Extremely Low Birth Weight and Accelerated Biological Aging

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BACKGROUND AND OBJECTIVES: Extremely low birth weight (ELBW) (<1000 g) survivors are exposed to elevated levels of physiologic stress during their lives and may be susceptible to accelerated aging. Using the oldest known longitudinally followed cohort of ELBW survivors, we compared biological aging in this group using an epigenetic clock to a sample of matched normal birth weight (NBW) (>2500 g) control participants.

METHODS: Buccal cells were collected from 45 ELBW survivors and 49 NBW control participants at 30 to 35 years of age. Epigenetic age was calculated from the weighted average of DNA methylation at 353 cytosine-phosphate-guanine sequence within DNA sites, by using the Illumina Infinium Human Methylation EPIC 850k BeadChip array.

RESULTS: Before and after statistically adjusting for neurosensory impairment and the presence of chronic health conditions, a significant sex by birth weight group interaction was observed in the 353-site epigenetic-clock assay (P = .03), whereby ELBW men had a significantly older epigenetic age than NBW men (4.6 years; P = .01). Women born at ELBW were not found to be epigenetically older than their NBW peers.

CONCLUSIONS: The results of this study suggest that prenatal exposures may play an important role in aging, and that men born preterm may experience accelerated aging relative to their peers. We further highlight the need to monitor and promote the health of preterm survivors, with a particular focus on healthy aging across the life span.

WHAT’S KNOWN ON THIS SUBJECT: Extremely low birth weight (ELBW) survivors are at a greater risk for common diseases of aging, and it is hypothesized that the severe early life adversity they encountered may confer a premature-aging phenotype.

WHAT THIS STUDY ADDS: A significant birth weight by sex interaction revealed that ELBW men had a greater average epigenetic age compared with those in the matched normal birth weight control group. ELBW men may have accelerated biological aging, putting them at risk for chronic illness in later adulthood.


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Drs Van Lieshout and Schmidt conceptualized and designed the study and reviewed and revised the manuscript; Drs McGowan and de Vega performed epigenetic analysis and reviewed and revised the manuscript; Mr Savoy performed statistical analysis and drafted and revised the manuscript; Dr Mathewson conceptualized the study, assisted in statistical analysis, supervised data collection, and critically reviewed the manuscript; Drs Morrison and Saigal conceptualized and coordinated the study, provided essential expertise, and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ARTICLE
Individuals born preterm are at increased risk for a range of health problems across the life span. The most vulnerable of these individuals are born <1000 g and referred to as extremely low birth weight (ELBW). The severe early adversity that these survivors face puts them at risk for dysfunction in a host of organ systems as well as elevated rates of disease. Given the increased rates and early emergence of chronic illness observed in individuals born at ELBW, it may confer a premature-aging phenotype characterized by accelerated cellular senescence and the development of diseases typically associated with older populations.

Chronological age is based on the calendar date on which one was born and only approximates an individual’s physiologic functionality and life expectancy. Because individuals age differently, aging research has increasingly adopted the concept of “biological age,” a holistic conceptual framework unifying environmental, lifestyle, and genetic factors that contribute to cellular senescence and, by extension, life span. Biological aging seeks to explain why such disparities in aging rate exist in the general population and why some groups experience a higher risk for early onset age-related decline. Accelerated biological aging has been conceptually linked to allostatic load, the accumulation of physiologic stressors that can potentially undermine homeostatic regulation, and is thought to underpin common diseases of senescence (including cardiovascular disease, metabolic disturbance, and cancer), and more precisely describe the cellular processes contributing to mortality as a person ages.

Although no single biomarker of biological aging exists, a number of different indices have been proposed. These range from measures of general health (such as body composition, functional impairment, and grip strength in elderly populations) to physiologic correlates, such as inflammation, thyroid function, and insulin resistance.

Emerging research has begun to shift our understanding of biological aging toward identifying proteomic and genomic mediators of cellular senescence upstream of specific forms of pathology (eg, cardiovascular disease). A benefit of this approach is that such markers may be present before disease onset, potentially offering an opportunity for preventing the development of or improving the course of illness. One example of such a marker is telomere length, which measures the number of replication cycles in a cell population. However, this measure does not directly assess differences in gene regulation and so has limitations.

More recently, a measure referred to as the epigenetic clock has garnered interest as a novel measure of biological aging. It indexes cytosine-5 methylation within cytosine-phosphate-guanine (CpG) dinucleotides, also known as DNA methylation, and is thought to occur upstream of previously identified aging metrics. Although it has been established that DNA-methylation level is strongly correlated with chronological age, specific patterns of methylation are known to vary significantly between cell lineage and tissue types. To address this inconsistency in the epigenetic clock developed by Horvath, 353 specific CpG sites are used, which are conserved across tissues and have been demonstrated to robustly predict the epigenetic clock. This approach is that such markers may be present before disease onset, potentially offering an opportunity for preventing the development of or improving the course of illness. One example of such a marker is telomere length, which measures the number of replication cycles in a cell population. However, this measure does not directly assess differences in gene regulation and so has limitations.

In this study, we used data from a longitudinally followed cohort of survivors of ELBW recruited at birth between 1977 and 1982 in Southwestern Ontario. A group of age, sex, and familial socioeconomic status (SES)–matched controls born at normal birth weight (NBW). Horvath's site epigenetic-clock assay was used to provide an estimate of biological age. Because there are sex differences in epigenetic-clock estimation, life span in the general population, and susceptibility to early life stress, we also investigated the impact of sex on epigenetic age in adult survivors of ELBW and control participants born at NBW.

**METHODS**

**Participants**

In this study, we used data from a longitudinally followed cohort of survivors of ELBW recruited at birth between 1977 and 1982 in Southwestern Ontario. A group of age, sex, and familial socioeconomic status (SES)–matched controls born at NBW were recruited at 8 years of age. SES was measured via the Hollingshead Two-Factor Index of Social Position, which was used to assess parental occupation and education to classify SES along a 5 point scale, with 1 equaling the highest SES and 5 equaling the lowest SES. This cohort was originally assembled to investigate the long-term health of...
ELBW survivors in light of advances occurring in neonatal intensive care in the 1970s and 1980s. In addition to data gathered during infancy and childhood, participants have completed follow-up visits in adolescence and adulthood. In the analyses presented in this study, we use data collected at 8 years of age and at age 30 to 35.

Initially, 394 infants born ELBW were recruited to the study, of which 179 (45%) survived to discharge. A total of 142 survivors of ELBW completed a follow-up visit at 22 to 26 years of age, and 99 remained in the study at the 30- to 35-year follow-up, at which time DNA samples for epigenetic analysis were available. We were able to collect buccal cell samples for epigenetic analysis from 45 of these individuals. NBW control participants matched on age, sex, and familial SES were recruited at 8 years of age (N = 145). Among these participants, 89 remained at 30 to 35 years, and 49 of them provided buccal cell samples for assay.

Written informed consent was obtained from parents after joining the study and participants (30–35) at all subsequent study visits. Approval for this study was obtained by the McMaster University and Hamilton Health Sciences’ research ethics committees. This study was conducted in agreement with the Declaration of Helsinki.

**Epigenetic Age Assay**

Buccal epithelial cells were collected by using sterile OmniSwabs (GE Whatman Microbiology Products, Marlborough, MA) and stored at −80°C before DNA extraction to assess biological aging by using DNA-methylation patterns. In this study, we used the Omega E.Z.N.A. Tissue DNA kit (catalog number D3396; Omega Bio-Tek, Norcross, GA) to extract purified genomic DNA from participant swabs. Next, DNA was eluted in a Tris-EDTA buffer (10 mM Tris-CL, pH: 8.5; 1 mM EDTA). Its concentration and purity were quantified by using a NanoDrop 2000c Spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Elutions were further purified by using the Qiagen MinElute Reaction Cleanup Kit (catalog number 28204; Qiagen, Toronto, Canada) when DNA purity did not meet standard absorbance criteria (i.e., A260/A280 = 1.8 to 2.0, and A260/A230 >2.0. The purified DNA was diluted to a final concentration of ~100 ng/μL.

Samples were assayed by using the Illumina Infinium Human MethylationEPIC 850k BeadChip array. To reduce between- and within-array variance, subset-quantile within-array normalization was used.35 Epigenetic age was defined as the weighted average of DNA-methylation levels at 353 Cpg sites, which were then transformed to “predicted” age via a calibration function following procedures the outlined in Horvath.22 Horvath used elastic net regularization across multiple large training data sets to identify the combination of Cpg sites that most strongly predict chronological age (of which 353 were selected) and simultaneously establish a reference level of methylation for a given chronological age (“calibration”). All analyses were performed by using Horvath’s22 DNA-methylation age and epigenetic-clock calculator in RStudio, of which a tutorial is provided through his original article. In our study, we used the recently developed 850k microarray, which is missing 17 of the 353 loci that composed the original DNA-methylation age estimator included on the older 450k array. These missing sites were imputed by using the methylation-age algorithm, but it has been previously observed that the newer 850k arrays may still slightly underestimate biological age in training data sets, compared to Horvath’s previous observations.36 Although these interarray deviations may be an important consideration when comparing our findings to other studies, because all participants’ samples were analyzed on the same 850k microarrays, differences between groups remain useful.

**Covariates**

We adjusted for a range of variables associated with epigenetic aging to attempt to isolate the effect of ELBW status on our aging biomarker (the prevalence of each of the covariates is summarized in Table 1).

**Presence of Neurosensory Impairment**

Because neurosensory impairment (NSI) can influence the development of pathology in a range of organ systems37 and is more common among those born at ELBW,38 NSI was considered an important covariate. We defined NSI as the presence of at least 1 of the following: blindness, deafness (or other sensory impairment), cerebral palsy, microcephaly, and/or mental retardation diagnosed by a developmental pediatrician in childhood.

**Chronic Health Problems in Adulthood**

Because chronic health problems have been associated with increased epigenetic age independent of birth weight,39 we also adjusted for this covariate in our adjusted statistical analyses. We controlled for the presence of ≥1 of the following: allergies, asthma, arthritis, rheumatism, high blood pressure, migraine headaches, chronic bronchitis or emphysema, sinusitis, diabetes, epilepsy, heart problems, cancer, ulcers, vision, hearing or other sensory problems, movement disorders, learning disability, attention-deficit/hyperactivity disorder, and emotional problems (depression and/or anxiety).

**Statistical Analysis**

Differences between participants born at either ELBW and NBW were examined by using t tests (for continuous data) and χ² tests (for

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categorical data), allowing us to isolate the observed relationship between birth weight and DNA methylation from the influence of extraneous variables. One-way analyses of variance were also employed to investigate attrition and nonresponse effects. Analysis of covariance procedures were used to evaluate the effect of birth weight status on DNA methylation, adjusting for the presence of NSI, and the count of chronic health problems at the age of 30 to 35 years. In addition to directly comparing average biological age as estimated by the epigenetic clock, we also computed a "difference in ages" variable by subtracting the participants' chronological ages from their epigenetic-clock estimates.27,40 A sex by birth weight interaction term was also included to investigate the moderating effect of sex on any putative differences in epigenetic age. Statistically significant interactions were also stratified to quantify the strength of association between birth weight status and epigenetic age in men and women independently. All statistical analyses were conducted by using IBM SPSS Statistics 22 (IBM Corporation).

**RESULTS**

The social and demographic characteristics of study participants are summarized in Table 1. Although those people born ELBW and NBW manifested predictable differences in birth weight, gestational age, and presence of NSI, there were no statistically significant differences in chronological age at the time of measure or number of self-reported chronic health conditions in this sample. The epigenetic-clock assay used in this study was an average of 4.54 years less than the chronological ages reported by NBW participants, which is significantly greater than the age-estimation error of 3.6 years reported by the assay's creator in a validation study in which training data sets were used that are representative of the general population.22 Because this longitudinal cohort is in their mid 30s, there has been loss of sample to follow-up. To reduce the likelihood that participant attrition did not bias the sample, we compared participants born at ELBW and NBW who remained in the study to the 30- to 35-year visit with those who did not. Among participants born at ELBW, men were more likely to leave the study before the 30- to 35-year visit than women ($P = .01$), as well as a slight but statistically significantly greater familial SES for those who remained than those who were lost to follow-up ($P = .01$). However, they did not differ by birth weight or gestational age. Men born at NBW

<table>
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<tr>
<th>No. patients</th>
<th>ELBW</th>
<th>ELBW Men</th>
<th>ELBW Women</th>
<th>NBW</th>
<th>NBW Men</th>
<th>NBW Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth wt</td>
<td>858 (125)*</td>
<td>861 (112)</td>
<td>856 (131)</td>
<td>3552 (391)*</td>
<td>3466 (406)</td>
<td>3268 (563)</td>
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<tr>
<td>NSI</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>17</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. chronic health conditions</td>
<td>3.0 (3.0)</td>
<td>2.1 (2.5)</td>
<td>3.6 (3.1)</td>
<td>2.2 (2.0)</td>
<td>1.4 (1.2)</td>
<td>2.7 (2.2)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 (7.4)</td>
<td>26.7 (5.1)</td>
<td>26.6 (8.5)</td>
<td>27.1 (5.9)</td>
<td>26.4 (4.7)</td>
<td>27.7 (6.9)</td>
</tr>
<tr>
<td>Cigarette smoking, n</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>20</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Years of education</td>
<td>15.5 (2.7)</td>
<td>15.2 (3.0)</td>
<td>15.7 (2.5)</td>
<td>16.4 (3.2)</td>
<td>16.0 (3.5)</td>
<td>16.7 (3.1)</td>
</tr>
<tr>
<td>SES at the age of 8 y</td>
<td>3.1 (0.9)</td>
<td>2.9 (1.0)</td>
<td>3.2 (0.8)</td>
<td>3.0 (1.0)</td>
<td>2.9 (1.2)</td>
<td>3.1 (0.8)</td>
</tr>
<tr>
<td>Chronological age, y</td>
<td>32.3 (1.6)</td>
<td>32.4 (1.4)</td>
<td>32.2 (1.7)</td>
<td>32.4 (1.3)</td>
<td>32.2 (1.3)</td>
<td>32.5 (1.3)</td>
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<tr>
<td>DNA-methylation age, y</td>
<td>29.0 (5.2)</td>
<td>31.4 (5.5)*</td>
<td>27.7 (4.5)</td>
<td>27.9 (5.1)</td>
<td>26.9 (4.8)</td>
<td>28.6 (5.1)</td>
</tr>
</tbody>
</table>

SES was measured when the participants were 8 years old, by using the Hollingshead index of social position. This scale denotes a score of 1 equals the highest social status and a score of 5 equals the lowest. —, not applicable.

* $P < .05$.

| Table 2 Analyses of Covariance for DNA-Methylation Age (353 CpG Sites) as a Function of Birth Weight Group and Sex, Unadjusted and Adjusted for Chronic Health Conditions, and NSI |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                   | $F$             | $P$             | $\eta^2$        |
| **Unadjusted (n = 92)** |                 |                 |                 |
| Birth wt group    | 2.88            | .09             | 0.032           |
| Sex               | 0.90            | .35             | 0.010           |
| Group × sex       | 6.68            | .01*            | 0.071           |
| **Adjusted (n = 85)** |                 |                 |                 |
| Chronic conditions| 0.09            | .77             | 0.001           |
| NSI               | 0.99            | .32             | 0.013           |
| Birth wt group    | 3.72            | .06             | 0.046           |
| Sex               | 0.02            | .90             | 0.000           |
| Group × sex       | 5.55            | .02*            | 0.067           |
| **ELBW (n = 40)**  |                 |                 |                 |
| Chronic conditions| 0.48            | .50             | 0.013           |
| NSI               | 1.04            | .32             | 0.028           |
| Sex               | 3.31            | .07             | 0.084           |
| **NBW (n = 45)**   |                 |                 |                 |
| Chronic conditions| 0.38            | .54             | 0.009           |
| Sex               | 2.85            | .1              | 0.064           |

* $P < .05$.
were also more likely to have left the study \((P = .01)\), but familial SES, gestational age, or birth weight did not predict attrition. Given that only a subsample of eligible participants at the age of 30 to 35 years provided buccal cell samples, we also compared those who provided samples for epigenetic assay at this follow-up point with individuals that did not. Because ELBW and NBW participants were recruited separately, nonresponse was examined separately in the 2 birth weight groups. In ELBW participants, neither sex \((P = .16)\), birth weight \((P = .12)\), nor familial SES \((P = .07)\) predicted nonresponse. However, ELBW participants providing buccal cells had a slight but statistically higher gestational age \((27.8 \text{ vs } 26.6 \text{ weeks}; P = .02)\). No statistically significant predictors of attrition were noted in NBW participants.

In unadjusted analyses in which we compared epigenetic age using DNA-methylation levels at 353 CpG sites, a significant birth weight group by sex interaction was observed \((P = .01)\). Stratification by birth weight and sex revealed that ELBW men were epigenetically older than NBW men by 4.5 years \((P = .01)\), 3.7 years older than ELBW women \((P = .02)\), and 3.0 years older than NBW women \((P = .07)\). After adjustment for NSI and the presence of a chronic health condition, this interaction remained statistically significant \((P = .02)\). In stratified analyses, ELBW men were 4.8 years older than NBW men \((P = .01)\), 2.7 years older than ELBW women \((P = .10)\), and 2.4 years older than NBW women \((P = .15)\) (Table 2).

Because we were interested in evaluating whether ELBW survivors were more likely to age prematurely (ie, the discrepancy between epigenetic clock and chronological age), we calculated the difference in epigenetic age and chronological age at the time of assessment. In agreement with our DNA-methylation analyses, a significant birth weight by sex interaction was also observed to predict premature aging in unadjusted analyses \((P = .02)\). Although the epigenetic clock underestimated chronological age in all groups, in ELBW men, this difference was \(<1\text{ year} \ (\text{mean} = -0.83; \ SE = 1.18)\), significantly smaller than the difference in NBW men \((\text{mean} = -5.22; \ SE = 1.6)\), ELBW women \((\text{mean} = -4.58; \ SE = 0.89)\), and NBW women \((\text{mean} = -4.07; \ SE = 0.90)\). Importantly, the biological-chronological age differential did not differ between NBW men, NBW women, and ELBW women. The birth weight by sex interaction persisted after adjustment with all covariates \((P = .04)\). These findings further support a differential rate of epigenetic aging among ELBW men in adulthood.

**DISCUSSION**

In this cohort of adult ELBW survivors and age-matched NBW control participants, men born at ELBW manifested accelerated biological aging relative to their peers born at NBW. To our knowledge, this is the first study that has identified accelerated aging in adults born at ELBW and suggests that suboptimal intrauterine and early postnatal development could promote enduring epigenetic adaptations in men born preterm. These changes could have important implications in terms of premature aging, disease susceptibility, and mortality, and highlight the need for monitoring and health promotion in preterm survivors across the life span.

Little research has been directly focused on the possibility that preterm survivors may be experiencing accelerated biological aging. In previous studies conducted in survivors of ELBW and very low birth weight \((<1500\text{ g})\), it is suggested that they may be at increased risk for chronic, complex diseases (eg, dysglycemia and hypertension\(^5,41\)) and that some of these may have an earlier age of onset than in individuals born at term and/or NBW.\(^42\) Studies that have longitudinally examined developmental trajectories in preterm survivors also suggest that a phenotype more vulnerable to accelerated aging may exist. For example, a measure of parasympathetic regulation of the cardiovascular system revealed a more pronounced decline in heart rate variability during adulthood in ELBW survivors.\(^42\) This group also appears to exhibit a blunted decrease in the normative reductions in depression and anxiety typically seen with age from adolescence to adulthood.\(^43\)

Although it is unclear why accelerated biological aging is seen in men born at ELBW, increased allostatic load could play a role. Allostatic load refers to the influence of stress on an organism’s ability to regulate its physiology in the face of unstable and unpredictable stimuli\(^44,45\) and has been implicated in biological aging.\(^46,47\) Indeed, correlations noted between allostatic load and epigenetic-clock measures are suggestive of a shared etiology.\(^48\) Given the additional burden of stress conferred by being born at ELBW, allostatic load may also be involved in the unique aging phenomenon exhibited by male survivors of ELBW. Indeed, male neonates are thought to be more susceptible to adverse perinatal exposures.\(^49\)

Epigenetic aging rates also have been observed to be higher in men, independent of early life stress.\(^50\) However, that our findings persisted despite adjustment for postnatal stresses suggest that perinatal adversity may play an important role in the processes leading to epigenetic aging in men born at ELBW. This is consistent with findings that male neonates are more susceptible to prenatal insults than girls.\(^51–53\)
Beyond enacting allostatic load, however, the specific mechanism(s) by which the early life environment influences DNA methylation are not known. In observations from preclinical research, a few potential candidate pathways are suggested. It may be the case that altered CpG methylation may be a byproduct of increased rates of DNA damage or impaired DNA-repair mechanisms. In this sense the epigenetic clock may be indexing DNA damage, which has been previously described as a core component of aging, independent of epigenetic regulation. Alternatively, severe stress exposure during prenatal development may induce DNA-methylation modifications in male survivors of ELBW at birth, which persists throughout adulthood. Early life adversity may also exert its influence on biological aging indirectly through associated mechanisms, such as systemic inflammation and oxidative stress, which have been implicated in both preterm birth and age-related decline.

The current findings suggestive of accelerated biological aging among men born at ELBW must be considered in light of this study’s limitations. First, this work is observational in nature, and so it is not possible to establish any causal links. In this sample, there was an ~4.5-year underestimation of chronological age by using the epigenetic age measure in participants born at NBW, greater than the 3.6-year underestimation reported by Horvath in a validation study. It is possible that this underestimation may have biased our results. However, given the consistency across groups and the fact that all participants used the same epigenetic-clock measure, the relative difference between these groups and men born at ELBW is still conserved. It may be the case that this difference in estimated age may be due to our use of an 850k microarray, as opposed to the 450k array originally used by Horvath.

Because this study is composed of a cohort followed over almost 40 years, significant attrition has occurred, and we were only able to collect buccal cells in a subsample of participants. Although participants were similar to those enrolled at study inception, the sample size and statistical power are limitations. This also limited our ability to study the influence of relatively rare traumatic experiences during childhood, which may serve as additional stressors capable of exerting influence on the biological age of survivors born at ELBW. Furthermore, survivors of ELBW recruited to this study were born 4 decades ago and so may not perfectly represent the care ELBW survivors receive today. Although we attempted to control for key covariates, it is possible that unmeasured confounders may partially influence observed associations, and so accelerated aging may be attributed to postnatal as well as prenatal exposures. Finally, for this study, we recruited a fairly homogenous sociodemographic group in southwestern Ontario with access to universally available health care, potentially limiting generalizability to other populations.

CONCLUSIONS
Although these findings require replication in other larger cohorts and examination of additional disease and aging biomarkers, in this study we provide preliminary evidence of a new link between ELBW and accelerated biological aging among men. In addition to providing potentially useful guidance for survivors of ELBW, their families, and health care providers, these findings could have important implications for understanding the etiology of diseases of aging as well as the influence of early life adversity on health in adult life. This work also further highlights the importance of monitoring the health of preterm survivors across the life span as well as the early detection and management of problems that can adversely affect health in the short- and long-term. If it is the case that men born at ELBW are more susceptible to age-related decline, it serves to emphasize the vital importance of the adoption of healthy lifestyles among these individuals as a means of promoting healthy aging across the life span. Forewarning of these risks may allow for ELBW survivors and their health care providers to proactively mitigate these risks while they are still healthy. This includes consuming a balanced diet and avoiding smoking and excess recreational substance use as well as the importance of proper sleep, regular exercise, stress management, cognitive stimulation, and the development of strong social networks to optimize health during early adulthood and beyond.

ABBREVIATIONS
CpG: cytosine-phosphate-guanine
ELBW: extremely low birth weight
NBW: normal birth weight
NSI: neurosensory impairment
SES: socioeconomic status

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