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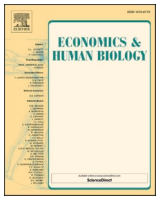

The intergenerational association of epigenetic modifications between mothers and offspring, from birth to adolescence

Chiara Costi [a,d,*], Giorgia Menta [b], Giovanni Fiorito [c], Conchita D'Ambrosio [a]

[a] University of Luxembourg, Luxembourg
[b] Luxembourg Institute of Socio-Economic Research (LISER), Luxembourg
[c] Clinical Bioinformatics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[d] University of Verona, Italy

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ABSTRACT

Epigenetic modifications, such as DNA methylation (DNAm), have an important role in human disease development, with early DNAm patterns potentially influencing health outcomes in later life. In this paper, we examine the intergenerational association of epigenetic mutation load (EML), a biomarker of epigenetic instability, identifying DNAm outliers. Using mother-child dyads from a UK-based cohort study, we examine the intergenerational association of EML at three time points: birth, childhood (mean age 7.5), and adolescence (mean age 17). We find significant associations of maternal EML with offspring EML during childhood and adolescence, while this association is absent at birth. This suggests that shared environment, rather than direct biological transmission, might be playing a larger role in this intergenerational correlation. When looking at the association between own EML, and maternal EML, with early-adulthood outcomes, results suggest that own EML predicts worse cognitive abilities later in life, while maternal EML is not directly associated to offspring's outcomes.

1. Introduction

The study of epigenetic processes has increasingly gained attention in recent years, with an emphasis on epigenetic modifications as a biological mechanism through which environmental factors influence health outcomes (Cavalli and Heard, 2019; Perera et al., 2020; Hanson and Skinner, 2016).

Epigenetic mechanisms are used by cells to regulate biological processes such as gene expression, genome imprinting and defence against viral sequences in response to environmental stimuli, without changing the DNA sequence (Handy et al., 2011). One of the most studied and better understood epigenetic modification is DNA methylation (DNAm), which involves the addition of methyl groups on the C5 position of a cytosine–phosphate–guanine (CpG) site (Lardenoije et al., 2015; Bird, 2002). Although epigenetic effects over the lifespan of both adults and children have been documented in the literature, relatively little is known about epigenetic associations across generations. While the presence of epigenetic transgenerational inheritance is well documented in organisms like plants and some animals (Hauser et al., 2011; Guerrero-Bosagna et al., 2018), evidence for such heritable transmission of epigenetic marks is less clear in mammals, particularly humans.

We here examine the intergenerational association of DNAm instability, measured by the Epigenetic Mutation Load (EML), between mothers and children from birth to adolescence. Following the approach outlined in Gentilini et al. (2015), we define stochastic epigenetic mutations (SEMs) as outliers of the distribution of DNAm. In other words, SEMs are CpG sites that are abnormally highly methylated or unmethylated.[1] Accordingly, the EML, defined as the total number of SEMs per individual, has been proposed as a biomarker of the individuals' overall methylation instability (Curtis et al., 2019). Our study uses data from the Accessible Resource for Integrated Epigenomic Studies (ARIES), a sub-study of the Avon Longitudinal Study of Parents and Children (ALSPAC). In addition to a variety of socio-economic and environmental variables, the dataset includes multiple measurements of DNAm for both mothers and their offspring, allowing the study of mother-child correlations over time. Furthermore, we investigate

* Corresponding author at: University of Verona, Italy.
E-mail addresses: chiara.costi@uni.lu (C. Costi), giorgia.menta@liser.lu (G. Menta), giovannifiorito@gaslini.org (G. Fiorito), conchita.dambrosio@uni.lu (C. D'Ambrosio).

[1] A more detailed definition of SEMs can be found in Section 2.2

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whether child and maternal EML are associated with a broad set of child health and socio-economic outcomes measured in early adulthood. Understanding this helps determine the extent to which an individual's own EML and maternal EML correlate with later life outcomes.

Our results document a 5 % intergenerational elasticity[2] between mother and child EML, which emerges in childhood and consolidates in adolescence, while the relationship is completely inelastic at the time of the child's birth. The late onset of this mother-child association of DNAm instability suggests that (unobserved) shared environment could trigger children's predisposition towards DNAm dysregulation after birth disproportionately more for those whose mothers have high EML. When following these children into their early adulthood years, we do not find evidence of a direct association between maternal EML and offspring's outcomes, such as health, income, or educational attainment. Similarly, we find no evidence of a strong relationship between children's own EML and their early adulthood outcomes, suggesting that the adverse effects of EML might start emerging only later in life. One exception is verbal IQ, whose negative association with child EML suggests that DNAm dysregulation might already play a role on early adulthood cognitive abilities.

These results are consistent with current theories of epigenetics suggesting a covariance between parent and child DNAm levels (Kile et al., 2010). Since mothers and children share the same environment, it is plausible that their DNAm levels could correlate due to similar environmental exposure, such as diet and the stressors like pollution, toxicants and temperature (Van Aswegen et al., 2021). Moreover, both theoretical and animal models suggest that epigenetic patterns might be inherited and passed on from parents to offspring (Guerrero-Bosagna and Skinner, 2012; Breton et al., 2021), with experimental studies involving mice and rats showing a parent-offspring inheritance of epigenetic patterns in response to environmental or metabolic factors, such as high fat diet and traumatic stress (Bohacek and Mansuy, 2013; Klengel et al., 2016; Heard and Martienssen, 2014; Illum et al., 2018; Gapp et al., 2014).

Non-environmental correlations in mother-child epigenome are instead less likely to be in place, since the mammalian epigenome undergoes global erasure and reprogramming during germ cell development and soon after fertilization (Liu et al., 2023; Iqbal et al., 2015). While some epigenetic studies investigating the transmission of DNAm in humans have considered in-utero exposure to traumatic events, such as genocides or famines, showing that the offspring of affected mothers display differential methylation levels compared to unexposed children (Perroud et al., 2014; Yehuda et al., 2016; Klengel et al., 2013; Tobi et al., 2014; Lumey et al., 2007), it remains challenging to provide robust evidence of transgenerational epigenetic inheritance in humans due to confounding by genetic, environment and cultural inheritance (Horsthemke, 2018; Fallet et al., 2023).

We contribute to the existing literature in several other ways. To our knowledge, only a few studies have investigated the association between parent and child DNAm, reporting positive mother-offspring associations in methylation levels at child's birth (Hu et al., 2023; Jiang et al., 2024) and in early adolescence (Van Aswegen et al., 2021; Tremblay et al., 2016). However, these studies examine the intergenerational association of DNAm within a cross-sectional and uni-generational framework, and often rely on small samples of mother-child dyads. Our study is the first to analyse the intergenerational association of DNAm instability, which is crucial for understanding the inheritance of epigenetic marks and the role of shared environment in these associations.

We also contribute to the limited literature on EML, by examining its association with early adulthood outcomes. Existing evidence suggests that epigenetic dysregulation, reflected in abnormal DNAm levels, plays a significant role in human disease and is linked to an increased risk of various pathological conditions (Jin and Liu, 2018; Robertson, 2005). These include chronic diseases (Lardenoije et al., 2015; Kiselev et al., 2021; Haque et al., 2016), cancer (Gagliardi et al., 2020; Gentilini et al., 2017; Yamashita et al., 2018), metabolic and psychological disorders (Robertson, 2005), and age-related conditions such as Parkinson's disease (Chen et al., 2022) and unhealthy aging (Gentilini et al., 2015; Wang et al., 2019; Fiorito et al., 2017). Our findings, which show null to modest associations in early adulthood, suggest that the adverse health effects of EML may emerge only later in life.

2. Data

2.1. Sample

We use data from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Fraser, et al., 2013; Boyd, et al., 2013), which is an ongoing cohort study containing a wide set of biological samples as well as phenotypic, environmental, genetic and linkage data.[3] Pregnant women resident in Avon (UK) with expected dates of delivery between April 1991 and December 1992 were invited to take part in the study, enrolling an initial 14,541 pregnancies with 13,988 children who were alive at 1 year of age. Informed consent was obtained from all participants. The dataset also contains socio-economic information of partners (Northstone et al., 2023). Behavioural questionnaire data of children from 22 years of age onwards were collected and managed using REDCap (Harris et al., 2009).[4]

A sub-set of 1,018 mother-offspring dyads were included in ARIES, and biological samples were collected the first time at child's birth (T0) for both mothers and children; samples were collected a second time only for children when they were on average 7.5 years old (T1); and for both mothers and children a third time during children's late adolescence, around 17 years old (T2). Consent for biological samples was gathered in accordance with the Human Tissue Act (2004). The estimation sample is composed of 746 mother-child dyads with valid epigenetic profiles at all time points.

2.2. Epigenetic Mutation Load (EML)

DNAm in ALSPAC was quantified using the Illumina Infinium HumanMethylation450K BeadChip assay (Illumina 450 K array). Cord and peripheral blood samples were collected according to standard procedures (Relton et al., 2015). Epigenetic mutations are defined as abnormal methylation events that deviate substantially from typical patterns observed in the population. These deviations may arise due to environmental exposures, aging, or stochastic epigenetic drift, and they can serve as markers of genomic instability. To quantify an individual's epigenetic mutation load (EML), we first identify stochastic epigenetic mutations (SEMs) – CpG sites where DNAm levels fall outside the expected range. The rationale behind this approach is that most CpG sites exhibit a relatively stable distribution of DNAm levels across individuals, so extreme values likely indicate dysregulation.

To formally define SEMs, we followed the method of Gentilini et al. (2015), which detects outliers in the DNAm distribution. For each CpG site, we first calculated the interquartile range (*IQR*) – the difference

[2] Elasticity is the responsiveness of one variable to changes in another. Intergenerational elasticity is typically estimated parametrically using a log-log regression of a child's outcome Y_C on the same parental outcome Y_P. The elasticity parameter is β, the estimated coefficient of Y_P, which is equivalent to $\frac{\%\Delta Y_C}{\%\Delta Y_P}$.

[3] Details of all the data is available through a fully searchable data dictionary and variable search tool that can be found at http://www.bristol.ac.uk/alspac/researchers/our-data/

[4] REDCap (Research Electronic Data Capture) is hosted at the University of Bristol. It is a secure, web-based software platform designed to support data capture for research studies.

between the 3rd quartile (Q3) and the 1st quartile (Q1) of DNAm beta values across all individuals. A CpG site was classified as a SEM for a given individual if its methylation value was unusually high or low, specifically higher than $Q3+(3\times \mathrm{IQR})$ or lower than $Q1-(3\times \mathrm{IQR})$. . Formally, for each CpG site k in $\{1,\ldots,K\}$:

$$SEM_k = \begin{cases} 0, \& \beta_k \in [Q_1 - 3\times IQR; Q_3 + 3\times IQR] \\ 1, \& \beta_k \notin [Q_1 - 3\times IQR; Q_3 + 3\times IQR] \end{cases}.$$

Our measure of interest is the epigenetic mutation load (EML), which is the sum of SEMs across all K measured CpGs.[5] Hence, for each individual i:

$$EML_i = \sum_{k=1}^{K} SEM_{ik}.$$

Since EML is not normally distributed (see Figures A1 and A2), we used a logarithmic transformation of EML for subsequent association analyses (Fiorito et al., 2021; Gentilini et al., 2015). In addition, we construct two separate measures of EML, one using only SEMs with extremely high DNAm values (hyper-methylated EML) and one using only extremely low values (hypo-methylated EML). In other words, while the EML is defined as the total number of SEMs, regardless of whether these outliers are extremely high or extremely low values, hyper-methylated EML only considers the sum of SEMs with extremely high values (above $Q_3 + 3\times IQR$). Similarly, hypo-methylated EML is defined as the sum of SEMs with only extremely low values (below $Q_1 - 3\times IQR$).

3. Empirical strategy and descriptive statistics

3.1. Empirical strategy

This study aims to investigate the association of maternal EML with child EML over time. We estimate the following linear regression model using Ordinary Least Squares (OLS):

$$EMLc_{it} = \alpha_0 + \alpha_1 EMLm_{it_0} + \alpha_2 EMLc_{i(t-1)} + \alpha_3 X_{it} + \varepsilon_{it}, \quad (1)$$

where $EMLc_{it}$ is child i's EML at time t, $EMLm_{it_0}$ is child i's mother's EML at T0 (and/or at T2 in an alternative specification), and $EMLc_{i(t-1)}$ is child i's EML in the previous period $(t-1)$. EML for both mothers and children is log transformed. The coefficient of interest is α_1, which can be interpreted as the intergenerational elasticity of EML. A positive estimate of α_1 is indicative of an intergenerational persistence of EML.

X_{it} is a vector of baseline characteristics and time-varying life events. The baseline characteristics included in X_{it} are child's gender, age and birth weight; mother's age at delivery, gestational length (in weeks), binary variables indicating C-section, maternal folic acid intake during pregnancy; and the socioeconomic variables of partner's occupational social class (a variable identifying occupations in: non-manual high skilled roles i.e., professional/managerial; non-manual skilled roles; and manual partly skilled/unskilled roles) and maternal educational attainment (a binary variable indicating the completion of higher-secondary education, namely the obtainment of A-levels or of an equivalent qualification).

The time-varying characteristics are external factors that could affect DNAm levels of both mothers and children. These count variables indicate how many times each of the following events occurred between two DNAm measurements: mother divorced/separated; mother reporting major financial problems; family living in a polluted neighbourhood; smoking (indicating mother smoking during pregnancy at T0, child passive smoke at T1, and child smoking at T2); obesity (reflecting maternal obesity pre-pregnancy at T0, and child obesity at T1 and T2); partner cruelty (indicating if the partner was cruel to the mother during pregnancy at T0, and cruel to the child at T1 and T2); traumas (indicating whether the mother was sexually abused pre-pregnancy at T0, and the child experience of any traumatic event at T1 and T2).

We additionally investigate whether own EML and maternal EML affect children's later life outcomes. For this research question, we estimate the following regression via OLS:

$$Y_{i(t+1)} = \beta_0 + \beta_1 EMLc_{it} + \beta_2 EMLm_{it_0} + \beta_3 X_{it} + u_{it}, \quad (2)$$

where Y_i is alternatively one of the child's outcome variables measured in early adulthood $(t+1)$. These include self-assessed general health measured on a 1–5 scale, with higher values indicating better health; health limitations, indicating the number of daily-life activities limited by health issues[6] (both of these health outcomes are measured when the child is 21 years old); a measure of verbal IQ proxied by the Wechsler Intelligence Scale for Children (WISC) vocabulary test, with higher values indicating higher knowledge, verbal productivity and concept formation (measured at age 24); income at age 25, measured as the monthly total take-home pay after tax and national insurance; and education, measured by a binary variable equal to one if the young adult obtained a university degree by age 26, and zero otherwise. All these outcomes, except for the binary education variable, are standardized to have mean zero and standard deviation one for comparison purposes.

As in Eq. (1), Eq. (2) also includes the same set of covariates X_{it} and EML is log transformed for both mothers and children. Both child EML and the covariates X_{it} are measured at T2, when the child is 17 years old on average. β_1 is the coefficient of interest, indicating if there is an association between child's EML and early adulthood outcomes. Maternal EML ($EMLm_{it_0}$) is measured at baseline (T0); its coefficient β_2 indicates if mothers' DNAm dysregulation is directly associated with children's outcomes later in life, above and beyond its potential indirect association operating through children's EML.

Table 1
Descriptive statistics of baseline characteristics.

	Mean	SD	Min	Max
Maternal age at birth (years)	29.62	4.51	16	42
Partner' occupational social class:				
Professional (high-skilled)	0.15		0	1
Non-manual (managerial/skilled)	0.44		0	1
Manual (manual-skilled and unskilled)	0.33		0	1
Maternal education (At least A-level)	0.49		0	1
Child sex: Female	0.51		0	1
Child birth weight (kg)	3.49	0.47	1.49	5.14
C-section	0.09		0	1
Gestational length (weeks)	39.60	1.48	30	44
Folic acid intake	0.24		0	1
N	746			

Notes: These characteristics are measured at child's birth (T0) and are time invariant. 8 % of observations are flagged as missing for partner's occupational social class.

3.2. Descriptive statistics

Baseline characteristics included in our analysis are displayed in Table 1. Mothers are on average 30 years old at delivery, 15 % of families are of high socioeconomic class (proxied by the partner's

[5] To ensure comparability of SEM counts across DNAm measurements taken at different time points, we anchor the definition of SEMs to the quartiles and IQR of the DNAm distribution at birth.

[6] Respondents were asked whether health limited the following activities: vigorous activities (such as running); moderate activities (like moving a table); lifting/carrying groceries; climbing several (or one) flights of stairs; bending/kneeling; walking: more than a mile, several hundred yards, one hundred yards; and bathing/dressing. Binary variables identify if respondents were limited in each activity. The variable used in the analysis is the sum of these binary variables, with higher values indicating more limitations.

occupational social class), half of the mothers in the sample have obtained at least an A-level degree or equivalent, around 10 % of mothers gave birth by C-section, and 24 % took folic acid supplements during pregnancy. Gestational length is approximately 40 weeks and child's birth weight is on average 3500 g, which is consistent with national statistics in the early 1990 s for England and Wales (Ghosh et al., 2018).

Child and mother EML, as well as other time-varying environmental covariates, are displayed in Table A1 (Supplementary Information). Overall, the characteristics of ARIES individuals are comparable to those in the rest of ALSPAC, with children in ARIES exhibiting similar levels of birth-related characteristics, while mothers included in ARIES are slightly older and more educated. The ARIES sub-sample is considered to be reasonably representative of the main study population (Relton et al., 2015).

4. Results

4.1. Intergenerational associations results

Table 2 shows the associations between baseline maternal EML and offspring EML at three points in time, when time-invariant and time-varying controls are sequentially included in the regressions. Given the observational nature of this study, the intergenerational link between mother and child's EML is likely confounded by unobserved factors and cannot be interpreted as causal. To mitigate concerns about unobserved confounders and omitted variable bias, we therefore control for a set of baseline variables determined at or before birth (e.g., birth-related and pregnancy variables, maternal education, paternal occupational social class) and a set of time-varying life events (e.g., traumas, pollution, major financial problems). Although we do not establish a precise causal relationship, this approach allows us to control for observable confounders captured in our dataset. The full list of results is displayed in Tables A2-A4 (Supplementary Information), where we show the coefficients of the whole set of variables included in the analysis.

Columns (1) to (3) of Table 2 show no significant associations between the mother's and the child's EML at child's birth (T0), irrespective of the covariates included in the analysis. The association becomes positive and significant during childhood (T1) and adolescence (T2). Regardless of the inclusion of observed life events that could simultaneously influence the child's and the mother's EML, the associations displayed in the first row remain stable and of similar magnitude across columns (4) to (9), indicating that the relationship is constant throughout childhood and adolescence and is orthogonal to the set of covariates included in the model. The stability of the coefficients further suggests that part of the variation in child EML is directly explained by maternal EML. Since the absence of intergenerational correlation at birth suggests no biological transmission, the direct effect we observe is likely due to unobserved environmental shocks.

While the association is statistically significant at least at the 95% level across all model specifications in periods T1 and T2, it is rather small in magnitude: a doubling of the mother's EML at the time of her child's birth is associated only to a 5% higher child EML in childhood ($p = 0.012$, 95% CI [0.011, 0.091]) and adolescence ($p = 0.009$, 95% CI [0.012, 0.088]), revealing a rather inelastic relationship between the two. Although a 5 % intergenerational elasticity may seem small in absolute terms, when compared to the point estimates of other covariates in the model (reported in Table A3), it is larger in magnitude than the coefficient for an additional week of gestation and is comparable to 60 % of the female premium in EML and to the 20 % of the obesity penalty. We also observe that during adolescence (T2), a doubling in the child's lagged EML is associated with a 13 % increase in their own current EML ($p = 0.000$, 95% CI [0.066, 0.196]) – an association that is 2.6 times the size of that with maternal EML. However, this association is not in T1, indicating a lack of intertemporal persistence of methylation dysregulation from birth into later years.

Importantly, maternal EML is also measured at T2. As a sensitivity test, the last two columns of Table A4 (in Supplementary Information) control for maternal EML at T2 instead of, or in addition to, baseline maternal EML at T0. Table A4 shows that maternal EML at T2 is only weakly associated to child's EML (column (4)), and its coefficient becomes no longer statistically different from zero when we also control for maternal EML at T0 (column (5)). This suggests that contemporary maternal EML is less predictive of the child's EML than maternal EML at T0. One possible explanation is that maternal EML at T0 likely captures the cumulative epigenetic signature of the mother's lifestyle and environmental exposures. Given the stability of family environments over time (Heckman and Mosso, 2014), maternal EML at T2 may not provide much additional explanatory power for the intergenerational association of EML.

4.2. Associations between EML and early adulthood outcomes

Table 3 shows the associations of children's EML measured during adolescence (T2) and maternal EML measured at child's birth (T0) on children's outcomes at different ages (from 21 to 26 years old), when pre-determined characteristics and time-varying life events are included in the regressions.

From the first row of Table 3, we observe a significant negative association with a measure of IQ, the WISC vocabulary test, in Column (3), where a doubling of the child's EML is associated to 23 % of a standard deviation decrease in vocabulary skills ($p = 0.014$, 95% CI [-0.407, -0.045]). Consistently, all associations with other early adulthood outcomes contained in Table 3, including health, income and post-secondary education, align with expectations: higher EML correlates with poorer health and socio-economic outcomes; however, none of the coefficients is statistically different from zero.[7]

Maternal EML may influence offspring outcomes primarily through two pathways: first, by shaping the child's own EML, and second, through its potential impact on maternal health and socioeconomic outcomes, which in turn affect offspring development. However, as shown in the second row of Table 3, the coefficients of maternal EML are always small in size and never statistically significant. Given that offspring's own EML in adolescence correlates with moderately worse early-adulthood outcomes, this suggests that the influence of maternal EML on offspring operates primarily through its indirect effect on the child's own EML rather than exerting an independent effect via maternal outcomes. In other words, the impact of maternal EML on offspring outcomes could be mediated by the extent to which children inherit or develop similar epigenetic patterns.

While many studies provide evidence of an association between DNAm dysregulation and age-related pathologies (Danese and McEwen, 2012; Lardenoije et al., 2015; Fiorito et al., 2019), here we do not find any significant associations with general health and health limitations (Columns (1−2)). A possible explanation for this result is that DNAm dysregulation does not influence young adults' health, while becoming a determinant of negative health outcomes in older age.

However, the lack of significance in our estimates could plausibly be attributed to the smaller sample size in this analysis. Many observations are lost due to attrition, as only individuals who remained in ALSPAC long enough to report early adulthood outcomes are included in our estimation sample.[8] Since all coefficients align with expectations, it is

[7] As shown in Table A5, results are the same when using non-linear models (ordered probit for ordinal outcomes and simple probit for binary ones) to estimate Table 3.

[8] Appendix Table A6 shows differences in mean characteristics between individuals included in the full sample and those in the adult follow-up samples. Respondents in the follow-up samples have similar characteristics compared to the full estimation sample, except from a higher proportion of women (who are known to display lower attrition levels than men in longitudinal samples, see Jacobsen et al., 2021; Mein et al., 2012; Post et al., 2012).

Table 2
The association of maternal EML with child EML.

	T0			T1			T2		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Maternal EML (T0)	−0.002	−0.007	−0.010	0.049**	0.047**	0.051**	0.041**	0.050***	0.050***
	(0.037)	(0.038)	(0.038)	(0.020)	(0.020)	(0.020)	(0.019)	(0.019)	(0.019)
Child EML (t−1)				−0.016	−0.014	−0.014	0.115***	0.125***	0.131***
				(0.019)	(0.019)	(0.019)	(0.033)	(0.033)	(0.033)
Pre-determined ch.		Yes	Yes		Yes	Yes		Yes	Yes
Life events			Yes			Yes			Yes
N	746	746	746	746	746	746	746	746	746

Notes: These are linear regressions, showing associations at offspring's birth (T0), at 7.5 years old (T1) and at 17 years old (T2). Robust standard errors are in parentheses. EML is log transformed. Pre-determined characteristics include child's gender, age, birth weight, C-section, gestation length; mothers' age at delivery, education level, folic acid intake; and partners' occupational social class. Life events include mothers' divorce/separation, major financial problems, living in a polluted area, smoking, obesity, partners' cruelty and traumas. *, ** and *** indicate significance at the 10 %, 5 % and 1 % levels respectively.

Table 3
The association of child EML with later outcomes.

	General Health	Health limitations	WISC Vocab. Test	Income	Uni. degree
	(1)	(2)	(3)	(4)	(5)
Child EML (T2)	−0.130	0.046	−0.230**	−0.153	−0.002
	(0.103)	(0.093)	(0.094)	(0.113)	(0.040)
Maternal EML (T0)	0.006	−0.030	0.064	0.001	0.010
	(0.052)	(0.042)	(0.040)	(0.061)	(0.018)
N	358	348	484	396	502
Mean of the outcome	2.765	0.902	8.205	3.513	0.743
SD of the outcome	0.923	1.789	2.752	1.231	0.437

Notes: These are linear regressions. For ease of interpretation, outcomes in columns (1) to (4) are standardized to have mean 0 and standard deviation 1. Robust standard errors are in parentheses. EML is log transformed. General health (higher values indicate better health) and health limitations are measured at 21 years old, WISC vocabulary test is measured at 24 years old, income is measured at 25 years old and university degree is measured at 26 years old. All regressions include pre-determined characteristics (child's gender, age, birth weight, C-section, gestation length; mothers' age at delivery, education level, folic acid intake; and partners' occupational social class) and life events (mothers' divorce/separation, major financial problems, living in a polluted area, smoking, obesity, partners' cruelty and traumas). *, ** and *** indicate significance at the 10 %, 5 % and 1 % levels respectively.

possible that we simply lack the statistical power to detect small to medium associations at conventional significance thresholds – associations that might have been observable with a larger sample. The lack of significant results could also be explained by the smaller variability in health limitations and general health of young individuals aged 21 years, who are generally healthier than older individuals. In the adult estimation samples in Table 3, only 11 % of respondents report having 3 or more daily-life activities limited by health issues, while 64 % do not report any health limitation. The distribution of general health behaves similarly, with 51 % of the sample reporting "Excellent" or "Very good" health and 10 % reporting "Fair" or "Poor" health.

5. Heterogeneity analyses

5.1. Intergenerational associations by sex

To understand whether the observed intergenerational associations differ by the child's biological sex, we conducted a heterogeneity analysis, presenting the results in Table 4. Here, we can see that there is a significant association between maternal EML and child EML in T1 and T2 for female children, while the coefficients for male children are statistically insignificant. These results are in line with previous observations suggesting that observed intergenerational associations could be due to a shared environment between mothers and offspring, with mothers exerting a greater influence on daughters (Holmlund et al., 2011).

It could be argued that the results of the heterogeneity analysis by sex are driven by the presence of the X chromosome in the female subgroup (Gentilini et al., 2015; Hu et al., 2023). For this reason, Table A7 in Supplementary Information shows the same set of results when we re-calculated EML removing chromosome X from the analysis. The results presented in Table A7 are equivalent to those in Table 4, showing that the heterogeneity analysis is not driven by the presence of the X chromosome.

5.2. Distinguishing between hypo- and hyper-methylation

While in the main analysis we considered the total number of SEMs forming the epigenetic mutation load, Table 5 disaggregates the main results by type of EML. Specifically, we looked at hyper- and hypo-methylated CpG sites, which are respectively based on the count of extremely high or extremely low DNAm values, for both mothers and their offspring. This approach enables us to identify which type of DNAm modifications primarily drive the observed intergenerational association with EML. As in the main analysis, EML was logarithmic transformed.

Here, we see that maternal hyper-methylated EML is significantly and positively associated with the child's hyper-methylated EML starting from period T1. In particular, a 100 % increase in hyper-methylated maternal EML is associated with an increase of 7 % ($p = 0.001$, 95%

Table 4
The association of maternal EML with child EML - by gender.

	T0		T1		T2	
	(1)	(2)	(3)	(4)	(5)	(6)
	Female	Male	Female	Male	Female	Male
Maternal EML (T0)	−0.057	0.020	0.075***	0.029	0.053*	0.036
	(0.054)	(0.055)	(0.027)	(0.030)	(0.028)	(0.026)
Child EML (t−1)			−0.017	−0.013	0.162***	0.128***
			(0.024)	(0.029)	(0.056)	(0.043)
N	382	364	382	364	382	364

Notes: These are linear regressions, showing associations at offspring's birth (T0), at 7.5 years old (T1) and at 17 years old (T2). Robust standard errors are in parentheses. EML is log transformed. All regressions control for pre-determined characteristics (child's gender, age, birth weight, C-section, gestation length; mothers' age at delivery, education level, folic acid intake; and partners' occupational social class) and life events (mothers' divorce/separation, major financial problems, living in a polluted area, smoking, obesity, partners' cruelty and traumas). *, ** and *** indicate significance at the 10 %, 5 % and 1 % levels respectively.

Table 5
The association of maternal EML with child EML, considering hyper- and hypo-EML.

	T0	T1	T2
	(1)	(2)	(3)
Panel A: Child hyper EML			
Maternal EML hyper (T0)	0.002	0.074***	0.048**
	(0.036)	(0.022)	(0.019)
Child EML hyper (t−1)		−0.010	0.173***
		(0.022)	(0.033)
Panel B: Child hypo EML			
Maternal EML hypo (T0)	−0.003	0.006	0.037*
	(0.040)	(0.020)	(0.020)
Child EML hypo (t−1)		−0.023	0.018
		(0.017)	(0.034)
N	746	746	746

Notes: These are linear regressions, showing associations at offspring's birth (T0), at 7.5 years old (T1) and at 17 years old (T2). Robust standard errors are in parentheses. EML is log transformed. All regressions include pre-determined characteristics (child's gender, age, birth weight, C-section, gestation length; mothers' age at delivery, education level, folic acid intake; and partners' occupational social class) and life events (mothers' divorce/separation, major financial problems, living in a polluted area, smoking, obesity, partners' cruelty and traumas). *, ** and *** indicate significance at the 10 %, 5 % and 1 % levels respectively.

CI [0.031, 0.116]) and 5% ($p = 0.013$, 95% CI [0.010, 0.086]) in the child's hyper-methylated EML in T1 and T2, respectively – a magnitude in line with that contained in Table 2. In contrast, hypo-methylated maternal EML is not associated with child EML in periods T0 and T1; in the latter, the coefficient for hypo-methylated EML is statistically different from that for hyper-methylated EML at the 1 % level. However, a positive relationship emerges in period T2, with a statistically insignificant difference between hypo- and hyper-methylated EML coefficients. Table A8 in the Supplementary Information replicates Table 2, considering aggregate child EML as the outcome, and only disaggregates mother's EML into hypo- and hyper-methylated EML. The sequential inclusion of the two in the model reflects their high correlation (correlation coefficient of 0.77). When controlling for maternal EML in both periods simultaneously, the results corroborate the findings of Table 5, with mother's hyper-methylated EML associated with larger (albeit insignificant) regression coefficients.

5.3. Heterogeneity by adversity intensity

To further explore the potential mechanisms underlying the intergenerational transmission of EML, we examine whether the association between maternal and child EML varies by the intensity of shared adversity. Specifically, we created a variable counting the number of adverse life events experienced by the family in each period of analysis. These include mothers' divorce or separation, living in a polluted area, smoking, obesity, and partners' cruelty.[9] Based on this variable, we defined three adversity groups: those who never experienced an adverse life event, those who experienced at most one, and those who experienced two or more. We then estimated our main model specification, incorporating binary indicators for each adversity group (using those who never experienced adverse life events as the reference category) and their interaction with maternal EML at time T0. As in our main analyses, we controlled for pre-determined characteristics and, when available, child past EML.

Table A9 presents the marginal effects of maternal EML across three adversity subgroups, defined by the number of adverse life events experienced by the family. The results suggest a clear gradient: the intergenerational association strengthens with increasing exposure to adversity. For families who did not experience any of the specified adverse life events, the association between maternal and child EML is consistently weak and statistically insignificant across all time periods. However, among families who experienced at least one adverse life event, the elasticity of maternal EML increases, particularly in adolescence (T2). Notably, in families with two or more adverse events, the estimated intergenerational elasticity reaches 12.5 % at T2, more than double the elasticity observed for those experiencing only one adverse event (5.9 %). This pattern suggests that shared environmental stressors may reinforce the intergenerational transmission of EML over time.

6. Conclusion

While the epigenetic literature has primarily examined the association between life events, DNAm profiles and health outcomes within a cross-sectional and uni-generational framework (Fiorito et al., 2019; Jiang et al., 2019), little is known about the intergenerational association of epigenetic mutations across generations and whether this relationship changes over time. In this paper, we investigate the intergenerational association of the epigenetic mutation load (EML) in mother-child dyads across three time points. We also examine whether own EML and maternal EML are correlated with early adulthood health and socio-economic outcomes.

Our results indicate that there is a 5 % intergenerational elasticity between mothers' EML and children's EML during childhood and adolescence, but not at child's birth. The absence of significant correlations at birth may have different, and likely complementary, interpretations. First, these results support the epigenetic erasure hypothesis (Liu et al., 2023) which claims that the epigenome undergoes global erasure and reprogramming during early embryonic development. Additionally, genetic variants inherited from the mother may not primarily determine the absolute EML at birth but rather influence the trend of epigenetic mutation accumulation over time, as previously suggested by Wang et al. (2019). In this scenario, genetic factors affecting the efficiency of epigenetic maintenance mechanisms (e.g., via DNMTs or TET enzymes and DNA repair related pathways) would modulate the rate at which epimutations accumulate over the lifetime (Montgomery et al., 2024). The results observed at child's birth may also be influenced by the greater heterogeneity of DNAm extracted from cord blood compared to the relatively more stable epigenetic profile for DNAm extracted from peripheral blood samples (Jiang et al., 2020). In this study samples, DNAm at T0 comes from cord blood drawn from the umbilical cord at delivery, while DNAm data at the subsequent time points – childhood and adolescence – are extracted from peripheral blood collected during clinic visits when the child is on average 7.5 and 17 years old, respectively. Finally, the later intergenerational association of DNAm we observe might instead indicate that the (unobserved) shared environment triggers children's predisposition towards DNAm dysregulation after birth, disproportionately more for those whose mothers have high EML.

Although we find evidence of an intergenerational association of EML, the results reveal no consistent associations between individual or maternal EML and early adulthood outcomes such as health, income, or educational attainment. While existing literature establishes an association between DNAm dysregulation and age-related conditions in older adults (Chen et al., 2022; Wang et al., 2019; Fiorito et al., 2017), our largely null findings in early adulthood suggest that the adverse effects of DNAm dysregulation may have a later onset, becoming evident only in later life.

An exception is vocabulary skills at age 24, which show a strong negative association with child EML, suggesting that DNAm dysregulation may adversely affect cognitive abilities later in life. The observed negative association also suggests that some effects may manifest earlier than other health outcomes. This finding is important given that low

[9] We excluded major financial problems and traumatic events, as they do not appear to worsen child EML outcomes (they consistently display negative, albeit not significant, coefficients in Tables A2 to A4).

cognitive ability is associated with negative later life outcomes such as lower economic productivity and lower lifetime earnings (Heckman et al., 2006; Green and Riddell, 2003; Lin et al., 2018). Although in our study DNAm dysregulation does not seem to directly affect income and education at 25–26 years old, DNAm instability could be a mechanism affecting economic outcomes in later adulthood through its negative association with cognitive ability in early adulthood. Further supporting the hypothesis about inherited genetic variants regulating trend of epimutation accumulation, literature also show common genetic variants associated with both, epigenetic age acceleration and higher risk of neurodegenerative diseases such as Alzheimer's disease (Liu et al., 2022). To summarize, genetic predispositions may drive EML accumulation over time, with health effects emerging once a critical threshold is surpassed. For this reason, early screening of DNAm patterns could help identify young individuals with abnormal methylation patterns and enable targeted interventions to reduce the potential long-term negative effects of low cognitive ability.

Further analyses in Section 5 suggest that the observed intergenerational association in T1 is heterogeneous, as it is mainly driven by the transmission of hyper-methylated SEMs. Hyper-methylated SEMs accumulate in genomic regions regulated by the Polycomb Repressive Complex 2 (PRC2), a set of proteins that establishes repressive chromatin marks (H3K27me3) which silence gene expression during development. Literature show that early-life environmental exposures can influence PRC2 activity, leading to long-term health consequences that manifest in adulthood. An example of such mechanisms is described by observation about maternal high-fat diet during gestation and lactation influencing epigenetic profiles in offspring, downregulating PRC2 components, and consequently upregulating genes associated with increasing adult cardiac dysfunction risk during adulthood (Blin et al., 2020). Furthermore, the intergenerational elasticity of EML is detected only between mothers and daughters, in line with the literature on intergenerational associations of behaviours and traits (Holmlund et al., 2011; Costi et al., 2024; Branje et al., 2020; Pavlova et al., 2022). We additionally provide evidence that the intergenerational transmission of EML strengthens with increasing exposure to adversity. These findings suggest that shared environmental stressors may amplify the intergenerational transmission of EML over time, potentially through mechanisms such as stress exposure, behavioural reinforcement, or constrained economic and social opportunities. Future research could further explore whether specific types of adversity differentially shape these patterns.

The generalizability of our findings is influenced by the sample composition of the ALSPAC and ARIES cohorts. While ARIES is broadly representative of ALSPAC (Relton et al., 2015), ALSPAC itself is not fully representative of the UK population (Boyd et al., 2013; Fraser et al., 2013), as it was drawn from the county of Avon – a relatively less diverse and more advantaged region. Additionally, selective attrition may bias estimates downwards, as disadvantaged individuals (who are arguably more likely to experience DNAm dysregulation) are also more likely to drop out of the sample. Consequently, our observed associations may represent a lower bound of the underlying true effects.

The findings of this paper are important for several reasons. First, the observed intergenerational association between mothers' and offspring's EML suggests that at least part of the variation in a child's EML is explained by maternal EML. This relationship appears to be primarily driven by the shared environment between mothers and children, as no such correlation was observed at birth. Additionally, this association does not seem to be explained by observable life events and family characteristics, suggesting that the intergenerational elasticity of EML could be driven by unobservable factors (e.g. diet, exposure to toxicants). Given that epigenetic mutations are modifiable, adopting healthy lifestyle choices could help mitigate the potential negative effects associated with this intergenerational link.

Last, since EML can serve as a biomarker of unhealthy ageing, with greater DNAm dysregulation linked to increased risks of pathological and chronic conditions, children of mothers with high EML may also face worse health and behavioural outcomes. Our results specifically indicate a strong negative correlation with cognitive abilities. Although the associations with other health and socio-economic outcomes are smaller and not statistically different from zero, the results align with expectations, indicating that higher EML is associated with poorer outcomes. A larger sample size could provide the statistical power needed to detect smaller effect sizes.

CRediT authorship contribution statement

Conchita D'Ambrosio: Writing – review & editing, Conceptualization, Funding acquisition, Investigation. **Giovanni Fiorito:** Writing – review & editing, Conceptualization, Formal analysis, Investigation. **Giorgia Menta:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization, Investigation, Methodology, Software. **Chiara Costi:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Investigation, Methodology, Software.

Ethics declaration

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

At age 18, study children were sent 'fair processing' materials describing ALSPAC's intended use of their health and administrative records and were given clear means to consent or object via a written form. Data were not extracted for participants who objected, or who were not sent fair processing materials.

Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and local research ethics committees (NHS Haydock REC: 10/H1010/70).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ehb.2025.101509.

Data Availability

The authors do not have permission to share data.

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