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Using Epigenetic Clocks to Characterize Biological Aging in Studies of Children and Childhood Exposures: a Systematic Review

Rashelle J. Musci[1], **Radhika S. Raghunathan**[2], **Sara B. Johnson**[1,2,3], **Lauren Klein**[2], **Christine Ladd-Acosta**[4], **Rosemary Ansah**[2], **Ronda Hassoun**[1], **Kristin M. Voegtline**[2,3]

[1]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, 624 N. Broadway, Baltimore, MD 21205, USA

[2]Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, USA

[3]Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Abstract

Biological age, measured via epigenetic clocks, offers a unique and useful tool for prevention scientists to explore the short- and long-term implications of age deviations for health, development, and behavior. The use of epigenetic clocks in pediatric research is rapidly increasing, and there is a need to review the landscape of this work to understand the utility of these clocks for prevention scientists. We summarize the current state of the literature on the use of specific epigenetic clocks in childhood. Using systematic review methods, we identified studies published through February 2023 that used one of three epigenetic clocks as a measure of biological aging. These epigenetic clocks could either be used as a predictor of health outcomes or as a health outcome of interest. The database search identified 982 records, 908 of which were included in a title and abstract review. After full-text screening, 68 studies were eligible for inclusion. While findings were somewhat mixed, a majority of included studies found significant associations between the epigenetic clock used and the health outcome of interest or between an exposure and the epigenetic clock used. From these results, we propose the use of epigenetic clocks as a tool to understand how exposures impact biologic aging pathways and development in early life, as well as to monitor the effectiveness of preventive interventions that aim to reduce exposure and associated adverse health outcomes.

Rashelle J. Musci, rmusci1@jhu.edu.

Declarations

Ethical Approval All procedures performed in the current study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Consent to Participate Informed consent was not required as no human subjects were used.

Conflict of Interest The authors declare no competing interests.

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Keywords

Epigenetic age; Biological clock; Biological adaptation; Hannum clock; Horvath clock; PedBE clock

Introduction

Increasingly, research has focused on understanding the distinction between chronological and biological age. Markers of biological aging help characterize underlying changes in health and development occurring at the cellular level, even in the absence of, or alongside, obvious phenotypic changes (Levine et al., 2018; Xia et al., 2017). In adults, links between biological aging, resulting loss of physiological integrity and functioning, and diseases of aging such as cardiovascular disease, neurologic disease, and cancer in adults are well established (Mattson & Arumugam, 2018). Studies of biological aging in children are beginning to accumulate (e.g., Binder et al., 2018; Brody et al., 2016a, b; Hamlat et al., 2021; McEwen et al., 2020; Peng et al., 2019; Shiau et al., 2018). Across the life course, quantitative biomarkers of cellular aging may capture processes including changes to DNA and chromosomes, RNA, and the transcriptome, metabolism, oxidative stress, mitochondrial dysfunction, cell senescence, and inflammation (Xia et al., 2017). Epigenetic age, which captures CpG methylation, is among the most common measures of biological age. Individuals who exhibit more rapid aging based on DNAm than would be predicted by their chronological age have increased risk of disease and mortality (Fransquet et al., 2019). Composite biomarker predictors, and in particular the epigenetic clock, hold promise for understanding heterogeneity of biological aging, as no single candidate biomarker (e.g., blood pressure) has been shown to be a robust indicator of all-cause mortality (Jylhävä et al., 2017). Moreover, the field's historical focus on adult populations and mortality precludes interpretation of aging as a continual process across the life course and minimizes growing recognition of sensitive periods in epigenetic programming (Marini et al., 2020). The focus of this systematic review is studies utilizing epigenetic clocks in pediatric research, which may help inform or identify sensitive periods in child development that are useful for prevention programming.

Epigenetic clocks are a biomarker of aging based on DNA methylation (DNAm). DNAm is measured for a set of CpG sites, the number and subset of which depend on the specific clock (Bell et al., 2019). Most of the extant literature relies on two clocks: the Hannum clock and the pan-tissue Horvath DNAm (Horvath) clock (Horvath, 2013). The Hannum clock includes 71 CpG sites from the Illumina 450 k methylation array, utilizing DNA from blood and age-related shifts in blood cell composition to determine biological age (Bell et al., 2019). The Horvath clock estimates DNAm age from most tissue and cell types based on methylation at 353 CpG sites (Bell et al., 2019; Horvath, 2013). More recently, several other epigenetic-based clocks in adults have been developed including PhenoAge (Levine et al., 2018), GrimAge (Lu et al., 2019), and DunedinPoAm (Belsky et al., 2017); evidence linking their relationship to health outcomes is an emerging area of research. Specific to infant and pediatric populations, the gestational age (Knight et al., 2016; Lee et al., 2019) and pediatric buccal epigenetic (PedBE) (McEwen et al., 2020) clocks were developed

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to investigate developmental biologic aging and impact on health outcomes. Accelerated biological aging early in the life course may serve to calibrate developmental processes based on environmental input. For example, accelerated biological aging in childhood is associated with earlier onset of puberty (Binder et al., 2018; Ellis et al., 2009). From an evolutionary standpoint, this serves to maximize opportunity for reproduction (Rickard et al., 2014).

Evaluating DNAm age in children and adolescents offers the opportunity to compare the biological impact of different physical, chemical, and social exposures at various points in development and to understand their potential implications for health and behavioral risk and resilience. However, in children and adolescents, the relationship between chronological and DNAm age as measured by epigenetic clocks developed for use in adults is less clear, in part because DNAm is more dynamic in early relative to later life (McEwen et al., 2020). To date, in studies using adult clocks, correlations between DNAm age and chronological age are the lowest in infancy and increase into adolescence (Simpkin et al., 2017). This lack of pediatric specification in some common clocks presents a challenge when inferring biological age with precision. To address this concern, infant- and pediatric-specific clocks have been developed to assess DNAm age from birth to adolescence (Bohlin et al., 2016; Knight et al., 2016; Lee et al., 2019).

In the current study, we focus on clocks that are easily accessible and replicable for prevention science researchers and have been previously used in pediatric samples (i.e., the Hannum, the pan-tissue Horvath, and the PedBE clock designed for use in pediatric populations). We focus on named epigenetic clocks, which are likely to be more accessible for the average non-epigenetic researcher and have the largest breadth of literature. Further, many named clocks have been manualized, meaning their estimation is easily done using publicly available software code and tutorials. Some studies not included in this review simply utilized a different named clock that has not been widely used in the pediatric literature or created their own metric of epigenetic aging (Bohlin et al., 2016; Knight et al., 2016; Lee et al., 2019). With the abundance of longitudinal data available in many preventive intervention trials along with existing cohort studies with prevention implications, we looked for clocks that were valid to use across multiple developmental periods such that inferences could be made about change over time. While this is an area of rapidly changing research, there is a substantial body of literature utilizing the Horvath and Hannum epigenetic clocks. The PedBE clock is newer (2019), but the focus and validity on pediatric populations were the basis for its inclusion here. The PedBE clock has demonstrated reliability and validity in multiple tissue types, which is common among clocks designed for use in children (Kling et al., 2020). The overall goal of this systematic review is to identify studies utilizing epigenetic clocks in pediatric research, provide some synthesis of their use in these studies, and make suggestions for how prevention scientists can incorporate biological aging into their research program.

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Method

Inclusion and Exclusion Criteria

We conducted a systematic review through February 2023 following Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Moher et al., 2009). Included studies met the following inclusion criteria: (a) published in English, (b) conducted in humans, (c) used the Hannum, Horvath or PedBE epigenetic clock as a biomarker of biological aging, and (d) the clock was used to measure DNAm in children (0–18 years) or during adulthood to evaluate the long-term correlates of an exposure and/or predictor (e.g., adverse childhood exposures, internalizing symptoms) during childhood (0–18 years). Because we were interested in the broad literature around epigenetic clocks in pediatric research, we did not include search terms for specific exposures. Studies were excluded if they were non-empirical (e.g., review, commentary, letter), they measured DNAm but did not include an epigenetic clock, or if they used clock other than the Horvath, Hannum, or PedBE.

Literature Search Procedure and Parameters

Relevant articles published through May 2021 were identified via a systematic search of PubMed New Interface, PsychINFO, and Google Scholar. A search string that incorporated three concepts, biological aging, DNA methylation, and children, was developed (see Supplemental Materials). Duplicates were identified and removed, and the remaining unique citations were imported into a web-based systematic review manager (Covidence, Veritas Health Innovation, Melbourne, Australia) for further evaluation. Inclusion and exclusion criteria were applied by review of titles first, then abstracts, and finally full text. Screening was conducted by two evaluators independently. Conflicts were resolved by two additional evaluators. Details of the search process and sample construction are summarized in Fig. 1. After the full-text review, a manual reference search was conducted for all included articles following a similar procedure outlined above.

Data Extraction

After full-text screening, the following information was extracted from each study, as applicable: study sample characteristics, study design, exposure(s) and/or predictor(s), outcome measure(s), age at which the epigenetic clock was used, clock type, biospecimen used, covariates, and method of analysis.

Quality Assessment

Studies were assessed for methodological quality using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort or Cross-Sectional Studies (https://joannabriggs.org/). Risk of bias evaluation was used to evaluate the quality of evidence but was not used to exclude articles from the review (Vardell & Malloy, 2013).

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Results

Study Design

Figure 1 provides a detailed summary of the screening and inclusion process. Of the 180 articles that were subjected to full-text review, 113 were excluded. A majority were excluded because they did not use an eligible epigenetic clock or focused entirely on an adult population. A total of 68 studies were included in the systematic review after full-text screening. Most of the included studies utilized epigenetic clocks as outcomes of interest, while some used these metrics of biological aging as a predictor in a health outcome model. Because of the complexity of many of the included studies, in this review, we focus on the main analysis of epigenetic age and do not explicitly discuss all analyses in a given study.

Study Sample Characteristics

Included studies were conducted with samples around the world including in Chile (Binder et al., 2018), Australia (Huang et al., 2019), Finland (Suarez et al., 2018a, b), the Republic of the Congo (Gettler et al., 2020), South Africa (Horvath et al., 2018a), and Ireland (Lecorguillé et al., 2023). Several studies used data from the large UK-based prenatal cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) (Lawn et al., 2018; Marini et al., 2020; Simpkin et al., 2016, 2017; Tang et al., 2020).

In the USA, four studies reported on research conducted in rural Georgia. Brody and colleagues (2016b) used data from two longitudinal studies: the Strong African American Healthy Adult Project (SHAPE) and the Adults in the Making (AIM) project. Chen and colleagues (2016) used data only from SHAPE. whereas Miller et al. used data from AIM. Similarly, Brody and colleagues (2016a) used data from the Strong African American Families (SAAF) study, a randomized prevention trial in rural Georgia. In a separate investigation, Jovanovic and colleagues (2017) used data from a longitudinal study of trauma exposure in children from an urban hospital in Atlanta, Georgia.

Biospecimen Type

A majority of studies ($n = 45$) extracted DNA from blood. Some used umbilical cord blood (Peng et al., 2019; Simpkin et al., 2016, 2017; Suarez et al., 2018a, b), while others used whole blood (Hamlat et al., 2021, among others) (see Tables 1 and 2). One study used dried blood spots from finger sticks (Gettler et al., 2020). One study used respiratory epithelial cells from nasal swabs (Cardenas et al., 2019). Many studies used saliva/buccal cells (Cerveira de Baumont et al., 2021; Clausing & Non, 2021; Dammering et al., 2021; Davis et al., 2017; Graw et al., 2021; Jovanovic et al., 2017; Mathewson et al., 2021; Nishitani et al., 2021; Phang et al., 2020; Sumner et al., 2019; Tollenaar et al., 2021; Van Lieshout et al., 2021, among others) (see Tables 1 and 2).

Sample Size

The average sample size of the included studies was 580.7 (SD = 791.7; median = 256.0; range = 35–5111 participants), but sample sizes varied widely. Fifteen studies included data from less than 100 participants (e.g., Binder et al., 2018; Davis et al., 2017; Gettler et al., 2020); 27 included between 100 and less than 500 participants (e.g., Austin et al., 2018;

Brody et al., 2016a, b; Chen et al., 2016; Horvath et al., 2018a; Miller et al., 2015; Phang et al., 2020; Shiau et al., 2018; Suarez et al., 2018a, b; Sumner et al., 2019), and 26 studies included more than 500 participants (e.g., Huang et al., 2019; Lawn et al., 2018; Marini et al., 2020; Simpkin et al., 2016, 2017; Tang et al., 2020).

Summary of Epigenetic Clocks Used

Only one study (Brody et al., 2016a, b) relied on the Hannum clock, and some (five) relied on the PedBE clock. The large majority of studies relied solely on the Horvath clock (31 studies) or utilized multiple clocks (31 studies) (see Table 1).

In most studies (75%, $n = 51$), epigenetic age was the outcome of interest (i.e., Austin et al., 2018; Brody et al., 2016a, b; Cardenas et al., 2019; Chen et al., 2016; Gettler et al., 2020; Javed et al., 2016; Jovanovic et al., 2917; Lawn et al., 2018; Marini et al., 2020; Miller et al., 2015; Phang et al., 2020; Shiau et al., 2018; Suarez et al., 2018a; Sumner et al., 2019; Tang et al., 2020). In these studies, the exposures were heterogeneous including perceived racial discrimination (Brody et al., 2016b), maternal dietary and macronutrient intake (Phang et al., 2020), HIV exposure and infection status (Shiau et al., 2018), and childhood adversity (Lawn et al., 2018; Marini et al., 2020; Sumner et al., 2019; Tang et al., 2020). The goal of these studies was to assess whether a particular exposure in childhood was associated with accelerated epigenetic age.

A minority of studies (25%, $n = 17$) used epigenetic age as a predictor of a later outcome such as pubertal timing (Binder et al., 2018), cardiovascular disease risk, body mass index (Huang et al., 2019), allergic phenotypes (Peng et al., 2019), or other indicators of growth and development (Davis et al., 2017; Simpkin et al., 2016, 2017) (see Table 1). Most of these studies included epigenetic age as a predictor of a particular health outcome.

In papers that used multiple clocks, researchers were often interested in comparing new epigenetic clocks, often those developed by the research team, to those already in use in the field (Graw et al., 2021; McEwen et al., 2020). For example, Graw and colleagues (2021) developed a novel epigenetic clock (NEOage) focused on age estimation of preterm infants. They compared their clock to more conventional clocks like Horvath and PedBE (McEwen et al., 2020). Many of the included studies qualitatively compared associations between epigenetic aging measured by specific clocks and their outcome of interest (Etzel et al., 2022). Some studies explored correlations between epigenetic age acceleration as measured by different epigenetic clocks. For example, Hamlat and colleagues (2021) found modest correlations between epigenetic age acceleration measured by the Horvath, Hannum, PhenoAge, and Grim age clocks. Please see Table 1 for additional studies that utilized multiple clocks.

Summary of Findings

Almost all studies showed that adverse exposures, in some form, between birth and 18 years were significantly associated with accelerated biological aging, with some exceptions; a study by Shiau and colleagues (2018) found no difference in accelerated biological aging when comparing HIV-infected children to HIV-exposed but uninfected children. Zannas and colleagues (2015) found an association with cumulative lifetime stress but not childhood

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maltreatment. Sumner and colleagues (2019) found a significant association between accelerated epigenetic age and threat-related early-life adversity but no association between epigenetic age and deprivation-related early-life adversity. Other studies supported the idea that environmental experiences and exposures can get under the skin to impact biological aging and risk of adverse health and developmental outcomes. Further, studies exploring the link between biological aging and another construct (e.g., mental health, physical health) generated mixed findings. For example, Shenk and colleagues (2021) found that accelerated epigenetic age significantly predicted PTSD status, and epigenetic age acceleration was also related to PTSD symptom severity. Huang and colleagues (2019) found that epigenetic age acceleration in adolescence was associated with inflammation, BMI measured 5 years later, and probability of cardiovascular disease in middle age.

Many of the included studies that reported on the correlation between epigenetic age and chronological age found a significant positive correlation between the two (Austin et al., 2018; Binder et al., 2018; Cardenas et al., 2019; Davis et al., 2017; Gettler et al., 2020; Jovanovic et al., 2017; Peng et al., 2019; Shiau et al., 2018; Sumner et al., 2019). Other studies either did not report correlations between epigenetic age and chronological age (e.g., Kim et al., 2022; Neri de Souza Reis et al., 2021 or reported low correlation between the two constructs (e.g., Simpkin et al., 2017; Tollenaar et al., 2021).

Discussion

Epigenetic clocks offer promise for researchers interested in elucidating the biological mechanisms by which environmental exposures early in life shape both short- and long-term health and behavioral outcomes. Epigenetic clocks offer a metric to capture and quantify developing individuals' adaptation to their environments across genes. For example, Marini and colleagues (2019) found that exposure to adversity in early and middle childhood was significantly associated to the Hannum-based epigenetic aging clock, and Jovanovic and colleagues (2017) found that epigenetic age acceleration in children was significantly associated with violence exposure. Moreover, epigenetic age may be particularly useful in prevention science for investigating potential biological impacts of preventive interventions. Prior research points to the need to incorporate precision approaches in prevention science (August & Gewirtz, 2019; Latendresse et al., 2018; Musci & Schlomer, 2018).

One of the studies included in this systematic review incorporated epigenetic clocks into a prevention trial, making it a particularly illustrative example for prevention scientists. Brody and colleagues (2016a) explored the impact of their Strong African American Families (SAAF) program on epigenetic age and investigated whether that relationship was mediated by reductions in harsh parenting. The authors found that the prevention program was associated with epigenetic age, more specifically, individuals in the intervention group had significantly lower epigenetic age at age 20 compared to those in the control group. This study also demonstrated moderated mediation such that the SAAF program led to lower epigenetic age compared to controls through reductions in harsh parenting among those who had a caregiver with high depressive symptoms. Brody and colleagues (2016a) may serve as a guide for other prevention researchers interested in understanding how their programming may disrupt the relationship between adverse exposures and biological aging.

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Monitoring program impacts at the level of gene expression can inform not only how environmental exposures impact health at the cellular level, but also point to modifiable intervention targets. Further, prior research demonstrates that DNA methylation is reversible, which suggests that the future of prevention science could include strategies to alter or prevent methylation patterns associated with negative outcomes, including, perhaps even medications that directly target methylation (Szyf et al., 2016).

It is important to note that across the existing literature, the correlation between chronological age and epigenetic age has been variable. This may be explained by differences in environments that may impact methylation patterns among participants in a given sample. Alternatively, this heterogeneity may be explained by features of the epigenetic clock used. Clocks trained on samples that are highly divergent from those in which they are used might generate particularly discrepant results between chronological and epigenetic age (McEwen et al., 2020). For example, the Horvath clock has demonstrated strong correlation between epigenetic age and chronological age in adult samples (Horvath, 2013). Clocks developed in adult samples have demonstrated low correlation in pediatric samples (McEwen et al., 2020). This has led researchers to develop more pediatric-focused epigenetic clocks that can more reliably characterize epigenetic aging in childhood.

Low correlations between epigenetic age as measured by epigenetic clocks developed in adult populations and chronological age may also influence associations between epigenetic age measured in childhood and later outcomes. For example, Simpkin and colleagues (2017) reported low correlations between epigenetic age in childhood and later pubertal status. Similarly, Tollenaar and colleagues (2021) reported low correlations between epigenetic age in childhood and later internalizing and externalizing symptoms. These low correlations were one of the reasons why there has been a recent push to develop pediatric-focused biomarkers of aging such as the PedBE clock (McEwen et al., 2020). While the correlation between these constructs may be an important factor in understanding accelerated aging, for most prevention researchers, it is likely that a lower correlation between epigenetic age and chronological age will not be impactful.

Methodological Considerations

A significant methodological consideration for ongoing research in biological aging is tissue choice and the comparison of clocks that rely on different tissue types. The collection of invasive biospecimens, including blood, can be particularly challenging in children in non-clinical settings. Unwillingness to consent to blood collection is a common reason for parents' declining participation in pediatric research (Gattuso et al., 2006). Saliva is significantly easier to obtain and more acceptable to study participants. From saliva samples, one can capture several different cell types including epithelial cells and leukocytes (Smith et al., 2015). Saliva and epithelial cells have been used in many epigenetic studies of behavior and psychopathology. Notably, Dempster et al. (2014) used buccal cells in a study of adolescent depression, and work by Lowe and colleagues (2013) suggests that buccal cells are more informative than blood for epigenome-wide association studies, given the closer lineage to neurological systems. The tissue issue also comes into play when researchers are interested in exploring DNA methylation patterns longitudinally; accessible

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biospecimens may differ depending on the developmental stage of the participants. This is not, of course, the end of the story as much remains uncertain with regard to how tissue type interacts with developmental stage to impact epigenetic age calculations.

Limitations

The current review is limited to studies that used the Hannum, pan-tissue Horvath, and the PedBE epigenetic clocks, given their relevance and popularity. However, new clocks are emerging and are increasingly being tailored for the investigation of specific outcomes or periods of development. For example, the PhenoAge clock has outperformed other clocks in predicting aging outcomes like Alzheimer's disease (Levine et al., 2018). Other clocks include the Grim-Age clock (Lu et al., 2019) and the Skin and Blood Clock (Horvath et al., 2018a). Our focus on Horvath, Hannum, and PedBE clocks only is certainly a limitation though we see this as an important contribution as prevention researchers explore ways to successfully integrate epigenetic analyses into their current line of research. As more clocks are developed in pediatric samples, studied, and their findings replicated, it will be important for prevention researchers to match the clock they choose to the sample to which they want to generalize.

Considerations for Future Research

There has been a notable increase in the use of epigenetic clocks in pediatric populations. Epigenetic clocks offer great promise for understanding how environmental exposures influence the biologic aging pathway during sensitive periods in development. Use of these clocks can aid prevention researchers interested in understanding the etiology of diseases and disorders, elucidating mechanistic pathways, and informing the creation or improvement of promotion, prevention, intervention, and treatment programming across the life course.

The ability of researchers to use many different types of biospecimens collected by large-scale epidemiology studies to measure DNA methylation as a predictor of biological aging offers the opportunity to retrospectively study the impact of a variety of environmental exposures on health outcomes. The ability to capture epigenetic data from archived or banked biospecimens may reduce participant burden and make studying epigenetics more accessible for prevention researchers. For example, several researchers have used banked dried blood spots initially captured at birth for newborn metabolic screening programs for other purposes such as calculating biological age (Hollegaard et al., 2013; Knight et al., 2016; McClendon-Weary et al., 2020).

In summary, while research is increasingly relying on epigenetic clocks to characterize biological aging, the bulk of the extant literature and methods are focused on adults and aging populations. Epigenetic clocks offer promise for prevention science researchers interested in elucidating the multideterminant etiology of mental, behavioral, and physical health problems. Researchers with an interest in methylation and epigenetics should explore the potential use of these clocks as an avenue to understand mechanisms of environmental exposures and adverse health outcomes.

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Supplementary Material

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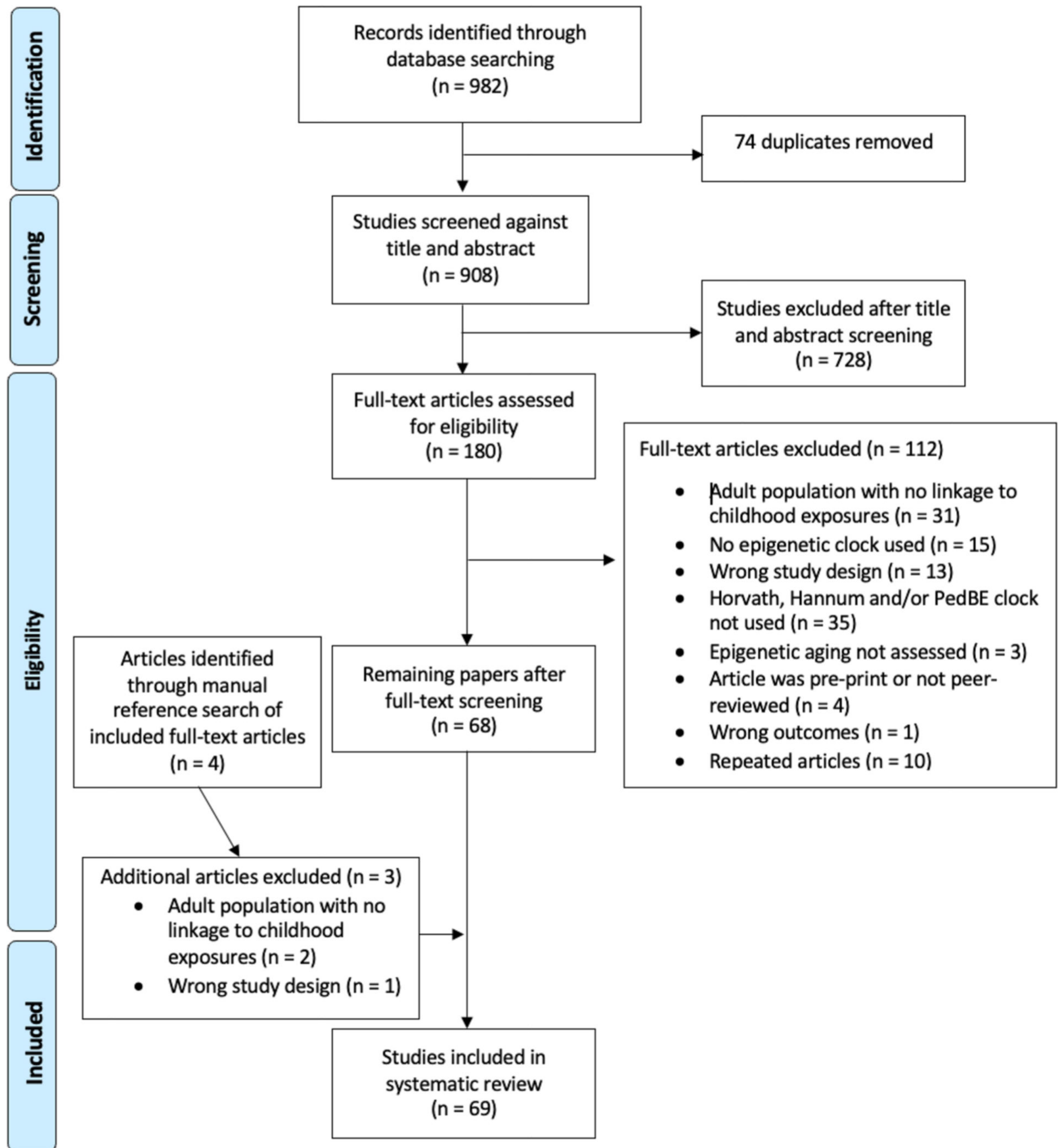

Fig. 1.

PRISMA flow chart of identification and elimination of studies for review. The search was completed through February 2023

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISM Group (2009). *P*referred *R*eporting *I*tems for Systematic Reviews and *M*eta-*A*nalyses: The PRISM Statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097

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Table 1

Characteristics of included studies when epigenetic clock measures were used as a predictor

Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
Binder et al. (2018)	Prospective cohort study	Randomly selected subset of girls from a longitudinal study examining growth and obesity (GOCS) in Chile who had epigenetic data at two waves	94 (100%)	Peripheral blood	Horvath	Middle childhood to adolescence	Epigenetic age acceleration (DNAm vs. chronological age residuals)	Pubertal timing (i.e.. Tanner staging, breast volume, menarche)
Bolhuis et al. (2022)	Prospective cohort study	Dutch low risk mother child dyads	193 (47.67% of offspring)	Buccal cells	PedBE	Age 6 and age 10	Attachment insecurity, epigenetic aging (mediator), telomere length (mediator	Pubertal onset, callous unemotional traits, aggression, risk-taking
Davis et al. (2017)	Longitudinal study	Adolescent girls who were in a longitudinal study examining familial risk (maternal history of MDD) and development	46 (100%) (*n* = 24 high risk, *n* = 22 low risk)	Saliva	Horvath	Middle childhood to adolescence	Epigenetic age acceleration	Diurnal cortisol, hippocampal volume, amygdala volume
Gomaa et al. (2022)	Prospective cohort study	Infants born very pre-term (24–32-week gestation)	35 (40%)	Buccal cells	PedBE	Within the first 2 weeks of life	Epigenetic age acceleration	Brain growth and neurodevelopmental outcomes (Bayley scales)
Graw et al. (2021)	Cross-sectional	Participants from the Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) study	542 (44.5%)	Buccal cells	NEOage, Horvath, PedBE	Preterm infants	Epigenetic age	Post-menstrual and postnatal age
Hoare et al. (2022)	Prospective cohort study	Baseline data from the Cape Town Adolescent Antiretroviral cohort study	180 (52.8% female)	Peripheral blood	Horvath	Middle childhood	Epigenetic age and HIV treatment	Brain volume, cortical thickness, cortical surface area, neuronal microstructure
Huang et al. (2019)	Prospective cohort study	Youth originally part of a longitudinal study commencing in the prenatal period in Western Australia (Raine study)	995 (49.6%)	Peripheral blood	Horvath and Hannum	Adolescence	Epigenetic age acceleration (intrinsic and extrinsic)	Adiposity & BMI, cardiovascular disease (CVD) risk factors (ages 17, 20, 22), predicting CVD development 30 years later
Manczak et al. (2023)	Multi-wave cohort study	Subset of the BiB study	154 (49.4% female)	Umbilical cord blood	Horvath	Birth	Epigenetic age and Maternal Hostility	Psychological symptoms
Neri de Souza Reis et al. (2021)	Cross-sectional	Mother-child dyads in São Paulo, Brazil. Children had an ASD diagnosis, ages between 3 and 7, and an IQ between 50 and 75	67 mothers (100%); 67 children (17.9%)	Whole blood	Horvath	Early childhood	DNA méthylation age acceleration, family social class, maternal schooling, maternal stress during gestation, toxic environmental exposures, familial psychiatric history, gestational complications	Autism Spectrum Disorder

Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
Peng et al. (2019)	Prospective cohort study	Children from a longitudinal pre-birth cohort study conducted in Boston, MA (Project Viva) with epigenetic data measured at birth, early childhood, and middle childhood; replicated methods in a subset of children in Costa Rica (Genetics of Asthma in Costa Rica Study)	Project Viva: 408 (49%) Genetics of asthma in Costa Rica: 159 (41%)	Umbilical cord blood (birth), peripheral blood (early and midchildhood)	Horvath and Hannum	Birth to middle childhood	Epigenetic age and epigenetic age acceleration at birth, early childhood and middle childhood	Allergic phenotypes in middle childhood (e.g., serum IgE, food allergen sensitization, asthma)
Shenk et al. (2022)	Accelerated cross-sequential prospective cohort	Subset of the Female Growth and Development Study (FGDS)	172 (100% female)	Whole blood	Horvath and Hannum	Adulthood	Epigenetic age and childhood sexual abuse	cortisol trajectories
Simpkin et al. (2016)	Prospective cohort study	Subset of children from a population-based cohort study in UK (ALSPAC) Replication of findings in a Danish sample of newborns (GOYA study)	ALSPAC: 1022 (52%) GOYA: 981 (not indicated)	Umbilical or blood (at birth); venous blood	Horvath and Hannum	Birth, childhood and adolescence	Repeated measures of epigenetic aging: raw age acceleration differences and age acceleration residuals	Horvath vs. Hannum performance, BMI, alcohol consumption, smoking, education, maternal health, and child health
Simpkin et al. (2017)	Prospective cohort study	Subset of children from a population-based cohort study in the UK (ALSPAC)	914 (51%)	Cord blood (time 1); venous blood (time 2)	Horvath	Childhood to adolescence	Repeated measures of epigenetic aging: raw age acceleration	Physical characteristics (height, weight, BMI, etc.); pubertal stage/onset age
Suarez et al. (2018b)	Prospective cohort study; cross-sectional analysis	Youth originally enrolled in a longitudinal study commencing when they were infants	239 (51.5%)	Blood	Horvath	Middle childhood to adolescence	Epigenetic age acceleration	Pubertal timing, physical growth, neuroendocrine parameters (i.e., cortisol), psychiatric and cognitive aging-related outcomes
Hoare et al. (2020)	Prospective cohort study; Cross-sectional analysis	Adolescents enrolled in Cape Town Adolescent Antiretroviral Cohort (CTAAC) study with epigenetic data	44 (54.5)	Blood (peripheral blood)	Horvath and Hannum	Middle childhood to adolescence	Epigenetic age acceleration residual and extrinsic epigenetic age acceleration	Cognitive functioning via neuropsychiatric battery of tests, brain structure and integrity via neuroimaging and DTI
Shenk et al. (2021)	Case-control study design	Children, with and without PTSD, recruited from child protective services in an urban Midwest county (USA)	70 (65.7)	Buccal cells	Horvath	Middle childhood to adolescence	Epigenetic age acceleration; lifetime exposure to child adversity	PTSD status (child PTSD symptoms scale)
Tollenaar et al. (2021)	Prospective cohort study	Children from an ongoing longitudinal study who were followed up from ages 2.5 to 10	148 (46.6)	Buccal cells	Horvath	Childhood	Internalizing and externalizing symptoms (CBCL), epigenetic age acceleration	Epigenetic age acceleration, internalizing and externalizing symptoms

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Table 2

Characteristics of included studies when epigenetic clock measures were used as an outcome or correlate

Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
Allen et al. (2022)	Longitudinal cohort study	Adolescents recruited in grades 7–8 in southeastern USA and followed into adulthood	154(56.5%)	Blood	Horvath, GrimAge	Midlife	Adolescent peer struggles	Epigenetic age acceleration
Austin et al. (2018)	Cross-sectional (2×2 design)	Healthy participants enrolled in a study on early-life and current adult socioeconomic status (SES) on health-related outcomes	335 (55%)	Blood	Horvath	Adolescence to adulthood	Early-life (0–5 years) and current (adult) socioeconomic status	Epigenetic age acceleration in monocytes
Beijers et al. (2023)	Prospective longitudinal cohort	Dutch low-risk community sample	193 (47.67%)	Buccal	PedBE	Age 6 and age 10	Cumulative risk measured	Epigenetic age, telomere length
Brody et al. (2016a)	Prospective cohort study	Subset of African American youth and families in rural Georgia who were originally a part of a prevention trial (SAAF)	Control: 157 (51%) Intervention: 242 (57%)	Blood	Horvath	Early adulthood	Parental depression; prevention program (moderation); harsh parenting and program effects	Epigenetic aging/age acceleration at age 22
Brody et al. (2016b)	Longitudinal study on two cohorts	African American youth in rural communities in Georgia, USA, who were from two longitudinal studies (SHAPE and AIM)	SHAPE: 322 (57.1%) AIM: 294 (63.6%)	Blood	Hannum	Early adulthood	Perceived racial discrimination and support in the family environment	Epigenetic aging in immune cells at age 22
Cardenas et al. (2019)	Cross-sectional	Children enrolled in a study to investigate nasal cellular epigenome and airway disease and environmental response (Project Viva)	547 (49.5%)	Respiratory epithelial cells (nasal swabs of anterior nares)	Horvath	Adolescence	Asthma, allergic asthma, biomarkers, allergic rhinitis	Epigenetic age acceleration
Cerveira de Baumont et al. (2021)	Observational study; cross-sectional analysis	Children and adolescents from public schools	234 (61% female)	Saliva	Horvath	Adolescence (time 1; age 13, time 2; age 17)	Anxiety symptoms	Epigenetic age/ acceleration
Chen et al. (2016)	Prospective cohort study	African American adolescents in Georgia, USA, who were followed from pre-recession to post-recession (2007–2010) to assess impact of macroeconomic conditions on health	330(53.6)	Blood	Horvath and Hannum	Early adulthood	Economic trajectories across period of Great Recession (2007–2010)	Epigenetic aging (leukocyte DNAm profiles), allostatic load, adolescent self-report of health (2010 at age ~ 19)
Clausing and Non (2021)	Longitudinal cohort study	Foreign-born immigrant Latina mothers over the age	71 mothers (100%<); 71 children (56.3%)	Saliva	Horvath, Hannum, PedBE, skin and blood age	Late childhood (ages 6–13)	Various psychosocial stress and resilience factors	Epigenetic age

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Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
		of 18 and their 6–13-year-old children						
Dammering et al. (2021)	Prospective cohort study; cross-sectional analysis	Children in the Berlin Longitudinal Study with history of maltreatment exposure with and without internalizing disorders	158 (46.2); 49 with current internalizing disorder and 109 without current internalizing disorder	Buccal	PedBE and Horvath	Early childhood	Maltreatment exposure; internalizing disorders	Epigenetic age and age acceleration
Dong et al. (2022)	Cohort study, matched controls	SJLIFE1 and SJLIFE2 participants enrolled in the St. Jude Lifetime Cohort Study, comprised of childhood cancer survivors. Community controls, with no history of childhood cancer	SJLIFE1: 2138 (47%); SJLIFE2: 502 (46.8%); 282 (51.4%)	Whole blood	Hannum, Horvath, PhenoAge, and GrimAge	Adolescence to midlife	Childhood cancer	Epigenetic age
Etzel et al. (2022)	Prospective cohort study; cross-sectional analysis	High-risk (82% investigated for maltreatment) children ages 8–14 years who are part of the prospective cohort Child Health Study (Pennsylvania)	273 (225 maltreated, 48 comparison; 50.5%)	Blood	HorvathAA, Hannum A A, GrimAgeAA, and PhenoAgeAA, DunedinPoAm	Middle childhood	BMI, exposure to maltreatment	Epigenetic age acceleration
Fiorito et al. (2017)	Prospective cohort study	Adults enrolled in independent prospective cohorts in Italy, Australia, and Ireland	5111 (48)	Peripheral blood	Horvath and Hannum	Adulthood	Early-life and current socioeconomic status	Epigenetic age acceleration (adulthood), noncommunicable diseases
George et al. (2021)	Cross-sectional	Socially stratified cohort of singleton births in 1 week of March 1946 in Britain (NSHD)	1376 (not reported)	Blood	Horvath, Hannum, PhenoAge, and GrimAge	Adulthood (53 years)	Childhood and adulthood social class/ socioeconomic position	Epigenetic age acceleration
Gettler et al. (2020)	Cross-sectional	Children of Bondongo families in a remote part of northern Republic of Congo who were in a study focused on fathering, family function and wellbeing	54 (51.9%)	Blood	Horvath and Hannum	Childhood to adolescence	Weight-for-height, height-for-age, antibody titers/inflammation, family environment	Epigenetic age acceleration (Horvath), intrinsic age acceleration (Horvath), extrinsic age acceleration (Hannum)
Gomez-Verjan et al. (2021)	Prospective cohort study	Subset of the Tlaltizapan cohort	39 (61.5% female)	Peripheral blood	Horvath & Hannum	Adulthood (age 57)	Years of schooling	Epigenetic age/ acceleration
Harris et al. (2022)	Observational; Cross-sectional analysis	Survivors of CNS tumors	83 (27.7% female)	Whole blood	Horvath	Middle childhood	Primary diagnosis, age at diagnosis	Epigenetic age/ acceleration
Hamlat et al. (2021)	Cross-sectional analysis	Premenopausal women enrolled in a larger project focused on chronic caregiver stress and aging in the	183 (100)	Whole blood	Horvath, Hannum, PhenoAge, Grim-Age	Adulthood	Early-life trauma (Child Trauma Questionnaire)	Epigenetic age acceleration (adulthood) and pubertal timing (self-

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Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
		University of California, San Francisco Autism Program						reported age at menarche)
Henckel et al. (2020)	Longitudinal case-control study	Subgroup of preterm and term born children with longitudinal blood samples in a case-control (LUFT) study	60 (43.3)	Umbilical cord blood and venous blood	Horvath	Infant to early childhood	Preterm vs. term birth	Epigenetic age change per year over first 2 years of life
Herrera-Moreno et al. (2022)	Birth cohort & prospective cohort study; Cross-sectional analysis	Participants in the Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) study	507 (44.9% female)	Cord blood	Horvath	Birth	Prenatal lead exposure	Epigenetic age/ acceleration
Horvath et al., (2018a, 2018b)	Cross-sectional	Perinatally HIV-infected (PHIV+) and HIV-uninfected (control) youth in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) study	PHIV+: 204 (51%) Control: 44 (55%)	Blood	Horvath and Hannum	Middle childhood to adolescence	Perinatal HIV infection; cognitive functioning (neuropsychological test battery)	Epigenetic age acceleration; extrinsic epigenetic age acceleration (FEA A)
Hughes et al. (2018)	Longitudinal cohort study	Participants from the UK Household Longitudinal Study	1099 (57.6%)	Whole blood	Horvath, Hannum	Adulthood	Current SES, childhood SES	Epigenetic age acceleration
Javed et al. (2016)	Meta-analysis & cross-sectional réplication	Mother-newborn dyads enrolled in a study examining prenatal exposures and intrauterine environment on newborns	Public dataset: 613 (31%) De novo data: 96 (not indicated)	Cord blood	Horvath	Neonatal	Sociodemographic and newborn characteristics	Epigenetic age acceleration, lymphocyte and immune markers (CD4 + and CDS+ T cell compartments)
Jovanovic et al. (2017)	Longitudinal study; cross-sectional analysis	African American children recruited as a part of a longitudinal study on trauma exposure in children (Atlanta, GA)	101 (54.5%)	Saliva	Horvath	Childhood to adolescence	Neighborhood violence and heart rate response to stressful task	DNAm age; epigenetic age acceleration
Joyce et al. (2022)	Prospective cohort studies	Participants from 3 US-based cohorts (CARDIA, FFCWS, PROGRESS) and one Mexico-based cohort (Project Viva)	CARDIA: 1036 (year 15 follow-up; 51.8); 1016 (year 20 follow-up; 50.9); FFCWS: 637 (not reported); Project Viva: 120 in early childhood and 460 in middle childhood); PROGRESS: not reported	Blood	Hannum, Horvath, PhenoAge, GrimAge, and DunedinPoAM	Infancy and childhood	Personal, parental, and neighborhood SES measures (i.e., education)	Epigenetic age and age acceleration

Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
Kim et al. (2022)	Longitudinal cohort study	Data captured from the Exploring Perinatal Outcomes in Children (EPOCH)	179 (49.7%)	Blood	Horvath	Age 10	Offspring diet, pubertal development, gestational diabetes mellitus exposure	Epigenetic age acceleration
Lawn et al. (2018)	Prospective cohort studies	Women in two cohort studies (ALSPAC and MRC National Survey of Health and Development; NHSD) with data on psychosocial adversity in childhood and epigenetic data collected at ages 29 and 47 (ALSPAC) or 53 (NSHD)	ALSPAC: 989 (100%) NHSD: 773 (100%)	Peripheral blood, buccal cells	Horvath	Adulthood	Psychosocial adversity in childhood	Epigenetic age acceleration in adulthood
Lecorguillé et al. (2023)	Prospective family study	The Lifeways Cross-Generation Cohort Study, families were recruited antenatally from two hospitals in Ireland	374 (244 mother child dyads, 130 father child dyads)	Saliva	PedBE	9.8 years	Parental dietary scores	Accelerated epigenetic age
Maddock et al. (2021)	Prospective cohort study	Subset of the National Child and Development study	1,376 (52.3% female)	Whole blood	Horvath & Hannum	Adulthood (age 53)	Height/weight	Epigenetic age/ acceleration
Marini et al. (2020)	Prospective cohort study	Subset of children from a population-based cohort study in UK (ALSPAC) at age 7	973 (50.2%)	Venous blood	Horvath and Hannum	Childhood	Adversity	Epigenetic age acceleration using both clocks
Mathewson et al. (2021)	Prospective cohort, matched Controls	Participants in the extremely low birthweight group were born in southern Ontario, matched with a normal birthweight group based on age, sex, ethnicity, and SES, based on lists provided by school boards	Extremely low birthweight: 45 (62.2%); normal birth weight controls: 47 (57.4%)	Buccal cells	Horvath	Middle adulthood	Cumulative risks (resting respiratory sinus arrhythmia, blood pressure, basal cortisol, grip strength, body mass index, and self-esteem)	Epigenetic age
McCrory et al. (2019)	Prospective cohort study	Subsample of the Irish Longitudinal Study on Ageing (TILDA) who had epigenetic data available	264 (50.2)	Blood	Horvath, Hannum, and Levine	Adulthood	Life course social class trajectory	Epigenetic age acceleration and allostatic load (immune, cardiovascular, metabolic, renal) in adulthood
McEwen et al. (2020)	Secondary analysis of prospective cohorts for clock development	Individuals (ages 0–20 years) from 11 cohorts with DNAm data	Training data: 1032 (52%) Test data: 689 (46.7%)	Buccal cells	Horvath and PedBE	Birth to young adulthood	Gestational age, birthweight, autism spectrum disorder (ASD) diagnosis	Epigenetic age and epigenetic age acceleration using and comparing both clocks
McGill et al. (2022)	Prospective cohort study	Mother-child dyads from two longitudinal cohorts (Basal Influences on	165 (47.3) in BIBO, 340	Buccal cells	PedBE and Horvath	Infancy (3–48 months) and	Maternal mood, symptoms of anxiety and depression in prenatal	Epigenetic age and age acceleration

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Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
		Baby Development (BIBO; Netherlands) and Growing Up in Singapore Towards Healthy Outcomes (GUSTO; Singapore))	(49.4) in GUSTO			childhood (6, 10 years)	and postnatal follow-up; child mental health	
Miller et al. (2015)	Randomized trial and prospective cohort study	African American adolescents enrolled in a randomized trial focused on substance and alcohol-use prevention (AIM; rural counties in Georgia, USA)	292 (63.7%)	Antecubital blood	Horvath and Hannum	Adulthood	Trajectories of self-control and socioeconomic disadvantage; BMI and life stress assessed in mediation models	Epigenetic age acceleration using both clocks at age 22
Nishitani et al. (2021)	Cross-sectional, matched controls	Children aged 2–9 years old who were removed from their biological parents by Child Protection Service, matched with children with no history of child maltreatment	Maltreated children: 25 (48%); healthy controls: 31 (58%)	Buccal cells	PedBE, SkinBlood, and Horvath	Early childhood (ages 2–9)	Child maltreatment	Epigenetic age acceleration
N wanaj i-Enwerem et al. (2021)	Prospective cohort study	Mexican American mothers and children who were enrolled in the CHAMACOS study followed up at child ages 7, 9, 14 years	238 children (54–59%-across time)	Blood	Horvath, Hannum, SkinBloodClock, Intrinsic, Extrinsic, PhenoAge, GrimAge	Childhood to adolescence (ages 7, 9, and 14 years)	Maternal preconception adverse childhood experiences	Epigenetic age acceleration
Okazaki et al. (2021)	Secondary data analysis	Four publicly available DNAm data sets of children with fetal alcohol spectrum disorder (FASD) and healthy controls	401 (49.1)	Buccal cells (2 data sets) and peripheral blood (2 datasets)	Horvath, Hannum, SkinBlood Age, PhenoAge, GrimAge	Childhood to middle childhood	Fetal alcohol spectrum disorder	Epigenetic aging measured by 5 clocks
Penova-Veselinovic et al. (2021)	Prospective and observational cohort study	Participants from Western Australia in the Growing Up Healthy Study (GUHS) and generation 2 of the Raine Study (RS). GUHS is a cohort of adolescents and young adults conceived through ART, while the Raine Study participants are a cross-section of a longitudinal study with mothers and their biological children	GUHS: 231 (47.2%); RS: 1188 (49.1%)	Whole blood	Horvath, Hanuum, PhenoAge [Levine], and skin Horvath	Adolescence	ART vs. natural birth	Epigenetic age
Phang et al. (2020)	Cross-sectional	Mother-newborn dyads enrolled in a study examining implications of maternal diet on newborn fatness and cardiovascular health	169 (53.2%)	Saliva	Horvath	Neonatal	Maternal dietary and macronutrient intake	DNAm age/predicted biological age at birth, epigenetic age acceleration; aortic intima-media thickness; HRV

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Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
Popovic et al. (2021)	Longitudinal case-control study	Subset of mothers and infants in the NINFEA Italian Birth Cohort with saliva samples	139 (43.2)	Saliva	Horvath and PedBE	Infancy	Parental socioeconomic status; pregnancy outcomes	Epigenetic age and age acceleration using both clocks
Reimann et al. (2022)	Prospective cohort study	Mothers enrolled from the ENVIRONAGE birth cohort, an ongoing prospective cohort with mother-newborn pairs recruited from East-Limburg Hospital in Genk, Belgium	190 mothers (100%); newborns: 190 (49.2%)	Cord blood	Horvath	Birth	Global méthylation, mtDNA, cord blood telomere length	Epigenetic age/age acceleration
Shiau et al. (2018)	Cross-sectional	HIV-infected, HIV-exposed uninfected (HEU), and HIV-unexposed uninfected (HUU) children who were part of a HIV research cohort study	178 (51.6%) (220 HIV-infected; 33 HEU; 25 HUU)	Venous blood	Horvath	Childhood	HIV exposure/infection status: HIV-infected, HIV-exposed uninfected, and HIV-unexposed uninfected	Telomere length, epigenetic age acceleration, systemic inflammation (IL-6, TNF-alpha), CD4 count
Shiau et al. (2021a)	Prospective cohort study	Children who were part of a HIV research cohort study, some exposed to HIV perinatally and others not exposed	39 (48.7%)	Peripheral blood	Horvath	Age 10.9 and age 16.8	HIV exposure/infection status: HIV-infected, HIV-exposed uninfected and HIV-unexposed uninfected	Epigenetic age acceleration
Shiau et al. (2021b)	Prospective study	Children of women (with and without prenatal gestational diabetes (GDM) who participated in the Tianjin GDM Prevention Program	1145 (47.8%)	Whole blood	Horvath and Hannum	Childhood	Exposure to gestational diabetes in utero	Epigenetic age of child
Suarez et al. (2018a)	Prospective cohort study	Mother-infant dyads in a cohort study (PREDO) examining prenatal exposures and intrauterine milieu on fetal development	814(47.2%)	Cord blood	Horvath	Neonatal	Maternal history of depression diagnosed pre-pregnancy; antenatal depression	Epigenetic gestational age (DNAm GA): internalizing/ externalizing problems in early childhood
Sumner et al. (2019)	Cross-sectional	Children dyads enrolled in a study examining early-life adversity, emotional regulation, and psychopathy	247 (47.8%)	Saliva	Horvath	Childhood to adolescence	Early-life adversity (threat- and deprivation-related)	Epigenetic age
Tang et al. (2020)	Prospective cohort study; cross-sectional analysis	Subset of children from a population-based cohort study in the UK (ALSPAC) with epigenetic data measured in adolescence	974 (51.3%)	Peripheral blood	Horvath	Adolescence	Adverse childhood experiences from cumulative ACEs and exposure to individual ACEs	Epigenetic age acceleration
Van Lieshout et al. (2021)	Case-control study	Extremely low birth weight survivors and matched controls	92 (59.8% female)	Buccal cells	Horvath	Adulthood (age 32)	Extremely low birth weight, number of chronic health conditions	Epigenetic age/ acceleration
Verlinden et al. (2023)	Longitudinal follow-up of randomized trial	Participants who were part of the PEPaNIC RCT, which studied children admitted	1,210 (N = 392 healthy controls,	Buccal cells	PedBE	3.8 years in healthy controls, 3.4	Critical illness, early parenteral nutrition vs. late parenteral nutrition	Epigenetic age deviation

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Study	Study design	Study population	Sample size (% female)	Tissue type	Epigenetic clock	Age of clock assessment	Predictors	Outcome
		to the PICU, and matched healthy children	N = 818 PICU patients)			in PICU participants		
Zannas et al. (2015)	Cross-sectional analysis	African American adults in the Grady Trauma Project (GTP); Caucasian adults in the Max Planck Institute of Psychiatry (MPIP) cohort	GTP: 393 (70.7) MPIP: 124 (35.5)	Peripheral blood	Horvath	Adulthood	Childhood trauma exposure (retrospective self-report), stressful life events, PTSD, and depression symptomatology	Epigenetic age acceleration in adulthood