Cardiac Autonomic Function in Adults Born Preterm

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Objective To evaluate cardiac autonomic function in adults born preterm.

Study design We studied the association between prematurity and cardiac autonomic function using heart rate variability measurements in 600 adults (mean age of 23.3 years) from a geographically based cohort in Northern Finland. There were 117 young adults born early preterm (<34 weeks), 207 born late preterm (34-36 weeks), and 276 born at term (≥37 weeks, controls). Autonomic function was analyzed by calculating time and frequency domain heart rate variability measurements using linear regression.

Results Compared with controls, the mean difference in root mean square of successive differences (indicating cardiac vagal activity) was −12.0% (95% CI −22.2%, −0.5%, adjusted for sex, age, source cohort, and season $P = .04$) for the early preterm group and −7.8% (−16.8%, 2.0%, $P = .12$) for the late preterm group. Mean differences with controls in low frequency power (indicating cardiac vagal activity, including some sympathetic- and baroreflex-mediated effects) were −13.6% (−26.7%, 1.8%, $P = .08$) for the early preterm group and −16.4% (−27.0%, −4.3%, $P = .01$) for the late preterm group. Mean differences in high frequency power (quantifying cardiac vagal modulation in respiratory frequency) were −19.2% (−36.6%, 2.9%, $P = .09$) for the early preterm group and −13.8% (−29.4%, 5.3%, $P = .15$) for the late preterm group. Differences were attenuated when controlled for body mass index and physical activity.

Conclusions Our results suggest altered autonomic regulatory control in adults born preterm, including those born late preterm. Altered autonomic regulatory control may contribute to increased cardiovascular risk in adults born preterm. *(J Pediatr 2019;208:96-103)*.

Each year, approximately 15 million infants worldwide are born preterm.[1] Preterm birth is associated with an increased risk of cardiovascular disease in adult life.[2-7] The risk factors for cardiovascular disease include increased blood pressure and blood pressure variability.[8-10] The mechanisms that link preterm birth with elevated blood pressure remain unclear.

Altered cardiac autonomic function, manifested as depressed vagal and augmented sympathetic activity, is an important risk factor for cardiovascular morbidities.[11-14] Heart rate (HR) variability (HRV) metrics are commonly used to assess cardiac autonomic function.[11] A substantial proportion of the development of the autonomic nervous system (eg, myelination of the vagus nerve, baroreflex sensitivity, and HRV) occurs during the third trimester and is interrupted at preterm birth.[15-17] Interrupted development of autonomic nervous system by preterm birth is likely to have consequences for autonomic control in later life. Altered cardiac autonomic function may be a potential candidate mechanism linking preterm birth with elevated blood pressure and cardiovascular risk factors in adulthood.

After birth, infants born preterm have altered autonomic control compared with those born at term.[18] Follow-up studies of those born very preterm (<32 weeks) or with an extremely low birth weight (<1000 g) suggested that decreased cardiac autonomic control was present in childhood and young

BMI	Body mass index
ESTER	Preterm Birth and Early-Life Programming of Adult Health and Disease
HF	High frequency
HFP	HF power
HR	Heart rate
HRV	HR variability
LF	Low frequency
LFP	LF power
rMSSD	Root mean square of successive differences
VLBW	Very low birth weight

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adulthood.[19-21] Research also indicated that adults who had an extremely low birth weight may experience premature decline in parasympathetic functioning during their 20s and 30s.[19] The findings of the aforementioned studies apply only to the smallest and most immature of infants. However, the majority of preterm births are moderate (32-33 weeks) or late (34-36 weeks). Although many risk factors for cardiometabolic disease found in very preterm infants are also found in moderate and late preterm infants, whether these include altered cardiac autonomic function is not known.[4,10] We hypothesized that preterm birth, throughout its entire range, is associated with decreased cardiac vagal control in young adults. We also hypothesized that higher blood pressure in adults born preterm may be linked to altered autonomic control.

Methods

The participants were part of the Preterm Birth and Early-Life Programming of Adult Health and Disease (ESTER) study, a geographically based study in Northern Finland in which preterm adults and randomly selected control participants were recruited through the Northern Finland Birth Cohort 1986 (born 1985-1986) or Finnish Medical Birth Register (born 1987-1989).[4,10]

The selection and inclusion criteria of the study population are presented in **Figure 1**. All the study participants were offered a HR monitor. After exclusions (**Figure 1**), 117 early preterm adults (<34 weeks), 207 late preterm adults (34-36 full weeks),[3] and 276 full term control adults with available and sufficient HR data were included in the analysis.

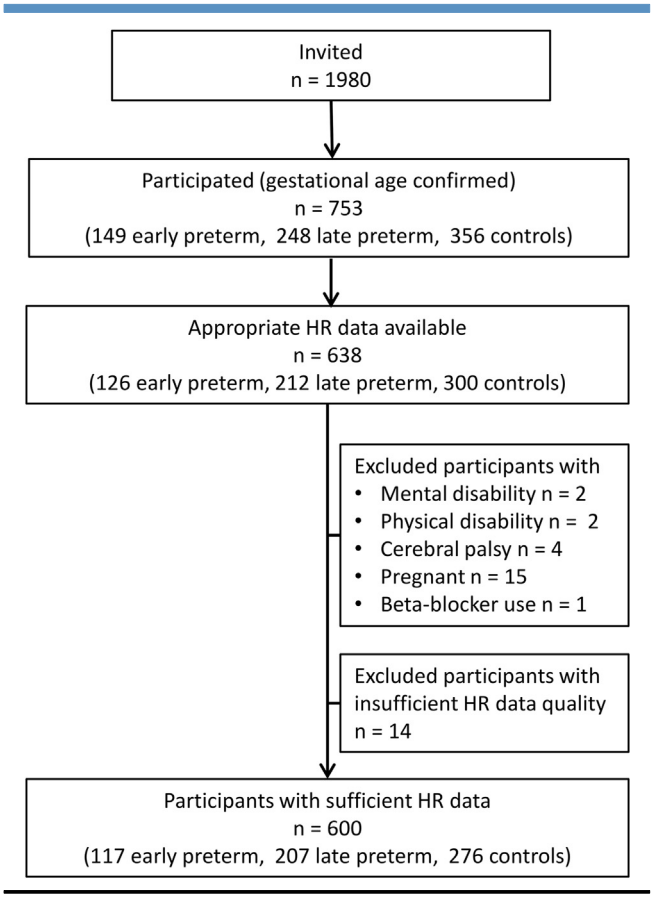

Figure 1. Flow chart of the study population.

Perinatal Data

Perinatal data on the participants recruited though the Northern Finland Birth Cohort 1986 have been reported previously.[22] Corresponding data on the subjects recruited through the Finnish Medical Birth Register were collected from the patients' records at birth hospitals and maternal welfare clinics.[23,24] Diagnoses of maternal gestational diabetes mellitus and gestational hypertension were confirmed according to the prevailing criteria at the time or by reviewing original hospital records.[22-24] Small for gestational age was defined as a birth weight below -2 SDs of the mean according to sex and length of gestation.[23,24] Very low birth weight (VLBW) was defined as a birth weight <1500 g.

Measurements

The subjects participated in clinical examinations at a mean age of 23.3 years (range 19.9-25.8 years).[4] During the clinical examination, R-R intervals were recorded (RS800CX and WearLink WIND transmitter, Polar Electro Oy, Kempele, Finland) at a spontaneous breathing frequency in a seated position at the beginning of the examination day during a 10 to 15-minute interview conducted by a study nurse.

To quantify cardiac autonomic function, the following measurements were obtained. In the time domain, the geometric mean HR and root mean square of successive differences (rMSSDs) were calculated. In the frequency domain, using a fast Fourier transform algorithm, low frequency (LF) power (LFP) (0.04-0.15 Hz), high frequency (HF) power (HFP) (0.15-0.40 Hz), and the ratio between LF and HF (LF/HF ratio) were determined.

Both rMSSD and HFP are considered metrics of cardiac vagal (parasympathetic) activity.[25] Variation in the HF band quantifies the amplitude of variation in the spontaneous respiratory frequency (0.20-0.25 Hz) of humans.[26] LFP includes some sympathetic- and baroreflex-mediated effects, in addition to cardiac vagal activity.[25,27] The LF/HF ratio is considered a marker of sympathovagal balance, although there is some controversy as to its interpretation.[28] We have included it to allow comparison with previous literature.

Analysis of HRV

In the analysis of HRV, 3-5 minutes of data were selected during a calm seated rest period at the beginning of the clinical examination. The most stationary 3- to 5-minute R-R interval data period with the lowest mean HR was selected based on a visual inspection. For 35, 44, and 521 participants, there were 3-4, 4-5, and at least 5 minutes of adequate stationary

data selected for the analysis. Previous studies suggested that 2 minutes or more of HR data was adequate for spectral analysis and that as little as 1 minute of rMSSD data was adequate.[25,29] R-R interval data were visually inspected for artifacts and ectopic beats and replaced with the local average. Sequences with more than 10 consecutive beats of ectopic beats or noise were deleted. R-R series with at least 3 minutes and a minimum of 90% of accepted R-R intervals were included in the analysis. The geometric mean HR, rMSSD, and frequency domain measurements of HRV by fast Fourier transform, LFP (0.04-0.15 Hz), HFP (0.15-0.40 Hz), and LF/HF ratio were then calculated using an in-house script (Hearts 1.2 software, University of Oulu, Oulu, Finland). The measurements had a skewed distribution and, thus, were transformed into a natural logarithm (ln) prior to analysis but were transformed back and reported in untransformed form in Table I and II, Table III and IV(available at www.jpeds.com).

Statistical Analyses

Data were analyzed using SPSS Statistics for Windows v 24.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Descriptive statistics for the study groups were presented as categorical variables or mean values and standard deviations. Group differences were calculated by ANOVO, the Pearson χ^2 test, or the Student *t* test. Linear and logistic regressions were used to analyze differences in continuous and categorical variables. Because there was no statistically significant sex interaction in the regression analyses, we present the main results pooled for both sexes. However, as previous studies on the association between birth weight and autonomic control have shown sex differences,[30] we also

Table I. Perinatal and neonatal characteristics of adults born early preterm, late preterm, and term (controls), in addition to current clinical and sociodemographic characteristics

	Early preterm (n = 117)					Late preterm (n = 207)					Controls (n = 276)			
Characteristics	**No.**	**%**	**Mean (SD)**	**Missing**	***P* value***	**No.**	**%**	**Mean (SD)**	**Missing**	***P* value***	**No.**	**%**	**Mean (SD)**	**Missing**
Perinatal and neonatal														
Born from multiple pregnancies	30	25.6			<.001	27	13.4			<.001	2	0.7		
Maternal hypertension†	14	12.0			.75	30	14.9		5	.23	30	10.9		1
Maternal preeclampsia‡	29	24.8			<.001	23	11.4		5	.008	13	4.7		1
Maternal gestational diabetes	2	1.7		19	.85	6	3.2		20	.22	4	1.5		7
Maternal smoking during pregnancy	18	16.2		6	.89	42	20.6		3	.76	44	16.2		5
Gestational age (wk)			31.8 (2.0)		<.001			35.8 (0.8)		<.001			40.1 (1.2)	
Birth weight (g)			1780 (493)		<.001			2651 (511)		<.001			3607 (479)	
Birth weight SD score			-0.72 (1.45)		<.001			-0.68 (1.3)		<.001			0.04 (1.0)	
Current														
Male sex	58	49.6			.94	101	48.8			.79	138	50.0		
Age (y)			23.1 (1.3)		.003			23.3 (1.3)		.04			23.5 (1.1)	
Parental education level				1	.23				4	.79				2
Basic or less or unknown	11	9.4				15	7.2				15	5.4		
Secondary	68	58.1				118	57.0				169	61.2		
Lower-level tertiary	10	8.5				28	13.5				37	13.4		
Upper-level tertiary	27	23.1				42	20.3				53	19.2		
Self-reported physical activity (MET h/wk)			23.3 (13.5)		.08			25.3 (14.7)		.61			26.0 (13.6)	
Season of clinical examination					.18					.06				
Winter	27	23.1				48	23.2				55	19.9		
Spring	33	28.2				68	32.9				70	25.4		
Summer	14	12.0				28	13.5				59	21.4		
Fall	43	36.8				63	30.4				92	33.3		
Daily smoking	50	24.2			.14	33	28.2			.01	59	21.4		
BMI (kg/m^2)			24.2 (4.5)		.34			24.5 (4.4)		.05			23.8 (3.9)	
Height (cm)														
Male			178.9 (6.9)		.37			177.7 (6.5)		.87			177.9 (6.9)	
Female			163.4 (4.9)		.31			164.6 (5.8)		.73			164.3 (6.0)	
Cohort of recruitment participation	40	34.2			<.001	99	47.8			.01	164	59.4		
Clinic systolic blood pressure§			119.2(13.2)		.03			118.0 (13.6)		.10			116.0 (12.5)	
Clinic diastolic blood pressure§			77.6 (8.9)		.007			76.6 (8.3)		.03			75.0 (7.3)	
HR (bpm)¶			71.8 (1.2)		.05			70.0 (1.2)		.46			69.2 (1.2)	
rMSSD (ms)¶			49.6 (1.8)		.13			51.1 (1.7)		.17			54.7 (1.8)	
LFP (ms^2)¶			1563.9 (2.1)		.10			1507.5 (2.1)		.01			1788.2 (2.1)	
HFP (ms^2)¶			881.2 (3.1)		.21			912.8 (2.8)		.21			1032.9 (3.1)	
LF/HF¶			1.8 (2.0)		.75			1.7 (1.9)		.49			1.7 (2.0)	

bpm, beats per minute; *MET*, metabolic equivalent.
**P* values refer to comparisons between preterm born subjects and controls using the Student *t* test or Pearson χ^2 test.
†Gestational or chronic hypertension.
‡Includes superimposed preeclampsia.
§Mean of 3 measurements.
¶Geometric mean.

Table II. Mean differences (95% CIs) in HRV between early and late preterm adults compared with controls, with a post hoc analysis comparing all adults born preterm to controls

		Early preterm		Late preterm		Post hoc analysis of all preterms	
Measurements	Model	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
Mean HR (Control mean: 69.2 bpm)	1	3.4 (−0.2 to 7.0)	.06	0.7 (−2.1 to 3.6)	.63	1.6 (−1.0 to 4.3)	.22
	2	2.0 (−1.8 to 5.9)	.31	0.3 (−2.7 to 3.3)	.86	0.8 (−2.0 to 3.6)	.57
	3	0.8 (−3.0 to 4.7)	.68	−0.5 (−3.5 to 2.6)	.77	−0.1 (−2.9 to 2.8)	.97
rMSSD (Control mean: 54.7 ms)	1	−12.0 (−22.2 to −0.5)	.04	−7.8 (−16.8 to 2.0)	.12	−9.3 (−17.3 to −0.6)	.04
	2	−11.4 (−22.5 to 1.3)	.08	−8.4 (−17.7 to 1.9)	.11	−9.3 (−17.9 to 0.1)	.05
	3	−7.7 (−19.4 to 5.8)	.25	−4.5 (−14.4 to 6.5)	.40	−5.5 (−14.6 to 4.5)	.27
LFP (Control mean: 1788.2 ms^2)	1	−13.6 (−26.7 to 1.8)	.08	−16.4 (−27.0 to −4.3)	.01	−15.5 (−25.1 to −4.5)	.01
	2	−14.6 (−28.5 to 2.0)	.08	−16.5 (−27.5 to −3.7)	.01	−15.9 (−26.2 to −4.1)	.01
	3	−9.8 (−24.7 to 8.2)	.27	−12.9 (−24.6 to 0.8)	.06	−11.9 (−23.0 to 0.8)	.07
HFP (Control mean: 1032.9 ms^2)	1	−19.2 (−36.6 to 2.9)	.09	−13.8 (−29.4 to 5.3)	.15	−15.7 (−29.6 to 0.9)	.06
	2	−19.4 (−38.0 to 5.0)	.11	−15.5 (−31.5 to 4.3)	.12	−16.7 (−31.4 to 1.2)	.07
	3	−12.3 (−32.9 to 14.6)	.34	−7.8 (−25.6 to 14.2)	.45	−9.3 (−25.6 to 10.7)	.38
LF/HF (Control mean 1.7)	1	6.9 (−7.8 to 24.0)	.37	−3.1 (−14.2 to 9.5)	.61	0.3 (−10.1 to 12.0)	.96
	2	5.9 (−9.8 to 24.3)	.48	−1.2 (−13.1 to 12.3)	.85	1.0 (−10.3 to 13.7)	.87
	3	2.9 (−12.6 to 21.2)	.73	−5.4 (−17.1 to 7.8)	.40	−3.0 (−14.0 to 9.6)	.63

Model 1 (n = 600): Age, sex, cohort of recruitment, and season of clinical examination.
Model 2 (n = 600): Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and parental smoking.
Model 3 (n = 583): Model 2 plus smoking, BMI, height, and physical activity.
All group means are geometric means. Mean differences have been calculated from log transformed values, back-transformed, and expressed as percentage difference.

present the results separated by sex. Regression model 1 included age, sex, cohort of recruitment, and season of clinical examination as covariates. Season was included as covariate due to strong seasonality of physical activity and other lifestyle factors in Northern Finland. Model 2 described the controlled total effect of preterm birth (the effect not explained by confounders) on autonomic cardiac control in adulthood. In addition to model 1 covariates, model 2 included educational attainment of the higher educated parent (indicating socioeconomic status), birth weight SD scores, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, and maternal smoking as covariates. Model 3 reflected the direct effect of preterm birth (the effect not mediated through current characteristics) on autonomic cardiac control. It included, in addition to model 2 covariates, smoking habits, body mass index (BMI), height, and physical activity. As reported in earlier research, adults born preterm have a higher BMI,[4] are less fit[31] and engage less in leisure time physical activities.[32] Therefore, BMI and physical activity were included as covariates.

Results

Perinatal, neonatal, sociodemographic, and clinical characteristics of the study groups are presented in Table I. Those born preterm had a lower birth weight SD score than controls. They were also more likely to be the result of multiple pregnancies, exposed to maternal preeclampsia more often, and had higher office blood pressure than full term controls. In terms of sociodemographic and clinical characteristics, the late preterm group had a higher BMI (P = .05), and the early preterm group had lower self-reported physical activity (P = .08), although neither difference reached statistical significance in this sample. In the late preterm group, mean LFP was lower (P = .01), and there were more daily smokers (P = .01) than in the control group. Otherwise, the sociodemographic and clinical background characteristics of the study groups were similar.

Nonparticipant Analysis

A detailed nonparticipant analysis of ESTER study participants has been published.[4] We now report on the comparison of participants who were excluded based on inadequate HRV data quality to the participants included in this report. In this study, there were 12.7% subjects excluded because of inadequate HRV data quality from the analysis in the early preterm group, 14.5% in the late preterm group, and 19.3% in the control group (χ^2, P = .13). When comparing the background characteristics of the excluded with those included in analysis, among the early preterm group, the excluded infants had more mothers with gestational diabetes (11.7% vs 1.7%, P = .02). Among the late preterm group, those excluded were younger (mean age 22.6 vs 23.3 years, P = .001), were less often part of the Northern Finland Birth Cohort (25.7% vs 47.8%, P = .01), and their mothers had more gestational diabetes (14.3% vs 2.9%, P = .003) when compared with the nonexcluded. In the control population, the excluded participants were older (23.8 vs 23.5 years, P = .03), had lower birth weight SD scores (−0.24 vs 0.04, P = .04), and higher diastolic blood pressures (77.5 vs 75.0, P = .03). For other characteristics presented in Table I, there were no differences between the excluded and included participants within any group.

Group Differences in Autonomic Function

Geometric means and SDs in HRV measurements for the adults born early preterm, late preterm, and term (controls)

are presented in Table I. We first compared these outcomes between the preterm groups and controls, adjusting for age, sex, cohort of recruitment, and season of clinical examination (Table II, model 1 and Figure 2; available at www.jpeds.com). The mean HR was slightly higher in the early preterm group, although these results were not statistically significant. Mean rMSSD, an indicator of cardiac vagal activity, was lower for those born early preterm and among all preterm young adults when compared with full term control participants. Furthermore, LFP, an additional indicator of cardiac vagal activity that also reflects sympathetic- and baroreflex-mediated effects, was lower for those born late preterm and among all preterm participants. The mean HFP, a measurement of cardiac vagal modulation in respiratory frequency, was also lower in all preterm groups, although the results were not statistically significant in any group (Table II). The LF/HF ratio, a measurement of sympathovagal balance, did not differ between the groups.

Adjustment for Parental, Prenatal, Sociodemographic, and Clinical Characteristics

When the regression analyses were further adjusted for birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and parental smoking in model 2, the results showed little change (Table II). When adjusted further for daily smoking, BMI, height, and physical activity in model 3, the results were no longer statistically significant (Table II). When the models were adjusted for sociodemographic and clinical characteristics, BMI and physical activity appeared to be the most important factors affecting between group differences in HRV measurements. For BMI, only statistical trends were noted, and each 1 kg/m^2 higher BMI predicted 1.0% lower rMSSD (95% CI -0.1%, 2.1%, P = .09), 0.9% lower LFP (-2.4%, 6.0%, P = .2), and 2.1% lower HFP (-0.1%, 4.3%, P = .06). Each metabolic equivalent hour/week more physical activity was associated with 0.5% higher rMSSD (0.2%, 0.8%, P = .003), 0.6% higher LFP (0.1%, 1.0%, P = .01), and 0.9% higher HFP (0.3%, 1.6%, P = .006). To indicate additional proportion of variance explained by adding a variable in the full model, we calculated R^2 change explained by the addition of BMI and physical activity, expressed in percentage points. Adding BMI in the model resulted in an R^2 change of 0.4% for HR, 0.5% for rMSSD, 0.2% for LFP, 0.6% for HFP, and 0.5% for LF/HF. For physical activity, corresponding numbers were 1.1%, 1.5%, 1.1%, 1.3%, and 0.5%. When adjusted for body fat percent instead of BMI in model 3, the results were similar (not shown).

Associations between Autonomic Measurements and Blood Pressure

Similar to the previously reported results in the ESTER study,[4,10] the current early preterm group had higher mean systolic and diastolic blood pressure when adjusted for sex, age, cohort of recruitment, and season of clinical examination (Table V). The late preterm group had higher mean systolic and diastolic blood pressure when adjusted for sex, age, cohort of recruitment, and season of clinical examination (Table V). Correlations between HRV measurements and blood pressure are shown in (Table VI; available at www.jpeds.com). When the difference in blood pressure between the preterm and term groups was further adjusted for rMSSD, HFP, and LFP, the differences attenuated slightly but remained statistically significant (Table V). An exception was in the difference in diastolic blood pressure in the late preterm group, which was 1.3 mm Hg (95% CI -0.2 to 2.7) higher when adjusted for sex, age, cohort of recruitment, season of clinical examination, and LFP.

Sex Differences and VLBW

Table III presents the results separately for women and men. The group differences in HRV measurements were nominally greater in men than women, especially for LFP, although no statistically significant sex interaction was found.

To allow comparison with previous literature, we present mean differences in HRV measurements for VLBW adults compared with controls (Table IV). No difference was statistically significant. However, the VLBW sample size was rather small (n = 28).

Discussion

We hypothesized that preterm birth, throughout its whole range, is associated with decreased cardiac vagal control in young adults. The results revealed lower mean rMSSD, lower mean LFP, and to lesser extent lower mean HFP among young adults born preterm compared with those born at term, although the differences were not statistically significant in all comparisons. Although the CIs leave some uncertainty specifically as to the difference in cardiac vagal control,

Table V. Mean differences (95% CIs) in systolic and diastolic office blood pressure between adults born early preterm and late preterm compared with controls, adjusted for HRV measurements

		Early preterm		Late preterm	
Measurements	Model	Mean difference in mm Hg (95% CI)	*P* value	Mean difference in mm Hg (95% CI)	*P* value
Systolic blood pressure	1	3.5 (1.2-5.8)	.003	2.2 (0.3 to 4.1)	.021
	2	3.1 (0.9-5.5)	.006	2.0 (0.2-3.9)	.034
	3	3.3 (1.0-5.5)	.005	2.1 (0.2-4.0)	.032
	4	3.2 (1.0-5.5)	.005	1.9 (0.0-3.8)	.048
Diastolic blood pressure	1	2.8 (1.1-4.6)	.002	1.7 (0.3-3.1)	.020
	2	2.4 (0.7-4.1)	.006	1.4 (0.0-2.8)	.046
	3	2.5 (0.8-4.2)	.004	1.5 (0.1-2.9)	.041
	4	2.5 (0.8-4.2)	.005	1.3 (−0.2 to 2.7)	.080

Model 1 (n = 600): Age, sex, cohort of recruitment, and season of clinical examination.
Model 2 (n = 600): Model 1 plus rMSSD.
Model 3 (n = 600): Model 1 plus HFP.
Model 4 (n = 600): Model 1 plus LFP.

overall our results are consistent with altered autonomic regulatory control in adults born preterm, including those born late preterm. This association was attenuated after adjustment for BMI and physical activity, suggesting it was mediated at least in part by these factors.

We also hypothesized that higher blood pressure in adults born preterm may be linked to altered autonomic control. Consistent with this, the associations between preterm birth and blood pressure were somewhat attenuated when adjusted for HRV measurements. Therefore, altered cardiac autonomic control may be one mechanism by which cardiovascular risk is increased in adults born preterm. However, our results retain an amount of uncertainty and thus the hypothesis needs to be tested again.

Mechanisms that link preterm birth with adult cardiovascular risk factors, such as high blood pressure, remain unclear. A previous study reported that differences in stress-induced blood pressure were stronger than those in resting blood pressure among preterm born men.[32] This finding provides support for altered autonomic regulatory control, including decreased cardiac vagal modulation, as underlying mechanisms linking preterm birth with adult cardiovascular risk factors. The findings of the present study are consistent with this idea. However, considerable proportion of variance in blood pressure variation remains unexplained by autonomic control measurements.

A number of previous studies provided evidence that altered sympathovagal balance or decreased vagal function were independent risk factors for all-cause mortality and a common underlying factor in all major risk factors for cardiovascular disease.[11-14] Most previous studies on cardiac control in preterm born subjects focused on outcomes in infants and children. A study on 9-year-old children suggested an association between low birth weight and autonomic control irrespective of gestational age at birth.[20] Relatively little is known on the outcomes of preterm birth to cardiac control in later life. It is possible that the alterations in cardiac autonomic regulatory control become more pronounced with increasing age and declining cardiovascular health. Impaired parasympathetic functioning and premature decline has indeed been shown in young adults born with an extremely low birth weight.[19,21] A study of low birth weight adults suggested that the autonomic nervous system response varied by sex.[33] In this study, there was no statistically significant sex interaction found in autonomic control.

The underlying biological mechanisms of the findings of the present study remain unclear. Altered autonomic control in infants born preterm has been previously reported.[18] Whereas the sympathetic branch of the autonomic nervous system appears to develop most rapidly in the first trimester, vagal (parasympathetic) control becomes more dominant later in fetal development at 25-30 weeks of gestation and increases substantially during the third trimester of pregnancy.[34,35] Previous studies showed that total myelinated vagus fibers in infants increased linearly with postconceptional age, leading to fewer total myelinated vagus fibers in preterm born infants than full term infants or adolescents.[17] Therefore, these studies argue, interrupted gestation leads to lower cardiac vagal control. Our findings are consistent with this and suggest that altered autonomic regulatory control is present at least in young adult life.

Our study suggested that some differences in autonomic control may be greater among preterm born men than women (eg, LFP), although we found no statistically significant sex interactions overall. This is in contrast with association between preterm birth and adult office blood pressure that is stronger among women than men.[30] Moreover, when low birth weight is used as an early life indicator, as summarized by a recent review,[30] the associations with autonomic nervous system response to stress is stronger among women, whereas associations with hypothalamic-pituitary-adrenal axis and total peripheral resistance are stronger among men.

A previous study of the sympathetic nervous system response to psychosocial stress based on measurements of plasma adrenalin and noradrenalin concentrations among VLBW young adults found no evidence of higher responses in those born VLBW compared with controls.[36] The same study found that the rise in noradrenalin concentrations after stress was lower in VLBW born women than in controls.[36]

Although we adjusted for a range of parental and prenatal confounders associated with preterm birth, these did not explain the associations between preterm birth and cardiac vagal control. This suggests that the associations we found are more likely to be associated with preterm birth per se rather than underlying causes of preterm birth. Previous studies from the same cohort showed that young adults born preterm had lower muscular fitness, lower perceived fitness, and higher body fat percentage than controls.[4,31] Studies also reported that physical activity, body composition, and autonomic nervous system function were intrinsically associated.[37-39] A recent study suggested that lifelong physical activity was positively associated with vagally mediated autonomic function, independently of traditional risk markers.[40] We found that the differences in autonomic control measurements between the study groups were attenuated when adjusted for physical activity and BMI, suggesting that lower rates of physical activity and increased adiposity might partly mediate altered vagal control in preterm born adults.

We have previously discussed the limitations of the ESTER Preterm Birth Study.[4] For the present study, usable HR data could not be obtained from a number of participants. Second, the recording of the R-R intervals was done during a study nurse visit that included a few questions on current health. Previous studies suggest that talking could impact to respiratory frequency and thus impact HRV measurements by increasing LFP and decreasing HFP.[41-43] However, this would be expected to introduce bias only if the effects of talking on HRV would differ between the preterm and term groups. Such an outcome is unlikely, but cannot be excluded.

Third, in some participants, the available stationary HR data was shorter than 5 minutes. However, the inclusion of findings only from those participants with at least 5 minutes of data in the analysis had minor effect on the results. Fourth,

the data quality of some R-R interval recordings was not sufficient for inclusion in the analysis. Therefore, the total sample size was limited, which might increase inaccuracy and lead to more conservative estimates.

We found that preterm born adults showed evidence of altered autonomic regulatory control compared with those born at term. This finding was also present for those born late preterm. The associations between preterm birth and higher blood pressure were somewhat attenuated when adjusted for HRV measurements, suggesting that altered autonomic regulatory control may contribute to the higher blood pressure. Consequently altered autonomic regulatory control may be one mechanism by which cardiovascular risk is increased in adults born preterm. Increased adiposity and reduced physical activity may partly mediate this association. From a clinical perspective, our results reinforce previous suggestions on the importance of health-enhancing physical activity and fitness among individuals born preterm. ■

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50 Years Ago in *The Journal of Pediatrics*

Pyogenic Hepatic Abscess in Infancy and Childhood

Dehner LP, Kissane JM. J Pediatr 1969;74:763-73

This retrospective series, reported from the Departments of Pathology and Pediatrics at the Washington University School of Medicine, of 69 institution-wide cases of liver abscesses found at the time of autopsy from 1917 to 1967 is worthy of our attention in 2019 for several reasons. First, liver abscess is rare (<0.5% of autopsies) in the early period (1917 to 1940) and still rare in the later period, almost 40% of cases occurred in children and 40% of cases in children occurred in infants under 12 months of age. Second, the pathophysiology is interesting. Bacteremic spread to the liver was the predominant source even before 1940, which upended the previously considered major preceding event to hepatic abscess, that is, septic thrombosis of the portal vein, usually as a complication of appendicitis with perforation. Before 1940, *Micrococcus pyogenes* (var.) *aureus* (aka *Staphylococcus aureus*) was the dominant etiology, and an unmanageable focus of infection elsewhere (without availability of effective antibiotic therapy) causing bacteremia in a previously healthy child was the pathophysiology. In the cases from 1940 to 1967, patients with hepatic abscess associated with bacteremia were likely to have underlying conditions (eg, leukemia or treatment with immunosuppressive drugs) and pathogens more frequently were gram-negative bacilli, *Pseudomonas* and *Candida* species. Third, hepatic abscess was not clinically recognized. In the pediatric cases, only 2 of 27 (7%) were suspected premortem.

Some of us remember the days, such as my resident days at St. Christopher's, when pathologists such as our Drs James B. Arey and Molly DaPena came out of the laboratory to speak kindly with parents, gaining autopsy rates of more than 80%. All the smart people in the hospital gathered in the autopsy theater when "Paging Dr Post" was announced overhead, and we residents flocked down to see unsuspected, amazing diagnoses laid plain, and seeds of understanding of unsolved mysteries taking hold (eg, DiGeorge syndrome coming to light through his presence at multiple "Dr Post's"). We residents also saw direct evidence of the good and the bad of our management. In 2019, under the double rubrics that by the time of death scans already have unearthed everything, and children (and their families) usually have suffered through multiple surgeries and attempts at curative therapies that have failed, autopsies are endangered procedures. And alas, opportunities to learn are missed—for families to understand the medical facts more completely, for experts without all the answers to consider the possibilities, and for trainees to appreciate the privilege and responsibility of being a doctor.

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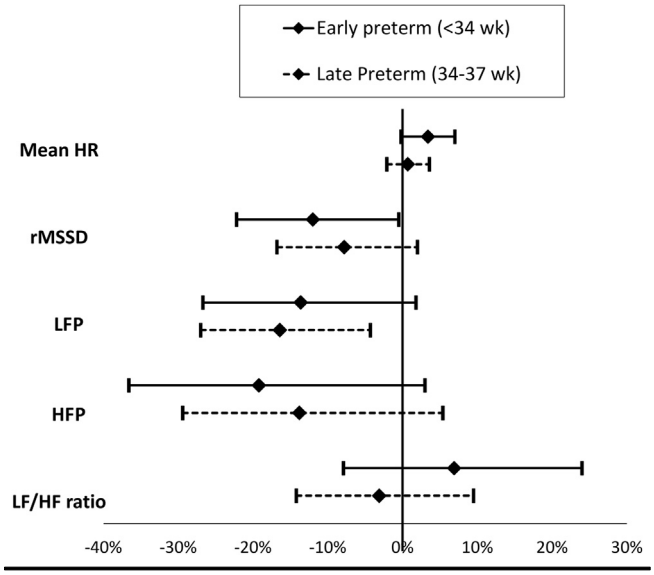

Figure 2. Mean percent difference in HRV measurements between early and later preterm young adults compared with controls born at term, with 95% CIs. The presented results are adjusted for age, sex, cohort of recruitment, and season of clinical examination.

Table III. Mean differences (95% CIs) in autonomic control measurements between adults born early preterm and late preterm compared with controls by sex

			Early preterm	Late preterm
Measurements	**Sex**	**Model**	**Mean difference (95% CI)**	**Mean difference (95% CI)**
Mean HR (Control mean: 71.4 bpm)	Women	1	2.9 (−1.9 to 7.9)	−0.2 (−4.0 to 3.8)
		2	0.9 (−4.4 to 6.5)	−0.8 (−4.7 to 3.3)
		3	−0.8 (−6.1 to 4.7)	−2.1 (−6.0 to 2.1)
Mean HR (Control mean: 67.1 bpm)	Men	1	3.8 (−1.4 to 9.2)	1.8 (−2.5 to 6.2)
		2	2.3 (−3.0 to 8.0)	1.1 (−3.4 to 5.8)
		3	1.6 (−4.0 to 7.4)	0.7 (−3.9 to 5.6)
rMSSD (Control mean: 53.8 ms)	Women	1	−11.4 (−25.9 to 5.9)	−6.8 (−19.4 to 7.9)
		2	−7.8 (−24.5 to 12.6)	−6.0 (−19.1 to 9.2)
		3	−1.5 (−19.4 to 20.5)	0.1 (−14.0 to 16.4)
rMSSD (Control mean: 55.6 ms)	Men	1	−12.7 (−26.6 to 3.9)	−9.6 (−21.8 to 4.6)
		2	−12.7 (−27.5 to 5.1)	−10.8 (−23.6 to 4.3)
		3	−9.8 (−25.6 to 9.4)	−8.6 (−22.3 to 7.5)
LFP (Control mean: 1584.7 ms^2)	Women	1	−11.4 (−30.1 to 12.3)	−12.8 (−28.1 to 5.8)
		2	−7.5 (−29.4 to 21.2)	−10.7 (−27.2 to 9.5)
		3	0.2 (−23.8 to 31.9)	−5.2 (−22.9 to 16.6)
LFP (Control mean: 2017.9 ms^2)	Men	1	−15.7 (−33.0 to 6.0)	−19.8 (−33.8 to −2.8)
		2	−19.6 (−37.1 to 2.6)	−22.7 (−37.0 to −5.1)
		3	−17.2 (−35.8 to 6.8)	−21.5 (−36.7 to −2.7)
HFP (Control mean: 1016.7 ms^2)	Women	1	−20.4 (−43.7 to 12.5)	−8.2 (−30.8 to 21.9)
		2	−15.5 (−42.7 to 24.7)	−7.6 (−31.1 to 23.9)
		3	−4.6 (−35.4 to 41.1)	5.2 (−21.7 to 41.2)
HFP (Control mean: 1049.4 ms^2)	Men	1	−18.5 (−42.3 to 15.1)	−20.2 (−40.2 to 6.6)
		2	−20.9 (−45.3 to 14.3)	−24.1 (−44.3 to 3.5)
		3	−14.7 (−41.9 to 25.1)	−20.2 (−42.3 to 10.2)
LF/HF (Control mean 1.6)	Women	1	11.4 (−9.2 to 36.6)	−5.0 (−19.6 to 12.2)
		2	9.4 (−12.9 to 37.5)	−3.4 (−18.7 to 14.8)
		3	5.0 (−16.8 to 32.5)	−9.9 (−24.4 to 7.4)
LF/HF (Control mean 1.9)	Men	1	3.5 (−16.8 to 28.6)	0.5 (−16.2 to 20.5)
		2	1.6 (−19.3 to 28.0)	1.8 (−16.1 to 23.6)
		3	−2.9 (−23.5 To 23.1)	−1.7 (−19.5 to 20.2)

Model 1 (Women: n = 303, Men: n = 297): Age, sex, cohort of recruitment, and season of clinical examination.
Model 2 (Women: n = 303, Men: n = 297): Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and parental smoking.
Model 3 (Women: n = 294, Men: n = 289): Model 2 plus smoking, BMI, height, and physical activity.
All group means are geometric means. Mean differences have been calculated from log transformed values, back-transformed, and expressed as percentage difference.

Table IV. Mean differences (95% CIs) in autonomic control measurements between very low birth weight adults compared with controls

		VLBW (<1500 g) n = 28	
Measurements	Model	Mean difference (95% CI)	*P* value
Mean HR (Control mean: 69.2 bpm)	1	6.7 (−0.1 to 13.9)	.05
	2	3.6 (−4.0 to 11.8)	.36
	3	1.4 (−6.2 to 9.7)	.72
rMSSD (Control mean: 54.7 ms)	1	−18.1 (−35.6 to 4.1)	.10
	2	−15.8 (−36.2 to 11.2)	.22
	3	−12.7 (−34.6 to 16.4)	.35
LFP (Control mean: 1788.2 ms^2)	1	−25.7 (−45.3 to 0.9)	.06
	2	−26.5 (−48.4 to 4.5)	.09
	3	−21.6 (−45.8 to 13.3)	.19
HFP (Control mean: 1032.9 ms^2)	1	−28.5 (−55.4 to 14.6)	.16
	2	−31.1 (−60.1 to 19.0)	.18
	3	−26.7 (−58.4 to 29.2)	.28
LF/HF (Control mean 1.7)	1	3.9 (−21.7 to 37.8)	.79
	2	6.6 (−23.4 to 48.2)	.70
	3	6.9 (−24.2 to 50.8)	.70

Model 1 (n = 304): Age, sex, cohort of recruitment, and season of clinical examination.
Model 2 (n = 304): Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and parental smoking.
Model 3 (n = 295): Model 2 plus smoking, BMI, height, and physical activity.
All group means are geometric means. Mean differences have been calculated from log transformed values, back-transformed, and expressed as percentage difference.

Table VI. Correlations between HRV measurements and office blood pressure

Measurements	Systolic blood pressure, mean of 3 measurements	*P* value	Diastolic blood pressure, mean of 3 measurements	*P* value
Mean HR	0.161	<.001	0.289	<.001
rMSSD	−0.144	<.001	−0.252	<.001
LFP	−0.146	<.001	−0.245	<.001
HFP	−0.127	.002	−0.232	<.001
LF/HF	0.046	.26	0.108	.008

The correlations have been calculated from log-transformed HRV measurements.