Published in final edited form as:

Int J Psychophysiol. 2014 August ; 93(2): 198–203. doi:10.1016/j.ijpsycho.2014.04.005.

Reduced respiratory sinus arrhythmia in adults born at extremely low birth weight: Evidence of premature parasympathetic decline?

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Abstract

Individuals born at extremely low birth weight (ELBW; < 1000 grams) are exposed to early adversity in multiple forms. Given that substantial development of the autonomic nervous system (ANS) occurs during the third trimester of gestation, ANS functioning may be altered in adults who were born before reaching 28 weeks of gestational age. The aims of the study were to: 1) determine whether two indices of ANS functioning [resting heart period (HP) and respiratory sinus arrhythmia (RSA)], differed between adult ELBW survivors and normal birth weight (NBW) controls, and 2) ascertain whether ANS functioning was differentially vulnerable to age-related decline in the ELBW participants. Resting HP and RSA (reflecting cardiac efficiency and responsive cardiac control, respectively) were assessed in 30 non-impaired ELBW survivors and 47 NBW controls at age 22–26 and again at 30–35 years. At each assessment, resting RSA was significantly lower in the ELBW group than in the NBW comparison group. In addition, individual differences in RSA within the ELBW group were poorly preserved over time. These

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Because the cardiac recordings at the first and second assessments were of different lengths (two and six minutes long, respectively), an additional ANOVA was carried out to assess the short-term stability of RSA between the first and second halves of the 6-minute files recorded at age 30–35. As before, RSA levels were lower in the ELBW group, $F(1, 75) = 5.11, p < .03$, partial $\eta^2 = .06$, with no interaction ($p > .95$). Unexpectedly, RSA levels decreased from the first half ($M = 5.94 \ln \text{ms}^2, SE = 0.14$) to the second half of the recording ($M = 5.77 \ln \text{ms}^2, SE = 0.13$), $F(1, 75) = 8.40, p < .01$, partial $\eta^2 = .10$. This instability suggested repeating the original regression analyses, using RSA at age 30–35 from each half of the cardiac recording as the dependent variable, in turn.

The new regression results were very similar to those of the original analyses. A significant interaction obtained when RSA at age 22–26 predicted RSA at age 30–35 based on the first half of the recording ($t = -2.25, p < .03$). A similar though less robust pattern resulted when RSA at age 30–35 was derived from the second half of the recording ($t = -1.89, p = .063$). In each case, follow-up analyses indicated that RSA at age 22–26 was a significant predictor of RSA at age 30–35 among controls ($ps < .01$), accounting for 15–23% of the variance, but not ELBW participants ($ps > .65$, F s not protected), as in the original analyses. Although RSA calculated at age 30–35 declined over the short term of the recording (6 minutes), associations between RSA measures across assessments remained very similar when predicting RSA at age 30–35 derived from half of the data, especially the association between RSA at age 22–26 and RSA from the *first* half of the recording made at age 30–35. We thank an anonymous reviewer for raising these issues.

findings are suggestive of a premature decline in parasympathetic functioning in some adult ELBW survivors.

Keywords

extremely low birth weight; heart rate variability; respiratory sinus arrhythmia; adult; cardiovascular risk; longitudinal

1. Introduction

Infants born at extremely low birth weight (ELBW; < 1000g) are among the tiniest, most vulnerable babies, but medical advances made in the last few decades have enabled the first generation of ELBW survivors to reach adulthood (Fanaroff, Jack et al., 2003). Adult ELBW survivors provide a unique opportunity to investigate the consequences of significant perinatal adversity for major physiological regulatory systems in humans.

Although it is possible to be born at term, and yet, have very low birth weight, most individuals born at ELBW are also born preterm (< 37 weeks' gestation). These infants are exposed to early adversity in multiple forms, including the stresses that contribute to their premature delivery, insufficient time to develop prior to birth, and exposure to medical procedures aimed at improving their odds of survival in the post-natal period. Because substantial development of the autonomic nervous system (ANS) occurs during the third trimester of pregnancy (Van Leeuwen, Lange et al., 1999), ANS functioning may be altered in individuals born prior to 28 weeks of gestation. Indeed, preterm birth has been linked to alterations in the development of the vasculature (Norman, 2008), ANS functioning (Yiallourou, Witcombe, et al., 2013), and cardiac rhythmicity (Wolfenstetter, Simonetti et al., 2012). Preterm birth also has been associated with higher blood pressure in adults (Bergvall, Iliadou et al., 2007; Dalziel, Parag et al., 2007) and lower heart rate variability (HRV) in children (Rakow, Katz-Salamon et al., 2013), especially if the children experienced growth-restriction in utero (Schneider, Fiedler et al., 2006). It is noteworthy that both high blood pressure and low heart rate variability are associated with cardiovascular morbidity later in life.

1.1. Heart Rate Variability

Resting heart rate is characterized by substantial variability in healthy young adults. High-frequency heart rate variability (HF) (and its natural log equivalent, respiratory sinus arrhythmia [RSA]) reflect a healthy irregularity in the cardiac signal that is primarily due to activity of the parasympathetic nervous system (90%; Randall, Brown et al., 1991) and is commonly used to index phasic vagal cardiac control in humans (Berntson, Bigger et al., 1997). The parasympathetic contribution to autonomic regulation is of critical importance (Reyes del Paso, Langewitz et al., 2013). Whereas resting heart rate indexes general cardiac efficiency, evidence from across the lifespan suggests that higher resting HRV indexes more responsive cardiovascular adaptation to changing environmental demands, more effective behavioral and emotional self-regulation (e.g., Thayer, Hansen et al., 2009), and a lower risk for cardiovascular disease (Dekker et al., 2000). After the attainment of peak levels in the

late teen years, resting RSA declines with increased age (Korkushko, Shatilo et al., 1991). Resting RSA is also sensitive to the effects of physical deconditioning, ill health, and the use of some medications. Notwithstanding these contextual effects, individual differences in resting RSA are reported to be substantial and appear to be stable over time in adults (Pitzalis, Mastropasqua et al., 1996).

1.2. Prematurity and increased risk for reduced heart rate variability

At birth, heart rate variability is lower in preterm than term infants (Patural, Pichot et al., 2008). Furthermore, maturation of RSA in preterm infants during the first 6 months of life exhibits a 2-3-fold reduction in magnitude as compared to term infants, suggesting that maturation of parasympathetic control may be suppressed in these individuals (Yiallourou et al., 2013). Results from both of these studies intimate that autonomic development does not “catch up” between birth and term-equivalent age. Accordingly, cardiac reactivity to stressors may be enhanced, i.e., poorly regulated, in these infants (Cohen, Vella et al., 2008). As well, myelination of the vagus nerve increases significantly between 33-35 weeks’ gestation, with the number of myelinated vagal nerve fibres reaching adolescent levels by full term (Sachis et al., 1982). The vagus nerve is the principal mediator of parasympathetic outflow to the heart, and critical to effecting rapid changes in heart rate. Importantly, its myelinated branch is involved in social communication processes and implementing calm behavioral states (Porges, 2007). Additional evidence suggests that the effects of preterm birth on autonomic regulatory systems may be enduring and not easily compensated, as the detrimental influence of preterm birth on RSA appears to be maintained into middle childhood in those born either preterm or small for gestational age (SGA; <10th percentile of birth weight for gestational age) (Rakow et al., 2013).

1.3. The present study

While the effects of preterm birth on RSA may persist from infancy into childhood, whether these effects extend beyond these developmental stages is not known. Accordingly, the first goal of this study was to determine whether being born at ELBW was associated with adverse effects on RSA in young adulthood. Given the life-long role of resting RSA as an index of efficient cardiovascular adaptability, a second goal was to compare age-related decline in mean levels of resting RSA in the ELBW group relative to NBW controls.

Autonomic measures (heart period (HP), the inverse of heart rate, and RSA) in ELBW and NBW participants were examined on two occasions, once at age 22-26, and again at age 30-35. Resting RSA was expected to be lower in adult ELBW survivors than in NBW controls at each assessment. Although both groups were expected to exhibit RSA decrements with increasing age, the mean decline was expected to be greater in the ELBW group. In addition, individual differences in RSA were examined at each assessment to ascertain whether age-related decline was consistent with each group, or whether decline in some individuals was greater than in others.

2. Materials and Method

2.1. Cohort and Participants

The cohort comprised ELBW survivors recruited at birth and a group of NBW controls recruited when both ELBW participants and controls were 8 years of age. Originally, the ELBW group included 397 mainly Caucasian infants who were born at extremely low birth weight between 1977 and 1982 within a geographically-defined area in southwestern Ontario, Canada. Gestational ages for the ELBW participants in this study ranged from 23 to 34 weeks. These infants weighed between 500 and 1000 grams at birth and have been followed longitudinally since, with assessments at age 3, 5, 8, 14, 22-26 and 30-35 years. Of the original cohort, 179 (45%) survived to hospital discharge, and 13 more children died subsequently. Of these 166 survivors, 142 participated in the young adulthood assessment (age 22-26) (see Saigal, Stoskopf et al., 2006). At the young adult assessment, a subset of 71/142 right-handed participants free of neurosensory impairments was tested in the Child Emotion Laboratory at McMaster University (Schmidt, Miskovic et al., 2008). Electrocardiogram (ECG) data were obtained from 67/71 (94%) of these non-impaired ELBW participants at 22-26 years of age and from 34/71 (48%) at age 30-35.

The age-, sex-, and socioeconomic status-matched control group consisting of 145 children born at normal birth weight (NBW, birth weight $\geq$ 2500 grams) has been assessed in tandem with the ELBW cohort at ages 8, 14, 22-26, and 30-35. Of these 145 NBW controls, 133 participated at age 22-26. From this group, a subset of 83/133 right-handed, control participants was tested in our laboratory. ECG data were obtained from 80/83 (96%) of these NBW control participants at age 22-26 and 48/83 (58%) at the current sweep (age 30-35).

As we wished to examine autonomic functioning at age 22-26 and also at age 30-35, all analyses were restricted to those participants for whom a complete set of ECG measures was available from both assessments. Applying this criterion reduced the pool of available participants, with losses deriving about equally from both time periods. In a few cases, losses were due to equipment difficulty or excessive artifact in the ECG recordings (6.0% at age 22-26, 7.3% at age 30-35). In all, complete ECG data were available from 30 non-impaired ELBW participants, and 47 non-impaired NBW controls.

2.2. Procedure

At each assessment, participants were introduced to the laboratory and briefed about the study procedures. After obtaining written consent, regional electroencephalogram (EEG) and ECG measures were collected. The EEG measures were collected using a lycra stretch cap (Electro-cap, Inc., Eaton, OH) as part of a larger study and are not presented herein. Following each assessment, participants received nominal remuneration for their participation. All laboratory procedures were approved by the participating university and hospital research ethics boards.

2.3. ECG Collection and Measures

2.3.1. ECG Recording—At the 22-26 year assessment, ECG was continuously recorded during 2 minutes of rest via two disposable ECG electrodes placed on the medial forearms,

while the participant sat quietly in a comfortable chair. At the 30-35 year assessment, baseline recordings were extended to 6 minutes and ECG electrodes were placed below the right clavicle and on the lower left rib area in a modified lead II configuration. Although a recording of one minute is sufficient to assess RSA, recordings of 5 minutes are recommended for comparison of short recordings across studies (Task Force, 1996). As well, respiration rate was not monitored in this study. While statistical control of respiration may be implemented to ensure that respiration rate does not influence RSA, spontaneous respiration rates during seated rest are slow enough to avoid any undue influence of respiration on RSA (Berntson et al., 1997; Denver, Reed, et al., 2007). ECG signals were recorded at each assessment, amplified by an individual SA Instrumentation Bioamplifier, filtered between 0.1 Hz (high pass) and 1000 Hz (low pass), and digitized at a sampling rate of 512 Hz. The acquisition software at age 22-26 was Snapshot-Snapstream (HEM Data Corp., Southfield, MI), and at age 30-35, SnapMaster (HEM Data Corp., Southfield, MI).

2.3.2 ECG Data Reduction and Quantification—Mean levels of heart period [HP] and RSA were derived offline from each ECG recording in its entirety. As heart rate is a non-linear transform of HP, indices of HP are preferred over heart rate in autonomic research. Changes in HP are constant across the possible range of HP values, whereas changes in heart rate are not (Berntson, Quigley et al., 2007). Cardiac R-waves from each resting condition were detected offline with a four-pass algorithm, which produced a visual display of the cardiac signal with the R-waves marked. Missing or spurious R-waves were edited manually according to recommendations by Berntson and Stowell (1998). The edited file of R-wave onset times was converted to interbeat intervals and then prorated into equal time intervals of 125 ms using a moving polynomial filter. This series was detrended using a high-pass filter with a period of 25 seconds, to allow analysis of both high-frequency variability (i.e., RSA, 0.12 to 0.40 Hz), and low frequency variability (LF-HRV, 0.04 to 0.12 Hz) in the signal. A discrete Fourier transform analysis, with a 32-second Hanning window and 50% consecutive overlap, was applied to quantify high-frequency variability in the signal, summed across the range of respiratory frequencies, and also low-frequency variability, summed across the LF-HRV range. High-frequency and low-frequency values (in ms²) were submitted to natural log transformations to normalize their distributions, yielding measures of RSA and LF-HRV for each assessment. The LF-HRV measure is not presented here.

2.4. Statistical analyses

Group differences and changes over time were assessed in separate ANOVAs for HP and RSA, respectively. The stability of individual differences in HP and RSA between assessments was initially assessed using exploratory Pearson correlational analyses. To ascertain the unique contributions of the predictors (HP or RSA at age 22-26) in the presence of relevant covariates, we carried out separate hierarchical regression analyses with HP or RSA at age 30-35 as the dependent variable, in turn. Covariates were entered on the first step to account for possible confounding variables, followed by the centered value of resting HP or resting RSA at age 22-26 on the second step, and the relevant interaction with group on the third step. Interaction terms were tested for statistical significance to determine whether group modified expected associations between HP or RSA at age 22-26 and age

30-35. A protected-*F* strategy was followed in reporting all regression results unless otherwise specified. IBM statistics, version 22.0 (SPSS Inc., USA) was used for all analyses.

2.5. Covariates

Although RSA did not differ between men and women in either group at either assessment, ($ps > .70$), RSA has been reported to vary by sex in some studies (Umetani, Singer et al., 1998). Therefore, sex was included as a covariate in the regression analyses. Because risks conferred by being born SGA may be independent of those conferred by being born at ELBW (e.g., Regev, Platt et al., 2003), SGA status (Kramer, Lusky et al., 2001) was also included as a covariate. A measure of overall health (SF-36, Ware & Sherbourne, 1992) was included because resting RSA varies with physical health and fitness levels (Davy, Miniclier, et al., 1996). Self-reported use of medications at age 22-26 and age 30-35 were included as covariates to account for any group differences in medication use. These indices were highly correlated, however, and medication use was greatest at the younger age ($p < .001$). The younger index was retained as a covariate in the final regression analyses as it was likely to account for more variance in the autonomic measures, which would challenge our main hypotheses rather than confirm them. Because greater body mass (BMI) has been associated with lower RSA in some studies (Molfino, Fiorentini et al., 2009), and overweight is a risk factor for cardiovascular disease, BMI at age 22-26 and age 30-35 were included as covariates. Body mass indices at age 22-26 and age 30-35 were also highly correlated. The higher BMI values at age 30-35 ($p < .001$) were retained for the final regression analyses, as they were likely to account for more variance. The highest level of education attained by participants at age 22-26 was included as an indicator of familial SES.

3. Results

Characteristics of our right-handed sample, free of neurosensory impairments, are presented in Table 1. Mean age did not differ between groups at either assessment (age 22-26: $p > .06$; age 30-35: $p > .15$), nor did group variances in the age increase between the first and second data collections (Levene's test, $ps > .14$), sex distribution ($X^2_{df=1} = 0.002$, *ns*), educational achievement ($X^2_{df=5} = 4.65$, $p > .45$) or the other covariates (general health, medication use, and BMI, $ps > .35$), with the exception of SGA status ($X^2_{df=1} = 17.83$, $p < .001$). ELBW participants who were excluded because of incomplete data did not differ from those who were included on any of the covariates ($ps > .09$), except for gestational age (excluded: 26.8 weeks vs. included: 27.9 weeks; $t(176) = 2.33$, $p < .03$), and the proportion of individuals born SGA: more of the excluded ELBW participants had SGA status than those ELBW whose data were included ($X^2_{df=1} = 7.46$, $p < .01$). These latter findings likely reflect the fact that the study sample was comprised of ELBW survivors with no major neurosensory impairments. Excluded NBW participants did not differ from those included in any of the covariates ($ps > .11$).

3.1. Group-level analyses

Mean autonomic values by assessment and group are presented in Figure 1 and Table 2. An ANOVA of resting HP data revealed no effects of group or assessment occasion and no interaction (all $ps > .14$). By contrast, overall resting RSA was significantly lower in the

ELBW group than in NBW controls, $F(1, 75) = 6.34, p < .01$, partial $\eta^2 = .08$, and, as expected, mean levels of RSA (in both groups) declined significantly at the second assessment, when participants were older, $F(1, 75) = 26.51, p < .001$, partial $\eta^2 = .26$. Group did not modify the mean level of RSA decline over time ($p > .70$).

3.2. Individual-level analyses

Exploratory zero-order correlational findings indicated that HP at age 22-26 predicted HP at age 30-35 in both groups ($ps < .01$), but a significant association between RSA at age 22-26 and RSA at age 30-35 was present only in the NBW group ($p < .001$; ELBW: $p > .65$). Results are illustrated in Figures 2.A and 2.B.

Associations between autonomic parameters (HP and RSA) at age 22-26 and age 30-35) were then assessed in the presence of relevant covariates in hierarchical regression analyses. Because interactions with group were of particular interest, the autonomic predictors (HP and RSA at age 22-26) were centered prior to being entered in the analyses. As expected, resting HP at age 22-26 accounted for significant variance in HP at age 30-35 (19%), across groups, $p < .001$, with no interaction ($p > .85$). Similarly, resting RSA at age 22-26 explained significant variance in RSA at age 30-35 (6%) across groups, $p < .04$. Body mass index also explained unique variance in RSA (12%) at age 30-35, across groups, $p < .01$. Finally, predictions of RSA at age 30-35 by RSA at age 22-26 differed significantly by group (interaction: $p < .04$). Regression results for HP and RSA are presented in Table 3.

To better understand the factors contributing to the interaction, resting RSA at age 30-35 was examined in separate regression analyses for each group, with covariates entered on the first step and RSA at age 22-26 on the second step. Among ELBW survivors, there were no associations between RSA at age 30-35 and the predictor variables ($ps > .19$), and the F -statistic was not protected. In this group, only BMI explained significant variance in RSA (16%, $p < .04$; $r(30) = -.43, p < .02$). Conversely, among NBW controls, RSA at 22-26 accounted for significant variance in RSA at age 30-35 (19%, $p < .01$), and BMI explained significant variance in RSA (9%) at age 30-35 as well ($p < .05$; $r(46) = -.31, p < .04$). Although the ELBW group ($M = 3.04, SD = 3.47$), exhibited a greater mean increase in BMI between assessments than did the control group ($M = 1.23, SD = 2.93$), $t = 2.45, p < .02$, we note that increases in BMI between assessments did not directly correlate with the declines in RSA in either group ($rs < .10, ps > .50$). Resting RSA results are presented, by group, in Table 4.¹

It should also be noted that the absence of correlation in RSA measures across time in ELBW survivors could not simply be attributed to low power in this smaller group. Parallel regression analyses of resting HP by group demonstrated that among ELBW survivors, HP at age 22-26 accounted for 25% of the variance in HP at age 30-35, $t = 2.85, p < .01$, results that were comparable to those of NBW controls (16%), $t = 3.12, p < .01$, though the F was protected only in the NBW group. In sum, individual differences in resting RSA were preserved at age 30-35 only among NBW controls. By contrast, individual differences in HP were preserved in both groups.

4. Discussion

Resting RSA reflects an individual's capacity for phasic vagal cardiac control. Although adult ELBW survivors did not differ from NBW controls in resting heart rate (the inverse of HP), they exhibited significantly less robust parasympathetic regulatory capacity (RSA) in their twenties and thirties than did their term-born counterparts. In addition, individual differences in resting RSA were not as well preserved over time among ELBW survivors as they were among NBW controls, despite robust correlations between resting HP at age 22- and age 30-35 in each group. Whereas individual levels of resting RSA at age 22-26 strongly predicted RSA almost a decade later among NBW controls, age-related RSA decline did not appear to be uniform in the ELBW group: RSA decline was greater in some ELBW individuals than in others. Interestingly, regression analyses also revealed that by age 30-35, higher BMI was inversely correlated with resting RSA in both groups, consistent with previously noted associations between lower parasympathetic control and greater body mass (Molfinio et al., 2009).

Group differences at each assessment between adults born at ELBW versus NBW in mean levels of resting RSA suggest that the autonomic sequelae of being born at ELBW may include a decrement in the capacity for parasympathetic regulation of heart rate. Such a decrement is reminiscent of declines usually attributed to aging, physical deconditioning, or certain medications (DeMeersman & Stein, 2007). Notably, however, ELBW participants were not older than NBW controls, no more obese than controls as indexed by body mass index at age 30-35 (although BMI was inversely associated with RSA in both groups), and did not report greater use of medications than controls. Thus, although adults born at ELBW on the whole did not differ from their NBW peers in physiological factors such as chronological age, physical conditioning, or rates of regular medication use, mean resting parasympathetic regulatory capacity was lower in the ELBW group. Moreover, there is complementary evidence to suggest that, young adults born at ELBW are a vulnerable group, exhibiting a greater tendency toward internalizing problems based on DSM-III-R criteria (APA, 1987) (Boyle et al., 2011) and subtle delays in brain maturation (Miskovic, Schmidt et al., 2009).

Contrary to our prediction, the magnitude of mean age-related change in RSA over time was not differentially greater for the ELBW group. However, *within* the ELBW group, individual differences in RSA (as opposed to mean levels), were less stable over time than among NBW controls. The lack of stability of individual levels of RSA suggests an accelerated decline of parasympathetic regulatory mechanisms in some ELBW survivors, via mechanisms that are as yet untested.

To date, diminished parasympathetic control has been associated with greater susceptibility to malignant cardiac arrhythmias and hypertension in typically developing adults. Reductions in resting RSA at a relatively young age may portend the premature development of similar cardiac problems in some ELBW survivors. As the first generation of ELBW survivors looks ahead towards middle-age, any pre-existing PNS vulnerability in this group is likely to be compounded by normal age-related declines in parasympathetic functioning (Umetani et al., 1998) and physical fitness (DeMeersman & Stein, 2007), age-

related increases in blood pressure variability (Uchino, Berg et al., 2006), and the potential development of cardiac risk factors such as atherosclerosis. In these cases, interventions such as aerobic exercise (e.g., Sloan, Shapiro et al., 2009) or biofeedback (e.g., Abukonna, Yu et al., 2013) may be warranted to support RSA levels over the long term.

A unique strength of this study lies in its repeated assessments about a decade apart, which allowed for longitudinal examination of changes in autonomic functioning in a distinctive and well-followed sample of ELBW survivors and their NBW peers. The regression results also highlight the utility of parsing individual differences within each group. This strategy enriches the conceptual and theoretical understanding of a particular health condition, and may also have practical implications for the management of the condition within heterogeneous groups. Nonetheless, our sample size was admittedly small as a result of loss to follow-up, a significant issue for most longitudinal studies. In addition, the exclusion of ELBW survivors with significant neurosensory impairments may limit the generalizability of the results. Although our finding relative instability of cardiac vagal control in some ELBW survivors requires replication in a larger cohort, even with this restricted, non-impaired sample, and controlling for key variables, the data were sufficient to identify group differences in RSA, both at age 20 (near peak levels) and approximately 10 years later when age-related change in RSA was clearly evident. Future autonomic studies may do well to include specific measures of cardiorespiratory fitness in order to predict ANS functioning more directly.

4.1. Conclusions

No longitudinal study to date has examined age-related change in measures of heart rate variability in adults born at ELBW. The present findings suggest that the early autonomic sequelae of preterm birth may extend into adulthood. Resting RSA may also be less stable over time in some ELBW survivors than is generally the case for NBW controls, suggesting a decrement in parasympathetic regulatory control that may warrant closer monitoring as ELBW survivors age. Altered parasympathetic regulation in adults born at extremely low birth weight may ultimately be useful for early detection of cardiac disease risk in this special population (Rakow et al., 2013), as well as for explaining differences between the cardiovascular risk profiles of ELBW survivors and adults born at normal birth weights.

Acknowledgments

This research was supported by a Canadian Institutes of Health Research (CIHR) grant (awarded to LAS) and a National Institute of Child Health and Human Development (NICHD, NIH) grant (awarded to SS). We wish to thank the many participants and their families for continued participation over the years and Nicole Folland, Paz Fortier, Sue McKee, Nancy Riddell, Victoria Stead, Jordana Waxman, and Shirien Yunus, for their help with data collection and data entry. We also wish to thank Vladimir Miskovic for his assistance with data reduction and comments on the manuscript.

Abbreviations

ELBW	extremely low birth weight
NBW	normal birth weight

SGA	small for gestational age
AGA	average for gestational age
ANS	autonomic nervous system
HP	heart period
HRV	heart rate variability
HF	high frequency heart rate variability
RSA	respiratory sinus arrhythmia
BMI	body mass index

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Highlights

- Autonomic function may be altered in adults born before 28 weeks' gestational age
- We compared autonomic function in 30 adults born extremely preterm and 47 controls
- Mean resting vagal control was lower in preterm adults, at age 22-26 and age 30-35
- *Individual differences* in vagal control were not stable over time in preterm adults
- Vagal control may decline prematurely in some survivors of extremely preterm birth

Figure 1. Group differences and change over time in mean levels of resting respiratory sinus arrhythmia (RSA).

A

B

Figure 2.

Scatterplot of associations between autonomic measures at age 22-26 and age 30-35, for (A) resting heart period (HP) and (B) resting respiratory sinus arrhythmia (RSA), by group.

a. In Figure 2B, the apparent ELBW outlier (bottom right) was not an outlier with respect to either of the predictors—resting HP and RSA at age 22-26. Despite being low for a young adult, this datum was retained as an accurate reflection of the individual's autonomic functioning at the second assessment. Removing the outlier does not allow the ELBW correlation to reach significance ($r(29) = .34, p < .07$).

Table 1

Characteristics of the sample.

	ELBW (<i>n</i> = 30)	NBW (<i>n</i> = 47)
<i>Variable</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
Birth Weight (grams) ^{***}	871 (118)	3420 (496)
Mean Gestational Age ^{***}	27.9 (2.4) weeks	Term
SGA/AGA ^{***}	13/17	2/45
Sex (M/F)	11/19	17/30
General Health (SF-36, T1)	77.77 (23.9)	77.47 (22.1)
Highest Education Level (T1)	2.50 (2.4)	2.77 (2.2)
Body Mass Index (T1)	23.9 (6.0)	24.4 (6.1)
Body Mass Index (T2) [†]	27.0 (7.7)	25.7 (5.3)
Regular Medication Use, T1 (y/n)	17/13	23/24
Regular Medication Use, T2 (y/n) [‡]	14/13	16/28
Age in years (T1)	23.0 (1.3)	23.5 (1.0)
Age in years (T2)	31.8 (1.6)	32.3 (1.4)

Education level of 3 = completed non-university diploma (e.g., community college) by age 22-26

^a Note: *** = $p < .001$ ^b SGA = small for gestational age; AGA = appropriate for gestational age^c SF-36 = Short Form Health Survey (Ware & Sherbourne, 1992)^d T1 = assessment at age 22-26; T2 = assessment at age 30-35^e Education level of 2 = completed trade certificate^f † BMI information at age 30-35 was not available for 1 NBW participant^g ‡ Self-reported medication use at age 30-35 was not available for 3 ELBW and 3 NBW participants.

Table 2

Group mean (SD) and stability coefficients for HP and RSA during resting baseline conditions assessed about a decade apart.

Measure	Age 22-26 mean (SD)	Age 30-35 mean (SD)	T1 to T2 t-value	Pearson <i>r</i> correlation
ELBW (<i>n</i> = 30)				
HP (ms)	840 (157)	809 (135)	1.16	.49**
RSA (ln ms ²)	6.37 (1.0) ^a	5.61 (1.2) ^b	2.85**	.08
NBW (<i>n</i> = 47)				
HP (ms)	830 (130)	812 (122)	0.92	.48**
RSA (ln ms ²)	6.84 (1.0) ^a	6.17 (1.1) ^b	4.70***	.57***

^aSignificance related to group differences (by *t*-test) is indicated by a, b = *p* < .05.

^bSignificance related to change over time (by paired *t*-test) is indicated by ** = *p* < .01, *** = *p* < .001.

^cSignificance of Pearson correlations between assessments is indicated by ** = *p* < .01, *** = *p* < .001.

Table 3

Results of separate hierarchical regression analyses of HP and RSA at age 30-35 on HP and RSA at age 22-26.

	Predictor	R^2	F	df	t	sr^2
Covariates		.10	1.26	6, 69		
	Sex				-.44	< .01
	Health				.48	< .01
	BMI				-1.63	.03
	Meds Use				.99	.01
	Education				.31	< .01
	SGA Status				.55	< .01
cHP		.19	18.03***	1, 68	4.25***	.19
cHP $\times$ Group		< .01	0.03	1, 67	-0.17	< .01
	Predictor	R^2	F	df	t	sr^2
Covariates		.17	2.29	6, 69		
	Sex				0.02	< .01
	Health				0.09	< .01
	BMI				-3.16**	.12
	Meds Use				-0.25	< .01
	Education				0.72	.01
	SGA Status				-1.18	.02
cRSA		.06	4.86*	1, 68	2.20*	.06
cRSA $\times$ Group		.05	4.71*	1, 67	-2.17*	.05

^a Note: * = $p < .05$, ** = $p < .01$, *** = $p < .001$ ^b $n = 76$ in these analyses, as BMI was unavailable for one NBW participant.

Table 4

Results of separate hierarchical regression analyses of RSA at age 30-35 on RSA at age 22-26, for each group.

ELBW (n = 30)	Predictor	R²	F	df	t	sr²
Covariates		.29	1.57	6, 23		
	Sex				1.54	.07
	Health				-0.11	< .01
	BMI				-2.28*	.16
	Meds Use				1.15	.04
	Education				0.66	.01
	SGA Status				0.49	< .01
RSA		< .01	0.04	1, 22	-0.19	< .01
NBW (n = 46)	Predictor	R²	F	df	t	sr²
Covariates		.19	1.51	6, 39		
	Sex				-1.13	0.3
	Health				0.25	< .01
	BMI				-2.11*	.09
	Meds Use				-1.13	.03
	Education				0.01	< .01
	SGA Status				-1.32	.04
RSA		.19	11.73**	1, 38	3.42**	.19

^aNote: * = $p < .05$, ** = $p < .01$

^b $n = 46$ in the NBW analysis, as BMI was unavailable for one NBW participant.