Introduction

Infants born at extremely low birth weight (ELBW) are exposed to multiple forms of prenatal and early postnatal adversity, including the stresses that contribute to premature delivery, and exposure to postnatal medical procedures administered to improve their odds of survival. Because heart rate variability, baroreflex sensitivity, and myelination of the vagus nerve undergo substantial development during the third trimester of pregnancy, the consequences of extremely preterm birth may include alterations in autonomic nervous system (ANS) functioning. Autonomic indices such as heart period (R-R interval) and high-frequency (HF) and low-frequency (LF) heart rate variability are reduced in infants born very preterm (28-32 weeks' gestational age) or small for gestational age, increasing their risk of poor systemic perfusion and adverse neurological events in early infancy. Moreover, autonomic development does not appear to “catch up” between birth and term-equivalent age. Accordingly, autonomic responsiveness has been shown to be reduced in children born preterm at age 9 or 10 years. Researchers have also reported higher blood pressure (BP) in young adults, adolescents, and children born very preterm. In children born extremely preterm, increases in BP may be evident as early as 2.5 years of age.

Relatively little is known about the longer term cardiovascular effects of being born extremely preterm. We do know that cardiac arrhythmias and subclinical atherosclerosis are more prevalent in adults born at low birth weight. Individuals born extremely small may also be prone to increased arterial stiffness and elevated BP in adolescence and young adulthood, especially males, and those who showed rapid weight gain in early childhood. Sequelae of extremely preterm birth appear to include reduced physical fitness in young adulthood.

In clinical settings, birth weight serves as an easily measured predictor of neonatal mortality and morbidity. Birth weight reflects gestational age, genetic inheritance, and
various intrauterine environmental exposures, including poor nutrition, restricted placental blood flow, and maternal factors such as gestational diabetes. A first step to ascertaining whether ELBW may influence autonomic functioning in adult life is to explore associations between birth weight and adult indices of heart rate, autonomic regulatory capacity, and BP in participants born at ELBW and their counterparts born full term and at normal birth weight (NBW).

Most studies of associations between birth weight and autonomic outcomes have defined birth weight as a categorical rather than a continuous variable. Because assessing groups as categories may fail to capture differences in biological or functional relations among variables, it may be more useful to assess individual differences along a continuum. Using continuous variables preserves more information in the data, thereby providing greater statistical power for finding effects. We used birth weight as both a categorical variable and as a continuous variable, adjusting group means and correlations for growth restriction because of its high prevalence in preterm infants (eg, 24% of ELBW infants are born SGA) and adverse consequences. Separating the relative contributions of being born preterm from those of growth restriction is important because preterm birth and growth restriction represent separate etiological pathways.

In healthy young adults, resting heart rate exhibits substantial variability. Higher levels of resting heart rate variability (HRV) have been linked to dynamic cardiovascular adaptation to environmental demands and a lower risk for cardiovascular disease. Resting heart rate is predominantly under the control of the parasympathetic nervous system, which is responsible for effecting rapid, beat-to-beat changes in heart rate. The cardiac signal may be decomposed to ascertain the power density of its major frequencies using spectral frequency analysis. HF HRV (above 0.12 Hz) in the cardiac signal is centered on the respiratory frequency and primarily reflects parasympathetic modulation of heart rate. LF HRV (about 0.10 Hz) may reflect activity of the arterial baroreflexes, which adjust heart rate and peripheral vascular resistance to offset sudden variations in BP whenever they occur in response to environmental or internal demands. Individual differences in resting heart rate and HRV are thought to originate in the prenatal period and persist in infancy, and remain stable in adulthood.

Both HF and LF are reported to increase substantially between 24 weeks’ gestation and term. In preterm neonates, higher resting HF signifies greater maturation of parasympathetic control. In adults, resting HF is positively associated with cardiovascular health, and competent emotion regulation, executive functioning, and attentional control. In neonates born preterm, baroreflex activity appears to be underdeveloped and matures more slowly than it does in full-term infants, signifying increased vulnerability to potentially dangerous hypotensive events. In adults, lower resting LF is associated with various forms of autonomic failure (eg, congestive heart failure). Like HF, baroreflex sensitivity normally shows progressive increases between 28 weeks’ gestation and term. However, preterm birth may delay the normal maturational increase in baroreceptor sensitivity, resulting in substantially reduced baroreflex control at 5 or 6 months corrected age. In adults, baroreflex sensitivity is considered a major prognostic indicator of cardiovascular health, that is reduced in hypertensive conditions. Importantly, HF and LF reflect 2 aspects of autonomic regulatory capacity, whereas heart rate (R-R) and BP (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) are net outcomes of autonomic regulatory processes.

Although the extant literature suggests that cardiovascular regulation may be altered in infants and children born at ELBW, relatively little is known about whether these autonomic differences persist in adulthood. Therefore, we tested whether birth weight predicted resting measures of autonomic regulation (R-R interval, HF, LF, SBP, and DBP) in young adults born at ELBW and their peers born at NBW, as a first step in examining the effects of extremely preterm birth on cardiovascular functioning. If being born at ELBW confers increased long-term cardiovascular risk, we would expect to see group differences in autonomic parameters, and/or differential associations between birth weight and autonomic parameters in adult ELBW survivors versus NBW controls. Specifically, we hypothesized that higher birth weights within the ELBW group would be associated with greater capacity for autonomic regulation (greater R-R interval, HF, and LF, and lower SBP and DBP) in adulthood, whereas the restricted range represented by NBW control participants would result in smaller correlations in this group. A third prediction was that associations among the autonomic parameters would differ between groups, suggesting altered functional relationships among these variables.

Method

Cohort and Participants

The cohort included ELBW survivors recruited at birth, and a group of NBW controls recruited when ELBW participants and controls were 8 years old. Originally, the ELBW group included 397 mainly Caucasian infants born between 1977 and 1982 within a geographically defined
area in south western Ontario, Canada Weighing between 500 and 1000 grams at birth, these infants have been assessed longitudinally at ages 3, 5, 8, 14, 22 to 26, and 29 to 36 years. Gestational ages for the ELBW participants ranged from 23 to 34 weeks, with 68% (n = 121) being born <28 weeks’ gestational age. Of the original cohort, 179 (45%) survived to hospital discharge, and 13 children died subsequently. Of the 166 survivors, 142 were contacted and invited to participate in the young adult assessment at age 22 to 26 at which time a subset of 71/142 right-handed participants free of major neurosensory impairments (eg, blindness, deafness, and cerebral palsy) was tested in the Child Emotion Laboratory at McMaster University. Usable electrocardiogram (ECG) data were obtained from 67/71. Resting HF (2 participants) or socioeconomic status (SES) information (5 participants) was unobtainable from some participants, leaving data from 60/71 (85%) of the ELBW survivors available for analysis. Blood pressure measures were missing for 1 ELBW participant and 1 NBW participant.

The age-, sex-, and SES-matched control group consisting of 145 children born at NBW has been assessed in tandem with the ELBW cohort at ages 8, 14, 22 to 26, and 29 to 36. Of these, 133 were assessed at age 22 to 26. From this group, a subset of 83/133 right-handed control participants was tested in our laboratory, yielding usable ECG data from 80/83. Resting HF was unobtainable from 1 participant, leaving data from 79/83 (95%) of the NBW controls available for analysis.

Procedure

Participants were introduced to the laboratory and briefed about the study procedures. Resting ECG and BP measures were collected after obtaining written consent. Resting R-R interval, HF, and LF were quantified noninvasively by spectral frequency analysis of the ECG. All laboratory procedures were approved by the participating university and hospital research ethics boards.

ECG Collection and Measures

ECG Recording. ECG was continuously recorded during 2 minutes of rest via 2 disposable ECG electrodes placed on the medial forearms while the participant sat quietly in a comfortable chair. Recordings made during the resting state, before any task has started, provide measures that are characteristic of the individual, as this state is assumed to be relatively free of external demands. A minimum recording length of 2 minutes is required for accurate assessment of LF. This recording length also meets the minimum required for calculating HF.

Because spontaneous respiration rates during seated rest are generally slow enough to avoid any undue influence of respiration, respiration rate was not monitored in this study. ECG signals were 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 was Snapshot-Snapstream (HEM Data Corp, Southfield, MI). Measures of maximum (SBP) and minimum (DBP) arterial pressure were collected by an ambulatory BP monitor while each participant was comfortably seated.

ECG Reduction and Quantification. Mean levels of R-R interval, HF, and LF were derived offline from each resting ECG recording in its entirety. Indices of R-R interval are preferred over heart rate in autonomic research, as heart rate is a non-linear transform of the R-R interval. Cardiac R-waves were detected offline with a 4-pass algorithm that produced a visual display of the cardiac signal with the R-waves marked (IBI Analysis, James Long Company, Caroga Lake, NY). Missing or spurious R-waves were edited manually according to Berntson and Stowell. The edited file of R-wave onset times was converted to interbeat intervals and prorated into equal time intervals of 125 milliseconds using a moving polynomial filter. This series was then detrended using a high-pass filter with a period of 25 seconds (frequency cut-off, 0.04 Hz), to allow quantification of both HF variability (ie, 0.12 to 0.40 Hz) and LF variability (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 HF variability in the signal, summed across the range of respiratory frequencies, and also LF variability, summed across the LF range. In keeping with common practice in current psychophysiological research, HF and LF values were then submitted to natural log transformations to normalize their distributions (ln ms²) before analysis.

Statistical Analysis

The variables of interest were R-R interval, HF, LF, SBP, and DBP. Group differences in mean levels were assessed using independent, 2-sided t tests. Separate regression analyses were performed to ascertain the variance explained by birth weight for each autonomic variable and group (Model 1, unadjusted). To assess the unique contribution of birth weight to predictions of autonomic activity, we ran a second, hierarchical, regression analysis for each autonomic variable with age, sex, SGA status, familial SES, and body mass index (BMI), entered as covariates on the first step, followed by birth
Table 1. Sample Characteristics.

| Variable                        | ELBW (n = 60), Mean (SD) | NBW (n = 79), Mean (SD) | Mean Difference† (95% CI) |
|---------------------------------|--------------------------|-------------------------|--------------------------|
| Mean gestational age***         | 27.4 (2.1) weeks         | Term                    |                          |
| SGA/AGA***                     | 19/41                    | 2/77                    |                          |
| Sex (male/female)              | 25/35                    | 34/45                   |                          |
| Birth weight (g)***            | 872 (114)                | 3403 (465)              | −2530.7 (−2638.7 to −2422.6) |
| Age in years*                  | 23.1 (1.2)               | 23.6 (1.1)              | −0.49 (−0.88 to −0.10)   |
| Adult height (cm)***           | 164.6 (10.3)             | 169.2 (10.2)            | −4.65 (−8.14 to −1.17)   |
| Adult weight (kg)              | 65.5 (16.3)              | 70.4 (16.6)             | −4.91 (−10.48 to 0.67)   |
| Body mass index (kg/m²)        | 24.1 (5.7)               | 24.5 (5.1)              | −0.35 (−2.16 to 1.46)    |
| Familial SES (age 8)           | 3.35 (0.8)               | 3.05 (1.0)              | 0.30 (−0.01 to 0.61)     |
| Resting R-R interval (ms)      | 841 (142)                | 852 (132)               | −10.86 (−57.13 to 35.41) |
| Resting HF (ln ms²)            | 6.65 (0.9)               | 6.93 (1.1)              | −0.29 (−0.63 to 0.05)    |
| Resting LF (ln ms²)            | 6.31 (1.0)               | 6.49 (0.9)              | −0.18 (−0.50 to 0.15)    |
| Resting SBPc (mm Hg)           | 118.7 (14.6)             | 119.2 (14.0)            | 2.47 (−5.34 to 4.41)     |
| Resting DBPc (mm Hg)           | 69.9 (10.1)              | 68.9 (9.1)              | 1.65 (−2.26 to 4.25)     |

Abbreviations: ELBW, extremely low birth weight; NBW, normal birth weight; SD, standard deviation; CI, confidence interval; SGA, small for gestational age; AGA, appropriate for gestational age; SES, socioeconomic status; R-R interval, heart period; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure.

†Group differences were assessed by t tests or χ² tests.

BPS data were unavailable for 1 ELBW participant and 1 NBW participant.

Results

Demographic and cardiovascular measures are reported in Table 1. The ELBW participants, included (n = 60) and excluded (n = 11), were similar with respect to demographic characteristics (birth weight, age, sex, SGA status, adult height, weight, and BMI, and familial SES, all Ps > .16). The NBW participants, included (n = 79) and excluded (n = 4), were also similar with respect to these characteristics (all Ps > .45).

Birth weight was normally distributed in the NBW group (Shapiro–Wilk, P > .70), but right-skewed in the ELBW group because comparatively fewer ELBW survivors were born at the very lowest birth weights (Shapiro–Wilk, P < .001). Each of the cardiovascular
and BP variables was normally distributed in the ELBW survivors (Shapiro–Wilk, $P > .08$) and their NBW ($P < .12$) peers. Although no group differences in the mean resting autonomic parameters reached significance (Shapiro–Wilk, $P > .09$), R-R, HF, and LF were numerically lower in ELBW survivors. In addition, a comparison of NBW controls with the smallest-born ELBW survivors revealed that HF in the controls was significantly higher than in the smallest ELBW survivors (divided by a median split at 920 g; NBW: mean = 6.93 ln ms$^2$, SD = 1.05; ELBW: mean = 6.44 ln ms$^2$, SD = 0.84), although no other subgroup differences reached significance ($P > .09$).

**Regression Models of Adult Autonomic Measures on Birth Weight in ELBW Survivors**

Results for the ELBW group are presented in Table 2 and Figure 1. In both regression models (unadjusted, adjusted), higher birth weight was associated with longer resting R-R intervals (slower heart rates), accounting for 13% of the variance in the R-R interval. Although the association of birth weight with R-R interval was significant for the ELBW group as a whole, this association depended mainly on the smallest survivors ($\leq 920$ g; $r[30] = .42, P < .03$). The correlation did not reach significance for ELBW participants with relatively higher birth weights (920-1000 g; $r[30] = .01, P > .95$; Fisher $r$-to-$z$, $P < .04$; see Figure 1). As well, NBW controls showed stronger partial correlations between LF and the R-R interval ($r = 2.73, P < .01$) and between LF and DBP ($r = 2.07, P < .04$; see Figure 2) than did ELBW survivors, who showed no such associations ($P > .45$).

In sum, for young adults who were born weighing less than 1000 g, relatively lower birth weight was associated with faster resting heart rate and greater DBP, and lower HF activity (parasympathetic regulatory capacity). In young adults born weighing >2500 g, birth weight was positively associated with HF and LF regulatory activity. Importantly, among NBW controls, LF regulatory activity was inversely correlated with resting heart rate and DBP, links that were absent in the ELBW survivor group.

**Discussion**

The goal of this study was to examine whether being born at ELBW conferred increased autonomic risks in adulthood. As a first step to answering this question, we tested for associations among birth weight and resting autonomic measures in young adults born at ELBW and their NBW peers. Although ELBW participants in this sample were slightly younger, shorter, and socioeconomically more disadvantaged than NBW participants, mean resting autonomic measures did not differ significantly between groups (in contrast to other studies$^{5,20}$). However, HF heart rate variability was significantly higher in NBW controls than in the smallest-born ELBW young adults, indicating that adult parasympathetic regulatory capacity may indeed be lower following extremely preterm birth. In addition, the groups showed distinctive associations between birth weight and autonomic regulation that were broadly consistent with other cardiovascular conditions reported in adults born extremely preterm (eg, cardiac arrhythmias$^{16}$ and hypertension$^{22}$). In adult ELBW survivors, smaller physical size at birth predicted faster resting heart rate, higher DBP, and lower capacity for parasympathetic regulation (HF), after adjusting for potential confounds. In control adults born at full term and at NBW, relatively lower birth weights were associated with lower levels of parasympathetic control (HF), and lower resting baroreflex activity (LF), but were unrelated to heart rate or BP measures.

**Resting Heart Rate (R-R Interval)**

As birth weight accounted for significant variance in resting heart rate in ELBW survivors after controlling for relevant covariates, the association between birth
### Table 2. Results of Regression Models of Resting Autonomic Variables on Birth Weight for the ELBW Groupa.

| Predictors | R² | FΔ | df  | B    | SE  | sr² |
|------------|----|----|-----|------|-----|-----|
| **R-R interval** |    |    |     |      |     |     |
| Model 1    |    |    |     |      |     |     |
| Birth weight | .13 | 8.55** | 1, 58 | 0.45 | 0.15 | .13 |
| Model 2    |    |    |     |      |     |     |
| Step 1     |    |    |     |      |     |     |
| Sex       |    |    |     |      |     |     |
| Age       |    |    |     |      |     |     |
| SGA status |    |    |     |      |     |     |
| BMI       |    |    |     |      |     |     |
| SES       |    |    |     |      |     |     |
| Step 2     |    |    |     |      |     |     |
| Birth weight | .13 | 8.47** | 1, 53 | 0.47 | 0.16 | .13 |
| **HF** |    |    |     |      |     |     |
| Model 1    |    |    |     |      |     |     |
| Birth weight | .08 | 5.10* | 1, 58 | .002 | .001 | .08 |
| Model 2    |    |    |     |      |     |     |
| Step 1     |    |    |     |      |     |     |
| Sex       |    |    |     |      |     |     |
| Age       |    |    |     |      |     |     |
| SGA status |    |    |     |      |     |     |
| BMI       |    |    |     |      |     |     |
| SES       |    |    |     |      |     |     |
| Step 2     |    |    |     |      |     |     |
| Birth weight | .07 | 4.60* | 1, 53 | .002 | .001 | .07 |
| **LF** |    |    |     |      |     |     |
| Model 1    |    |    |     |      |     |     |
| Birth weight | <.01 | 0.02 | 1, 58 | .000 | .001 | <.01 |
| Model 2    |    |    |     |      |     |     |
| Step 1     |    |    |     |      |     |     |
| Sex       |    |    |     |      |     |     |
| Age       |    |    |     |      |     |     |
| SGA status |    |    |     |      |     |     |
| BMI       |    |    |     |      |     |     |
| SES       |    |    |     |      |     |     |
| Step 2     |    |    |     |      |     |     |
| Birth weight | <.01 | 0.05 | 1, 53 | .001 | .001 | <.01 |
| **SBP** |    |    |     |      |     |     |
| Model 1    |    |    |     |      |     |     |
| Birth weight | .06 | 3.72† | 1, 57 | −0.03 | .02 | .06 |
| Model 2    |    |    |     |      |     |     |
| Step 1     |    |    |     |      |     |     |
| Sex       |    |    |     |      |     |     |
| Age       |    |    |     |      |     |     |
| SGA status |    |    |     |      |     |     |
| BMI       |    |    |     |      |     |     |
| SES       |    |    |     |      |     |     |
| Step 2     |    |    |     |      |     |     |
| Birth weight | .04 | 3.10† | 1, 52 | −0.03 | .02 | .04 |
| **DBP** |    |    |     |      |     |     |
| Model 1    |    |    |     |      |     |     |
| Birth weight | .07 | 3.94† | 1, 57 | −.02 | .01 | .06 |
| Model 2    |    |    |     |      |     |     |
| Step 1     |    |    |     |      |     |     |
| Sex       |    |    |     |      |     |     |
| Age       |    |    |     |      |     |     |
| SGA status |    |    |     |      |     |     |
| BMI       |    |    |     |      |     |     |
| SES       |    |    |     |      |     |     |
| Step 2     |    |    |     |      |     |     |
| Birth weight | .07 | 4.77* | 1, 52 | −.02 | .01 | .07 |

Abbreviations: ELBW, extremely low birth weight; df, degrees of freedom; R-R interval, heart period; SGA, small for gestational age; BMI, body mass index; SES, socioeconomic status; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*aBirth weight predictions did not change when regressions were performed on untransformed HF and LF data. HF, Model 1: B = 2.92 (SE = 1.19), P < .02. Model 2, Step 2: B = 3.84 (SE = 1.23), P < .03. LF, Model 1: B = 0.93 (SE = 1.12), P > .40. Model 2, Step 2: B = 0.93 (SE = 1.09), P > .35. **P < .01. *P < .05. †P < .06. ‡P < .09.
Figure 1. Pearson (r) correlations between birth weight and resting R-R, HF, LF, SBP, and DBP, by group.

*Correlations differed significantly by group, $z = 2.27, P < .03$ (2-tailed). ‡Correlations differed marginally by group, $z = 1.73, P < .09$ (2-tailed).
Table 3. Results of Regression Models of Resting Autonomic Variables on Birth Weight for the NBW Group.

|               | Predictors  | $R^2$ | $F$Δ | df  | B     | SE    | $sr^2$ |
|---------------|-------------|-------|------|-----|-------|-------|--------|
| **R-R interval** |             |       |      |     |       |       |        |
| Model 1       | Birth weight | .02   | 1.48 | 1, 77 | 0.04  | 0.03  | .02    |
| Model 2       | Step 1      | .09   | 1.37 | 5, 73 |       |       |        |
|               | Sex         | 11.91 | 31.83| <.01 |       |       |        |
|               | Age         | −0.42 | 15.01| <.01 |       |       |        |
|               | SGA status  | −130.00 | 97.01| .02  |       |       |        |
|               | BMI         | −6.64* | 2.93 | .06  |       |       |        |
|               | SES         | −9.99 | 16.74| <.01 |       |       |        |
| Step 2        | Birth weight | .02   | 1.36 | 1, 72 | 0.04  | 0.03  | .02    |
| **HF**        |             |       |      |      |       |       |        |
| Model 1       | Birth weight | .06   | 4.58* | 1, 77 | 0.001 | .000  | .06    |
| Model 2       | Step 1      | .18   | 3.15**| 5, 73 |       |       |        |
|               | Sex         | 0.28  | 0.24 |       |       |       | .02    |
|               | Age         | −0.04 | 0.11 | <.01 |       |       |        |
|               | SGA status  | −1.70 | 0.73 | .06  |       |       |        |
|               | BMI         | −0.06* | 0.02 | .07  |       |       |        |
|               | SES         | −0.26* | 0.13 | .05  |       |       |        |
| Step 2        | Birth weight | .04   | 3.48† | 1, 72 | 0.000 | 0.000 | .03    |
| **LF**        |             |       |      |      |       |       |        |
| Model 1       | Birth weight | .13   | 11.24**| 1, 77 | 0.001 | .000  | .13    |
| Model 2       | Step 1      | .18   | 3.12* | 5, 73 |       |       |        |
|               | Sex         | −0.15 | 0.21 |       |       |       | .01    |
|               | Age         | 0.05  | 0.10 | <.01 |       |       |        |
|               | SGA status  | −0.98 | 0.64 | .03  |       |       |        |
|               | BMI         | −0.04* | 0.02 | .05  |       |       |        |
|               | SES         | −0.29* | 0.11 | .08  |       |       |        |
| Step 2        | Birth weight | .10   | 10.15**| 1, 72 | 0.001 | 0.000 | .10    |
| **SBP**       |             |       |      |      |       |       |        |
| Model 1       | Birth weight | <.01  | 0.02 | 1, 76 | 0.00  | .003  | <.01   |
| Model 2       | Step 1      | .35   | 7.64***| 5, 72 |       |       |        |
|               | Sex         | −13.74***| 2.87 | .21  |       |       |        |
|               | Age         | 1.05  | 1.36 | .01  |       |       |        |
|               | SGA status  | 17.80* | 8.71 | .04  |       |       |        |
|               | BMI         | 0.76** | 0.27 | .07  |       |       |        |
|               | SES         | −1.32 | 1.53 | .01  |       |       |        |
| Step 2        | Birth weight | <.01  | 0.02 | 1, 71 | 0.000 | 0.003 | <.01   |
| **DBP**       |             |       |      |      |       |       |        |
| Model 1       | Birth weight | .01   | 0.71 | 1, 76 | −0.002 | 0.002 | .01    |
| Model 2       | Step 1      | .16   | 2.69* | 5, 72 |       |       |        |
|               | Sex         | −2.86 | 2.12 | .02  |       |       |        |
|               | Age         | 0.25  | 1.00 | <.01 |       |       |        |
|               | SGA status  | 17.38** | 6.41 | .09  |       |       |        |
|               | BMI         | 0.46* | 0.20 | .06  |       |       |        |
|               | SES         | 1.43  | 1.12 | .02  |       |       |        |
| Step 2        | Birth weight | <.01  | 0.13 | 1, 71 | −0.001 | 0.002 | <.01   |

Abbreviations: NBW, normal birth weight; df, degrees of freedom; R-R interval, heart period; SGA, small for gestational age; BMI, body mass index; SES, socioeconomic status; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Birth weight predictions did not change when regressions were performed on untransformed HF and LF data, except Model 1 birth weight prediction of HF now reached significance. HF, Model 1: $B = 1.08$ (SE = 0.41), $P < .02$. Model 2, Step 1: $B = 0.99$ (SE = 0.43), $P < .03$. LF, Model 1: $B = 0.68$ (SE = 0.20), $P < .01$. Model 2, Step 2: $B = 0.64$ (SE = 0.21), $P < .01$.

**$P < .001$. ***$P < .01$. **$P < .05$. †$P < .09$. **$P < .001$. ***$P < .01$. **$P < .05$. †$P < .09$. **
weight and heart rate must be attributable to some factor other than age, sex, SGA status, familial SES, or adult body size.*† One possibility is that ELBW survivors may be prone to alterations in cardiac morphology and function that promote faster resting heart rates.

The birth event induces profound changes in infants’ circulatory functioning.\textsuperscript{59,60} In humans, early birth may result in increased ventricle mass and other changes in gross cardiac morphology (eg, shorter ventricles with smaller internal volumes\textsuperscript{61,62}), changes that are likely to be irreversible.\textsuperscript{26} Moreover, the severity of adverse cardiac remodeling increases with shorter gestational periods.\textsuperscript{61,62} Evidence from nonhuman animal models suggests that a premature increase in the hemodynamic load instigated by early birth may lead to increased collagen deposition (fibrosis or stiffening) in myocytes of the heart’s left ventricle\textsuperscript{59} that may affect its structure, and potentially, its function. Like the heart, the vasculature may be subject to remodeling in individuals born very small. Deficient elastin synthesis in the large arteries and aorta has been proposed as a causal mechanism for vascular changes that predispose individuals to increased risk of hypertension and cardiovascular disease.\textsuperscript{63,64,65}

Structural alterations that decrease flexibility in the heart or vasculature may necessitate increased cardiac activity, including a faster heart rate, in order to maintain adequate stroke volume and BP in ELBW populations.

Although the association of birth weight with R-R interval was significant for the ELBW group as a whole, scatterplots suggested that the association depended mainly on the smallest-born survivors (≤920 g). No association was apparent for those ELBW participants with relatively higher birth weights (≥920 g), nor for control participants, whose intrauterine cardiac development had proceeded without being interrupted by early birth. These differential associations suggest a possible threshold effect of gestational age, beyond which cardiac remodel-

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### Table 4. Partial Correlations (pr) Among Resting Autonomic Measures and Blood Pressure Measures by Group, Controlled for Growth Restriction (SGA Status)\textsuperscript{a}.

|          | Birth Weight | RR   | HF   | LF   | SBP  | DBP  |
|----------|--------------|------|------|------|------|------|
| **ELBW (n = 59)** | Birth weight | —    |      |      |      |      |
| RR       | .34**        | —    |      |      |      |      |
| HF       | .23          | —    | .32* |      |      |      |
| LF       | —.09         | .01  | .44**|      |      |      |
| SBP      | —.25†        | —.22 | —.12 | .06  |      |      |
| DBP      | —.30*        | —.45***| —.14 | .10  | .69***|      |
| **NBW (n = 78)** | Birth weight | —    |      |      |      |      |
| RR       | .11          | —    |      |      |      |      |
| HF       | .20          | —    | .56***|      |      |      |
| LF       | .34**        | .44***| .68***|      |      |      |
| SBP      | .05          | —.31***| —.18 | —.09 |      |      |
| DBP      | —.03         | —.45***| —.39**| —.26*| .54***|      |

Abbreviations: SGA, small for gestational age; ELBW, extremely low birth weight; NBW, normal birth weight; R-R, interval, heart period; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Bold values identify significantly stronger correlations in NBW controls than ELBW survivors, by Fisher’s r-to-z transformation (2-tailed): LF-Birth Weight, \textit{z} = 2.54, \textit{P} < .02. LF-R-R: \textit{z} = 2.73, \textit{P} < .01. LF-DBP: \textit{z} = 2.07, \textit{P} < .04.

**\textit{P} < .01. ***\textit{P} < .001. †\textit{P} < .06.

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* A covariate representing “age at hospital discharge” was added to the regression analyses of R-R interval, HF, LF, SBP, and DBP for the ELBW group, to account for possible differences in lung development and perinatal comorbidities. Age at hospital discharge was not directly associated with any of the autonomic parameters (all \textit{P} s > .55), and including it in the regression analyses did not change the significance of associations between birth weight and the autonomic variables in ELBW survivors.

†Self-reported smoking status, alcohol use, and sleep quality were collected from both groups at the young adult assessment. The groups did not differ on any of these adult lifestyle variables (\textit{P} s > .19), and none of them was associated directly with the autonomic indices in either group (all \textit{P} s > .08), with 2 exceptions: in the NBW group, heavy alcohol use was associated with shorter resting R-R interval, accounting for 6% of the variance, \textit{B} = −113.8 (49.7), \textit{P} < .03, and sleep restlessness explained 3% of the variance in SBP, \textit{B} = 3.05 (1.6), \textit{P} < .06. Adding the lifestyle variables to the covariates did not change associations between birth weight and any of the autonomic parameters in either group.

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The birth event induces profound changes in infants’ circulatory functioning.\textsuperscript{59,60}
Correlations between birth weight and resting parasympathetic activity were of similar magnitude in adults born at ELBW and at NBW. These parallel findings suggest that the development of parasympathetic regulation of heart rate may begin comparatively early in gestation.\(^{31}\) Fetal heart rate is known to rise to 175 bpm by 9 weeks' gestational age, declining thereafter to about 150 bpm by 16 weeks\(^ {66}\) and 140 bpm by term.\(^ {1}\) Diminishing fetal heart rate during the second and third pregnancy trimester reflects ongoing development of the parasympathetic nervous system, which gradually overtakes the accelerating effects of developing sympathetic control.\(^ {1}\) If parasympathetic control of heart rate increases from 9 weeks' gestational age, then vagal development is likely to be well underway at the time of birth even in individuals born before the third trimester.\(^ {6,67}\) The absence of group differences in resting HF across the whole sample suggests that vagal function may “catch up” by young adulthood in many ELBW survivors.
Resting Baroreflex Regulation (LF)

The main mechanism for modulating heart rate and vascular resistance in response to sudden variations in BP is the baroreflex. Like parasympathetic regulation (HF), baroreflex sensitivity shows a linear increase with gestational age in nonhuman animal models and in human infants. Baroreflex activity tends to be underdeveloped in infants born preterm, and its postnatal maturation may remain delayed, even by theoretical term. Here, a robust, positive association between birth weight and baroreflex activity (LF) was evident among NBW controls (P < .01), even after familial SES and adult body size were accounted for, while no association was observed in ELBW survivors (P > .85). These differential associations suggest the dependence of LF development on reaching an advanced gestational age. In addition, consistent with reports of reduced HRV in groups with lower SES, LF was lower among controls who experienced lower SES during development. Among ELBW survivors, female sex was associated with lower LF, in line with studies showing that baroreflex activity is sexually dimorphic in humans and nonhuman animals, and lower in females.

Blood Pressure (SBP and DBP)

Much evidence links relatively lower birth weights to elevated BP levels in individuals born very preterm or even near term. Stroke volume, systolic and diastolic functioning, and right ventricular ejection fraction all appear to be adversely affected in adults born preterm. Studies of children and adolescents indicate that these associations appear early. They may also amplify with age, given that BP increases occurring between childhood and young adulthood are larger in individuals born at low birth weights. Like cardiac remodeling, the degree of BP deviation in young adulthood is graded with the degree of prematurity.

While some studies have found stronger links between very low birth weight and SBP than DBP, others report only altered DBP in adults born very preterm. Here, we found that with SGA status controlled, lower birth weights in the ELBW group predicted higher minimum arterial pressures during the relaxation segment of the cardiac cycle (DBP, Table 4). This association suggests that diastolic relaxation in ELBW survivors may be sluggish or incomplete, with possible negative consequences for cardiovascular functioning. Indeed, evidence suggests that diastolic functioning in young adults who were born very preterm is comparable to that of control adults who are 10 years older.

Associations Among Autonomic Variables

Although the ELBW and NBW groups did not differ with respect to mean levels of resting heart rate, HRV, or blood pressure, they exhibited important differences with respect to associations involving resting baroreflex (LF) activity. Whereas NBW controls exhibited strong positive correlations between LF and R-R interval, and significant negative correlations between LF and DBP, both heart rate and diastolic relaxation in the ELBW group appeared to be independent of baroreflex activity. These differential findings suggested that in adult ELBW survivors, resting heart rate and DBP may not be well-controlled by the baroreflexes. Baroreflex insufficiency may have a role in explaining the development of higher BP, and possibly, lower fitness in adults born at ELBW, although these hypotheses remain to be explored in future studies.

Limitations

Some study limitations should be borne in mind when interpreting the findings. First, the exclusion of ELBW survivors with significant neurosensory impairments limits the generalizability of our results to adults born extremely preterm with relatively intact levels of functioning. However, given that our general goal was to examine autonomic effects of being born extremely small, it was deemed prudent not to introduce the confound of serious neurosensory impairment (e.g., cerebral palsy).

Second, although the Task Force of the European Society of Cardiology guidelines state that 2-minute recordings meet the minimum requirements for assessing HF and LF, we acknowledge that the recommended length for short ECG recordings is 5 minutes, and that conforming to this standard allows easier comparisons across studies. Measures of LF are adversely affected if too few cycles are recorded or if the detrending period is too short (eg, 10 seconds, frequency cutoff, 0.10 Hz). Adherence to the minimum recording length will have reduced this possibility, and we took care to alter the period of the high-pass filter from the usual 10 seconds to 25 seconds when detrending the cardiac signal, to allow accurate calculation of LF.

Third, we acknowledge that it is preferable to record respiration when assessing HF, in order to demonstrate that any reported group differences or condition effects involving HF were not simply attributable to changes in respiratory rate or volume. Fortunately, the effects of spontaneous breathing on resting HF are likely to be small. As well, because there were no obvious group differences in resting HF, we inferred that both
resting parasympathetic activity and respiration rates were similar across groups.

Fourth, our indices of cardiovascular functioning were limited to resting heart rate, spectral measures of HRV (HF and LF), and BP. Examining whether birth weight predicts autonomic reactivity—ie, autonomic changes between rest and physical or psychological stress tests—would allow ecologically valid observations of the autonomic system “in action.” Finally, although our sample size was reasonably large for studies of extremely preterm birth, the present findings require replication with adult ELBW cohorts from other locations, representing other demographic categories. Nonetheless, after controlling for intrauterine growth restriction and other key variables, the data from this sample were sufficient to identify significant group differences in the associations between birth weight and autonomic regulatory parameters, more than 20 years after birth.

Conclusions
The strengths of this study include the availability of a geographically determined cohort (reducing the impact of referral biases) and reasonably high follow-up rates in adulthood. The major findings were that adult parasympathetic regulatory capacity was significantly reduced in the very smallest-born ELBW survivors, and that associations between birth weight and resting autonomic measures differed between ELBW survivors and their NBW counterparts, suggesting increased cardiovascular risk in individuals born extremely preterm.

Within the group of ELBW survivors, those born at relatively lower birth weights had faster resting heart rates, lower resting parasympathetic activity (HF), and higher resting DBP. Within the NBW control group, relatively higher birth weights were associated with greater parasympathetic (HF) and baroreflex (LF) activity, and both resting heart rate and DBP were closely aligned with baroreflex control (LF). Notably, and reported for the first time in young adults born at ELBW, neither resting heart rate nor BP appeared to be well-coordinated with baroreflex activity (LF), the principal mechanism for short-term, reflexive control of BP. We conclude that autonomic functioning may be significantly altered in young adulthood for those born extremely preterm. Given these circumstances, early monitoring for symptoms of hypertension and cardiac disease may be warranted in this special population as its members grow older.

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Author Contributions
KJM contributed to conception and design, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. RJVL contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. SS contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MHB contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. LAS contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KMM contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KJM contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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