 10.7554/eLife.54870. PMID: 32367804; PMCID: PMC7282814. |
| **GrimAge** | Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, Hou L, Baccarelli AA, Li Y, Stewart JD, Whitsel EA, Assimes TL, Ferrucci L, Horvath S. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging* (Albany NY). 2019 Jan 21;11(2):303-327. doi: 10.18632/aging.101684. PMID: 30669119; PMCID: PMC6366976. |

**SUPPLEMENTAL TABLE FOR THE CLOCKS (per what Sarah sent us on Oct 1, 2021)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clock** | **Reference** | **Generation** | **n CpGs** | **n biomarkers** | **Biomarker details** | **Training data** | **Test data** | **Summary** |
| **Horvath** | Horvath, S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14:R115. | 1st | 353 | 0 | NA | Uses 39 datasets, **total n**=3931, **array** = 27k (26) and 450k (13), **sample type** = 27 tissue/cell types | uses 31 datasets, **total n**=3211, **array** = 27k (20) and 450k (11), **sample type** = 22 tissue/cell types | The Horvath clock was designed as a multi-tissue age estimator. 353 CpGs were selected by regressing a transformed version of chronological age on all CpGs, using elastic net. To construct the clock, CpGs are weighted by their regression coefficients, and the average of these is taken to produce an epigenetic age estimate. |
| **Hannum** | Hannum, G, Guinney, J, Zhao, L, Zhang, L, Hughes, G. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell. 2013;49:359-367 | 1st | 71 | 0 | NA | **n**=656 (GSE40279) **sample type** = whole blood, **array** = 450k | NA | The Hannum clock is a blood-based age estimator. They used elsatic net which selected 71 CpGs (including gender, BMI, diabetes status, ethnicity, and batch in the model). CpGs are weighted by their regression coefficients, and the average of these is taken to produce an epigenetic age estimate. |
| **EpiToc (Yang)** | Yang, Z, Wong, A, Kuh, D, et al. Correlation of an epigenetic mitotic clock with cancer risk. Genome Biol. 2016;17:205. | 1st | 385 | 0 | NA | **n**=656 (GSE40279) **sample type** = whole blood, **array** = 450k | GSE42861 (controls only), **n**=335, **sample type** = PBL, **array** = 450k | EpiToc is a mitotic clock indicating the number of stem cell divisions. CpGs are selected by regressing age on DNA methylation sites (adjusting for cell type, batch and sex), and 385 sites which were associated with age at FDR<0.05, within 200bp of transcription start sites, become hypermethylated with age, and marked with PRC2 in HESCs were taken forward to make up the clock. The clock is calculated as the average DNA methylation across the 385 sites. |
| **Zhang (2019)** | Zhang, Q, Vallerga, CL, Walker, RM, et al. Improved precision of epigenetic clock estimates across tissues and its implication for biological ageing. Genome Med. 2019;11:54. | 1st | 514 | 0 | NA | **n**=13566 (13 datasets), **sample type**= whole blood (n=13307) + saliva (n=259), **array**=450k and EPIC (reduced to common sites) | **n**=95 (GSE41169), **sample type** = whole blood, **array**=450k | This clock aimed to build a 'perfect' age estimator by using a much larger training dataset. They create two predictors by regressing age on DNA methylation, one using elastic net and one using BLUP; they select elastic net as the most accurate predictor, using 514 CpGs. The clock is built using the weighted average of the CpGs (using model coefficients) plus the model intercept. |
| **MiAge(Youn and Wang)** | Youn, A, Wang, S. The MiAge Calculator: a DNA methylation-based mitotic age calculator of human tissue types. Epigenetics. 2018;13:192-206. | 1st | 268 | 0 | NA | **n**=4020 8 TGCA cancer + adjacent normal tissue datasets (BRCA, COAD, HNSC, KIRP, LIHC, PRAD, THCA, UCEC), **array** = 450k, **sample type** = tumour and adjacent tissue | **n**=2221 5 TGCA cancer +adjacent normal tissue (BLCA, KIRC, LUAD, LUSC, and STAD), **array**=450k, **sample type** = tumour and adjacent tissue | MiAge is a mitotic age estimator, estimating cell divisions. 268 DNAm sites that increase with age were selected using a formula that uses probabilities to calculate change from predicted original methylation level at each site (with change estimating the number of cell divisions; increased number of divisions will result in a greater number of somatic replication errors). The clock is calculated by comparing methylation at each CpG to the expected level under the MiAge model, and the resulting clock is the sum of squares of the difference between observed and expected methylation levels, summed over all samples at each CpG, and then summed over all CpGs. |
| **DNAmTL (Lu)** | Lu, AT, Seeboth, A, Tsai, P, et al. DNA methylation-based estimator of telomere length. Aging (Albany NY). 2019;11:5895-5923 |  | 140 | 0 | They use telomere length to represent aging | **n**=2256 (718 from WHI and 1538 from JHS), **array** = 450k (WHI) and EPIC (JHS), **sample type** = blood | Test 1: **n**=1078 (100 WHI, 100 JHS, 878 FHS). Test 2: **n** = 9815 (Bogalusa, Twins UK, Lothian Birth cohorts, InCHIANTI), **array** = 450k(FHS, WHI, InCHIANTI,Lothian Birth cohorts, Bogalusa, Twins UK) and EPIC (JHS), **sample type** =blood | DNAmTL is a DNA methylation estimator of telomere length. Leukocyte telomere length was regressed on blood DNA methylation to select 140 CpGs that were associated with telomere length, using elastic net. DNAmTL is constructed by taking the weighted average of these CpGs. The authors find that DNAmTL is more closely related to age than measured telomere length. |
| **Zhang mortality** | Zhang, Y, Wilson, R, Heiss, J, et al. DNA methylation signatures in peripheral blood strongly predict all-cause mortality. Nat Commun. 2017;8:14617 | 2nd | 514 | 1 | all cause mortality | ESTHER cohort (**n**=954 discovery and 1000 validation). **Sample type** = whole blood, **array** = 450k | KORA cohort (**n**=1727) **sample type** = whole blood, **array** = 450k | The Zhang mortality clock is a mortality predictor, with a higher score indicating a higher risk of mortality. 58 CpGs were found to be assocaited with all-cause mortality using Cox regression; from these 10 CpGs were selected to comprise the mortality score using LASSO Cox regression. The mortality score is constructed by taking the weighted average of the CpGs (using the LASSO coefficients to weight them). |
| **PhenoAge (Levine)** | Levine, ME, Lu, AT, Quach, A, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY). 2018;10:573-591. | 2nd | 513 | 10 (selected from 43 using cox penalised regression - hazard of aging related mortality regressed on biomarkers) | Albumin, Creatanine, serum glucose, log CRP, lymphocyte %, MCV (mean red cell volume), red cell distribution width, alkaline phosphatase, white blood cell count, age. **Construction**: parametric proportional hazards model estimating 10 year mortality risk, converted to units of years | phenoage biomarker prediction: NHANES III to select biomarkers (**n**=9926) and NHANES IV to validate (**n**=6209). DNAm site selection in InCHIANTI (**n**=456), sites common to 27k/450k/epic, **sample type** = buffy coat, **array**=450k. | **n** = 7417 (4207 WHI; 2553 FHS; 657 NAS; 1747 JHS). **Array** = 450k (WHS, FHS, NAS), EPIC (JHS). **Sample type** = blood | Phenoage was developed using three steps. Firstly, a composite measure of 'phenotypic age' was constructed by regressing the hazard of aging-related mortality on 42 clinical biomarkers plus chronological age, using Cox penalised regression. Nine biomarkers plus chronological age were selected and in the second step these were combined via a parametric proportional hazards model estimating 10 year mortality risk, converted to units of years to form a phenotypic age estimate. As the final step, this phenotypic age estimate was then regressed on DNA methylation data using elastic net, which selected 513 CGs. The Phenoage estimate of age, in years, is then calculated using the weighted average of the 513 CpGs, using the elastic net coefficients for weighting. |
| **DunedinPoAm** | Belsky DW, Caspi A, Arseneault L, Baccarelli A, Corcoran DL, Gao X, et al. Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. eLife. 2020;9. | 2nd | 46 | 18 (selected as these were the only ones measured at all 3 timepoints) | HbA1C, Cardiorespiratory Fitness (rev), Waist-hip ratio, FEV1/FVC (rev), FEV1 (rev), Mean arterial pressure, BMI, Leukocyte telomere length (rev), Creatinine clearance (rev), Urea Nitrogen, Lipoprotein(a), Triglycerides, Gum health, Total cholesterol, White blood cell count, hsCRP, HDL cholesterol (rev), ApoB100/ApoA1. **Construction**: all scaled to mean of 0 and SD of 1, with some reversed | **Dunedin cohort. n:** 810. **Sample type:** whole blood. **Array**: 450k | **n**=3019 (1175 US; 771 NAS; 1658 E-Risk; 186 CALERIE) **sample type** = whole blood, **array** = 450k (NAS, E-Risk), EPIC (US, CALERIE) | DunedinPoAm was created by firstly modelling rate of change in 18 biomarkers over 12 years in the same individuals. The rates of change were combined into a composite measure termed 'Pace-of-Aging'. Then elastic net was used to select CpG sites that predict this 'Pace-of-Aging' measure. |
| **GrimAge** | Lu, AT, Quach, A, Wilson, JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY). 2019;11:303-327. | 2nd | 1030 | 7 (selected from 88 as they are physiological risk factors and stress factors, and had DNAm sites in elastic net, and are predictive of mortality), plus age sex and DNAm smoking pack-years | chronological age (Age), sex (Female), and DNAm based surrogates for smoking pack‐years (DNAm PACKYRS), adrenomedullin levels (DNAm ADM), beta‐2 microglobulin (DNAm B2M), cystatin C (DNAm Cystatin C), growth differentiation factor 15 (DNAm GDF‐15), leptin (DNAm Leptin), plasminogen activation inhibitor 1 (DNAm PAI‐1), tissue inhibitor metalloproteinase 1 (DNAm TIMP‐1). | FHS offspring study: trainingsubset **n**=1731. **Sample type** = buffy coat, **array** = 450k | **n**=7375 (FHS offspring study test subset n=625, WHI BA23 (N=2107), WHI EMPC (N=1972), JHS (N=1747), and InChianti study (N=924)), **sample type** = blood, **array**= 450k (FHS, WHI, InCHIANTI) and EPIC (JHS) | GrimAge was created using a two step process. In the first step, elastic net was used to identify DNAm sites that could be used as surrogate markers for 88 plasma proteins and smoking pack years (including chronological age and sex in the models). 12 of these surrogate markers plus smoking pack years were sufficiently accurate in training and test datasets. The second step regresses time to death (all cause mortality) on chronological age, sex, 12 DNAm surrogate protein markers and DNAm markers for smoking pack years; 7 DNAm markers plus age, sex and the pack-years DNAm markers were selected by the model, then the linear combination of the selected variables is transformed into an age estimate. |