

Low back pain, disability, and biological aging: routinely measurable clinical clocks versus epigenetic clocks (NHANES)

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Research Article

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Abstract

Purpose.

In small, selected samples, biological-age clocks have been associated with low back pain and disability, raising the prospect of an aging-based risk marker. It remains untested whether a clinical clock measurable at the bedside carries the same signal as the epigenetic clocks that cannot reach it, and whether either tracks low back pain in an unselected national population. We compared routinely measurable clinical aging clocks with epigenetic clocks for their association with low back pain and disability in a nationally representative sample.

Methods.

Cross-sectional analysis of NHANES 1999–2002 adults, reported following STROBE. Clinical clocks (phenotypic age [PhenoAge], Klemmera–Doubal biological age) were derived from routine blood chemistry; epigenetic clocks (first-generation, second-generation, and pace-of-aging) from the DNA-methylation subsample. Outcomes were self-reported low back pain in the past three months and physical-function disability. We used survey-weighted regression with hierarchical false discovery rate control; the same-name pair, clinical PhenoAge versus its methylation counterpart (DNAm-PhenoAge), was the primary contrast.

Results.

In the DNA-methylation subsample ($n = 2,532$ with complete clock and covariate data; design-effective $n \approx 1,268$), no aging clock was associated with low back pain in the past three months. Adjusted odds ratios per SD ranged from 0.64 to 0.99, and every 95% confidence interval crossed 1 (clinical PhenoAge 0.64, 0.25–1.65; DNAm-PhenoAge 0.84, 0.49–1.42). The same-name pair showed no difference between clinical PhenoAge and DNAm-PhenoAge (ratio of odds ratios 0.80, 0.15–4.25; $p = 0.79$). No clock was associated with physical-function disability after false discovery rate control. The only association reaching nominal significance was between clinical PhenoAge and the deficit-accumulation frailty index ($p = 0.012$), an expected correlation given their shared physiological inputs.

Conclusion.

Neither routinely measurable clinical aging clocks nor epigenetic clocks were associated with low back pain or disability, and the two phenotypic-age measures showed no significant difference. The aging-clock signals reported in small, selected cohorts did not generalise to the population. Biological-age acceleration is not a bedside risk marker for low back pain, and epigenetic clocks add no value over clinical clocks for this outcome.

1. Introduction

Low back pain is the leading global cause of years lived with disability, and its burden rises steeply with age [1]. Yet chronological age poorly predicts which older adults develop disabling low back pain—patients of the same age differ widely in their course. Persistent and recurrent low back pain accounts for most of this disability [2], and identifying who is at risk remains an unmet clinical need.

Spine practice already recognises this gap. Frailty, an accumulation of health deficits reflecting biological rather than chronological aging, predicts adverse surgical outcomes better than age; once frailty is accounted for, chronological age is no longer an independent predictor of adverse events [3], and frailty indices outperform age and comorbidity thresholds for complications and mortality after spinal surgery [4]. Each observation rests on one premise: how fast a patient has biologically aged may refine spine risk beyond the calendar. Whether the same holds for the onset of disabling low back pain, rather than for poorer surgical outcomes, remains open.

Biological aging can now be quantified directly, beyond the clinical deficits frailty counts. It manifests as measurable hallmarks—epigenetic change, cellular senescence, telomere attrition—that can be condensed into aging clocks [5]. Two clock families differ in a way that matters clinically. Clinical clocks, such as phenotypic age, are computed from routine blood chemistry a clinician already orders [6]; epigenetic clocks—first-generation chronological predictors, second-generation mortality predictors, and pace-of-aging measures—require DNA methylation, which is not available at the bedside. The distinction is practical: a clinical clock that captured the relevant signal would be deployable at no added cost, whereas an epigenetic clock would not.

The promise rests on small, selected samples. Among 118 adults, a faster pace of biological aging separated chronic low back pain from pain-free controls with one of the largest effect sizes reported for any pain biomarker [7]; among 83 adults with spinal deformity, biological-age clocks tracked frailty and disability [8]. At national scale the evidence is sparser and mixed: epigenetic aging has accompanied high-impact pain [9], yet a national NHANES analysis found that the association between chronic pain and epigenetic age did not survive adjustment for lifestyle [10]. Two questions remain unanswered. First, whether an aging-clock signal for low back pain survives in an unselected national population; this has been tested neither for the routinely measurable clinical clocks nor for back pain specifically. Second, the question that decides deployability: whether a clinical clock measurable at the bedside matches the epigenetic clocks that cannot reach it.

We tested both questions. In NHANES 1999–2002 we placed routinely measurable clinical clocks head-to-head against epigenetic clocks for low back pain and physical-function disability, centred on the same-name pair: clinical phenotypic age versus its methylation counterpart. We asked whether biological-age acceleration is a usable, population-level risk marker for back pain, and whether a clinical clock could serve at the bedside.

2. Materials and Methods

Hypothesis

We hypothesised that clinical and epigenetic measures of biological aging are discordantly associated with low back pain and disability. For the pre-specified same-name pair (clinical phenotypic age and its methylation counterpart), we expected the two to diverge despite sharing a construct; across families, we expected pace-of-aging and second-generation clocks to associate more strongly than first-generation chronological clocks. The alternative hypothesis was concordance across clock types, or no association beyond chronological age.

Design, setting, and ethics. This was a cross-sectional analysis of NHANES, cycles 1999–2000 and 2001–2002, reported following STROBE and in accordance with the Declaration of Helsinki. NHANES was approved by the NCHS Research Ethics Review Board and participants gave written informed consent; this secondary analysis required no further approval.

Participants. Participants were community-dwelling adults. Clinical clocks could be computed for all adults, but the clinical-versus-epigenetic comparison was confined to the DNA-methylation subsample (adults aged ≥ 50 years; $n = 4,449$), of whom 2,532 had complete clock and covariate data; the wider ≥ 20 -year sample served as population context (Table 1). Eligibility criteria and the participant-flow diagram are provided in the Online Resource. The analysis plan was preregistered in a public registry prior to any inferential analysis (identifier on the title page).

Exposures — aging clocks. Clinical (blood-chemistry) clocks were phenotypic age (PhenoAge) [6] and Klemera–Doubal biological age (KDM) [11], computed from routine blood chemistry and haematology using an NHANES-referenced implementation [12]; homeostatic dysregulation is reported in the Online Resource. Epigenetic clocks comprised first-generation chronological predictors (Horvath [13], Hannum [14], and the skin-and-blood clock), second-generation mortality predictors (DNAm-PhenoAge [6] and GrimAge2 [15]), and a pace-of-aging measure (DunedinPoAm [16]); cell-composition-independent and -dependent acceleration (IEAA/EEAA) followed Chen [17]. Each clock was expressed as age acceleration (the residual from regressing the clock on chronological age) and standardised to a per-SD scale.

Outcomes. The primary outcomes were self-reported low back pain in the past three months (NHANES Miscellaneous Pain questionnaire, item MPQ070) [2] and physical-function disability (self-reported limitation on the NHANES Physical Functioning questionnaire). A radicular-symptom gradient and measured gait speed were secondary outcomes (Online Resource).

Covariates. Models adjusted for chronological age, sex, race/ethnicity, education, body-mass index, smoking, alcohol, and physical activity. To avoid conflating overlapping constructs, frailty (a deficit-accumulation index of 18 self-reported physician-diagnosed conditions) was treated as the clinical-vulnerability exposure, comorbidity (Charlson index) as a covariate, and physical function as an outcome.

Statistical analysis. All analyses incorporated the NHANES sampling weights, strata, and primary sampling units using Taylor-series linearization [18], in R with the survey package. The primary contrast was the same-name pair, clinical PhenoAge versus DNAm-PhenoAge, each related to low back pain by survey-weighted logistic regression and to the physical-function disability score by survey-weighted linear regression, adjusted for the covariates above. Remaining clocks were compared by conceptual family. Multiplicity was controlled hierarchically: the primary same-name pair, then group-wise false discovery rate (FDR) control, then unadjusted exploratory tests. Because depression in 1999–2002 was assessed only in a half-sample aged 20–39 and is therefore unavailable in our ≥ 50 -year subsample, the robustness of associations to this unmeasured confounder was quantified with the E-value [19].

Clinical relevance and sample size. Because this is an observational association study, the classic minimal clinically important difference does not directly apply. We pre-specified a clinically meaningful association as an odds ratio of at least 1.20 per SD for low back pain and reported all effects on an interpretable per-SD scale. The empirically estimated minimum detectable effect in the analytic core was an odds ratio of approximately 1.14 per SD (Online Resource).

Software and AI disclosure. A large language model (Claude, Anthropic) assisted with drafting and code review; all analyses, interpretations, and final content were verified by the authors, who accept full responsibility.

3. Results

Of the combined 1999–2002 sample, 10,291 adults aged ≥ 20 years had the low back pain item (context layer) and 2,532 adults aged ≥ 50 years had complete epigenetic-clock and covariate data for the head-to-head comparison (core layer; survey design-effective $n \approx 1,268$). The weighted prevalence of low back pain in the past three months was 40.0%. Sample characteristics are shown in Table 1.

No aging clock was associated with low back pain. Adjusted odds ratios per SD ranged from 0.64 (clinical PhenoAge) to 0.99 (Klemera–Doubal acceleration), and every 95% confidence interval crossed the null (Tables 2 and 3; Fig. 1). The pre-specified primary contrast, the same-name pair (Table 2, Panel A), yielded odds ratios of 0.64 (0.25–1.65) for clinical PhenoAge and 0.84 (0.49–1.42) for DNAm-PhenoAge, with no difference between them (ratio of odds ratios 0.80, 0.15–4.25; $p = 0.79$). First-generation, second-generation, and pace-of-aging epigenetic clocks were uniformly null, as were the cell-intrinsic and cell-extrinsic acceleration measures and both telomere-length measures (DNAm and qPCR; Online Resource). Benjamini–Hochberg correction within clock families left no association significant (minimum $q = 0.71$ for low back pain).

No clock was associated with physical-function disability after FDR control: standardised β coefficients were small (range – 0.016 to 0.075 per SD) and none survived correction (Tables 2 and 3). The only association reaching nominal significance in the entire analysis was between two overlapping exposure constructs, clinical PhenoAge and the deficit-accumulation frailty index ($\beta = 0.026$ per SD, $p = 0.012$);

because both summarise shared physiological decline, this correlation is expected and does not represent an independent predictive signal for the pain or disability outcomes.

Table 1
Characteristics of the study sample (NHANES 1999–2002)

Characteristic	Context sample (≥ 20 y)	DNAm subsample (≥ 50 y)
n (unweighted)	10,291	4,449
Age, years, mean	46.1	66.8
Female, %	52.2	50.3
Body-mass index, mean	28.0	28.5
Deficit-accumulation index (18 conditions), mean	0.089	0.150
Charlson comorbidity index, mean	0.33	0.65
Low back pain, past 3 mo, %	39.1	38.6

Context-sample values are survey-weighted (WTMEC4YR); DNAm-subsample values are unweighted descriptive means for the DNA-methylation subsample (≥ 50 years). The DNA-methylation head-to-head analyses used the special subsample weight (WTDN4YR). Race/ethnicity, education, smoking, alcohol, physical activity, and physical-function disability are detailed in the Online Resource.

Table 2
Primary contrast (same-name pair) and clinical aging clocks for low back pain and disability *Panel A. Pre-specified primary contrast (same-name pair)*

Measure (PhenoAge)	OR per SD (95% CI)	p
Clinical PhenoAge	0.64 (0.25–1.65)	0.35
Epigenetic DNAm-PhenoAge	0.84 (0.49–1.42)	0.54
Difference (clinical – epigenetic) †	0.80 (0.15–4.25)	0.79

Panel B. Clinical aging clocks

Clinical clock	Low back pain — OR per SD (95% CI)	Disability — β per SD (p)
PhenoAge acceleration	0.64 (0.25–1.65)	0.039 (0.57)
Klemera–Doubal (KDM) acceleration	0.99 (0.40–2.42)	–0.016 (0.66)

Survey-weighted; adjusted for age, sex, race/ethnicity, education, BMI, smoking, alcohol, physical activity, and Charlson comorbidity index. Disability (physical-function limitation) modelled on a continuous scale (β per SD). † Difference expressed as the ratio of odds ratios from a single joint survey model (survey-contrast of standardised coefficients). Homeostatic dysregulation reported in the Online Resource. All low-back-pain confidence intervals include the null (OR = 1).

Table 3
Epigenetic aging clocks for low back pain and disability, by conceptual type

Epigenetic clock	Type	Low back pain — OR per SD (95% CI)	Disability — β per SD (p)
Horvath	1st-gen	0.86 (0.56–1.31)	0.003 (0.92)
SkinBlood	1st-gen	0.84 (0.49–1.43)	0.047 (0.12)
Hannum	1st-gen	0.79 (0.45–1.36)	0.016 (0.58)
DNAm-PhenoAge	2nd-gen	0.84 (0.49–1.42)	0.039 (0.27)
GrimAge2	2nd-gen	0.97 (0.41–2.30)	0.075 (0.22)
DunedinPoAm	pace	0.87 (0.53–1.43)	—
IEAA	cell-intrinsic	0.92 (0.71–1.17)	—
EEAA	cell-extrinsic	0.87 (0.63–1.20)	—

Same covariate set as Table 2, additionally adjusted for six DNA-methylation cell proportions. The pace measure available in NHANES is DunedinPoAm; EEAA is an approximation because the public file lacks the enhanced-Hannum cell types. No epigenetic clock was associated with disability after Benjamini–Hochberg correction; disability β for pace and derived measures is reported in the Online Resource.

A comprehensive post hoc exploratory sweep (210 survey-weighted tests: every clock against every outcome, quartile contrasts, clock-by-modifier interactions, sex- and age-stratified and non-linear models, and all pairwise between-clock discordance contrasts) yielded no association surviving false-discovery correction. The only internally consistent pattern, a clock-by-age interaction on physical-function limitation, did not survive correction and is reported as hypothesis-generating only (Online Resource, ESM 2.1 and Table S5).

4. Discussion

In a nationally representative sample, biological-age acceleration—clinical or epigenetic—was not associated with low back pain or with physical-function disability. The pre-specified same-name pair was unequivocal: clinical phenotypic age and its methylation counterpart carried the same null signal, their difference was not significant, and neither clock family identified who had back pain. Contrary to our hypothesis of discordance, the clinical and epigenetic measures did not diverge. A clinical clock measurable at the bedside added nothing; the epigenetic clocks that cannot reach the bedside added nothing either.

The contrast with prior reports is instructive, not contradictory. The large effects came from small, selected samples—chronic low back pain against pain-free controls [7], surgical deformity cohorts [8]—designs built to separate clinical extremes. Our estimate comes from an unselected national population, where the same clocks moved no measure of back pain or disability. Both can hold at once: a signal that distinguishes pre-selected extremes need not survive in the general population, the very setting in which it would have to operate to justify screening. A parallel NHANES analysis of chronic pain is consistent with ours: an apparent epigenetic-aging association was fully attenuated once lifestyle was accounted for [10]. Whether lifestyle confounds or mediates that link is a causal question; ours is prognostic—whether a clock adds risk information beyond the inexpensive, routinely recorded variables it would have to improve upon. Conditioning on those variables is the test a bedside marker must pass, not overadjustment, and the clocks did not pass it.

Crucially, these clocks were not inert: in the same NHANES subsample, the epigenetic clocks predict all-cause mortality [20], and the clinical phenotypic-age measure tracks cognitive performance where chronological age does not [21]. The null is therefore outcome-specific—these clocks work, but not for low back pain—rather than a failure of measurement. They have shown their value in selected clinical cohorts and for other outcomes; that value did not extend to back pain at the population scale.

A mechanism may explain the gap. Symptomatic intervertebral discs show accelerated cellular senescence even in younger patients [22], yet local disc-level aging need not surface in systemic blood chemistry or leucocyte methylation. The data source itself is not blind to low back pain: in the same survey, greater appendicular muscle mass was protective against it in over 11,000 adults [23]. A musculoskeletal exposure registered an association while systemic biological-age acceleration did not, locating the null in the biology of aging clocks, not in the data, the outcome, or statistical power. The clinical message follows directly. Frailty, an accumulation of clinical deficits validated for surgical risk, is conceptually distinct from these molecular and physiological aging clocks; it remains, alongside chronological age, a practical axis for risk stratification in spine practice [24, 25], whereas ordering a clinical or epigenetic aging clock to stratify low back pain is not supported by these data. Biological-age acceleration is not a bedside risk marker for this condition.

The study has clear strengths: prospective preregistration before any inferential analysis, a large nationally representative sample with survey-weighted estimation, and the first head-to-head comparison

of clinical and epigenetic aging clocks for back pain. It also has limitations. The cross-sectional design precludes causal inference, and the survey-effective sample limited the minimum detectable effect to an odds ratio of approximately 1.14 per SD, below our pre-specified clinically meaningful threshold of 1.20; an effect large enough to matter clinically would have been detected. Depression was assessed in 1999–2002 only in a half-sample aged 20–39 and so was unavailable in the ≥ 50 -year analytic sample; the sensitivity of the findings to this unmeasured confounder was examined with the E-value (Online Resource). The pace measure in NHANES is DunedinPoAm, the predecessor of the DunedinPACE used in analogous reports; the same measure was likewise unassociated with pain in the parallel NHANES analysis [10]. Extrinsic acceleration was approximated because the public file lacks the enhanced-Hannum cell types. Low back pain was captured as three-month prevalence rather than a duration-defined chronic phenotype; however, the most comparable NHANES analysis applied a strict chronic-pain definition and likewise found no association after adjustment [10], making phenotype dilution an unlikely explanation for the null.

5. Conclusion

In a nationally representative sample, neither routinely measurable clinical aging clocks nor epigenetic clocks were associated with low back pain or disability, and the two phenotypic-age measures showed no significant difference. The aging-clock signals reported in small, selected cohorts did not generalise to the population. Biological-age acceleration is not a usable bedside risk marker for low back pain, and epigenetic clocks add no value over clinical clocks for this outcome.

Declarations

Author Contribution

A.C.K. was the sole contributor to this work. A.C.K. conceived and designed the study, curated the data, performed the statistical analysis, interpreted the results, prepared the figure and tables, and wrote and revised the manuscript. A.C.K. read and approved the final version and takes full responsibility for the integrity of the work.

Data Availability

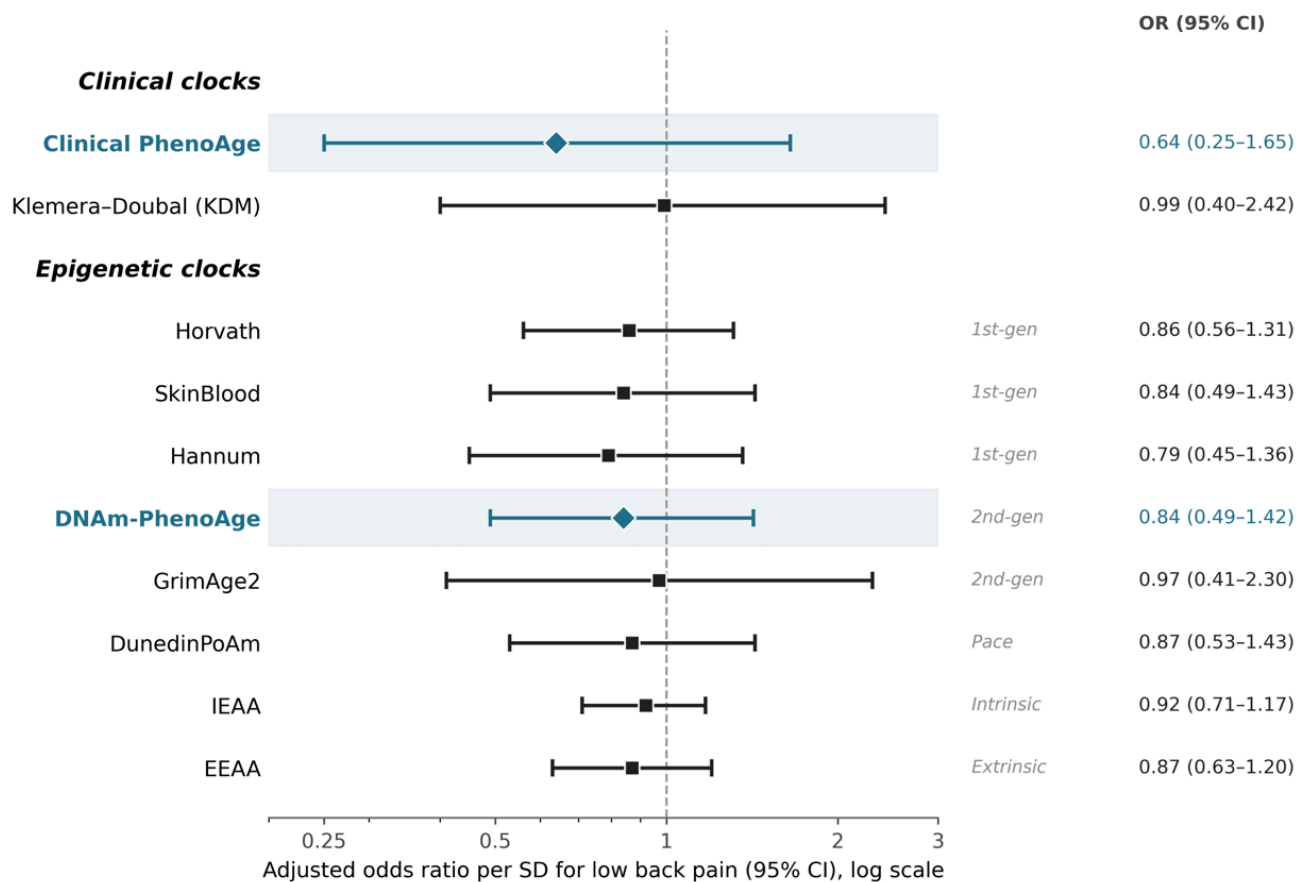
The data analysed in this study are publicly available from the U.S. National Center for Health Statistics (NCHS) National Health and Nutrition Examination Survey (NHANES), cycles 1999–2000 and 2001–2002, at <https://www.cdc.gov/nchs/nhanes/>. No new data were generated. The prospectively registered analysis plan, the analysis code (data-preparation and analysis scripts), and the full variable mapping are deposited in an Open Science Framework repository and will be made openly available with a permanent DOI upon acceptance; they are available to the editor and reviewers on request in the interim.

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Figures



Diamond = pre-specified same-name pair (clinical PhenoAge vs DNAm-PhenoAge).

Figure 1

Forest plot of adjusted odds ratios per SD (95% CI) for low back pain across the full clock panel, highlighting the same-name pair (clinical PhenoAge vs DNAm-PhenoAge); reference line at OR=1. Clinical clocks are shown at the top, epigenetic clocks grouped by conceptual type below; the x-axis is on a logarithmic scale.

Supplementary Files

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