Postexercise Heart Rate Recovery in Adults Born Preterm

Risto Karvonen, MD[1,3], Marika Sipola, MD, PhD[1,3], Antti M. Kiviniemi, PhD[4], Marjaana Tikanmäki, MD, PhD[1,3], Marjo-Riitta Järvelin, MD, PhD[2,5,6,8], Johan G. Eriksson, MD, PhD[1,7,9], Mikko P. Tulppo, PhD[4], Marja Vääräsmäki, MD, PhD[2,3,4], and Eero Kajantie, MD, PhD[1,3,9,10]

Objective To evaluate postexercise heart rate recovery (HRR) in adults born preterm.

Study design We studied the association between preterm birth and postexercise HRR in 545 adults (267 women) at 23.3 years of age (range 19.9-26.3 years). One hundred three participants were born early preterm (<34 completed weeks), 178 late preterm (34-36), and 264 were full term (control group). HRR was calculated as change in heart rate (HR) 30 seconds and 60 seconds after cessation of submaximal step test and maximum HR slope during the first minute after.

Results Mean peak HR was 159.5 bpm in the early preterm (P = .16 with controls), 157.8 bpm in the late preterm (P = .56), and 157.0 bpm in the control group. Mean HRR 30 seconds after exercise was 3.2 bpm (95% CI 1.1-5.2) lower in the early preterm group and 2.1 bpm (0.3-3.8) lower in the late preterm group than the full term controls. Mean 60s HRR was 2.5 (−0.1 to 5.1) lower in the early preterm group and 2.8 bpm (0.6-4.9) lower in the late preterm group. Mean maximum slope after exercise was 0.10 beats/s (0.02-0.17) lower in the early preterm group and 0.06 beats/s (0.00-0.12) lower in the late preterm group.

Conclusions Our results suggest reduced HRR after exercise in adults born preterm, including those born late preterm. This suggests altered reactivation of the parasympathetic nervous system, which may contribute to cardiovascular risk among adults born preterm. *(J Pediatr 2019;214:89-95)*.

Preterm birth is associated with several elevated cardiovascular risk factors in later life,[1-6] such as elevated blood pressure,[7] greater blood pressure variability,[8] and altered autonomic control.[9] A substantial proportion of the autonomic nervous system development (myelination of the vagus nerve, baroreflex sensitivity, and the heart rate [HR] variability) occurs during the third trimester of gestation.[10,11] Although preterm birth interrupts gestation in the second or third trimester, altered cardiac autonomic function may be one mechanism explaining the association between preterm birth and cardiovascular risk factors in adulthood.

Infants born preterm exhibit impaired parasympathetic modulation of the heart and lower sympathetic modulation of blood pressure.[12] Decreased cardiac autonomic control has been proposed to extend at least to childhood and young adulthood for those born very preterm (<32 weeks) or with extremely low birth weight.[13-15] Among the general population, impaired cardiac autonomic function, expressed as depressed vagal (parasympathetic) control, is an important and independent risk factor for overall mortality and an underlying factor in several major risk factors for cardiovascular morbidities.[16-19]

During exercise, the increase in HR is considered to result from both the withdrawal of the parasympathetic and activation of the sympathetic nervous system.[20] The decrease in the HR immediately after cessation of exercise is suggested to result from the reactivation of parasympathetic nervous system.[21] Attenuated heart rate recovery (HRR) after exercise, an indicator of reduced parasympathetic activity, is an independent and powerful predictor of overall mortality.[22,23] Abnormal HRR after submaximal exercise has been reported to

BMI	Body mass index
ESTER	Preterm Birth and Early-Life Programming of Adults Health and Disease
HR	Heart rate
HRR	Heart rate recovery
HRR_{30s}	Peak HR – HR at 30 seconds after exercise
HRR_{60s}	Peak HR – HR at 60 seconds after exercise
VLBW	Very low birth weight

From the Departments of [1]Chronic Disease Prevention and [2]Children and Families, National Institute for Health and Welfare, Oulu and Helsinki, Finland; [3]PEDEGO Research Unit, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; [4]Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; [5]Biocenter Oulu, Oulu, Finland; [6]Unit of Primary Care Unit, Oulu, Finland; [7]Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [8]Department of Epidemiology and Biostatistics, Imperial College London, MRC Health Protection Agency (HPA) Centre for Environment and Health, School of Public Health, London, United Kingdom; [9]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway; and [10]Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

The ESTER study was supported by grants from the Academy of Finland (SALVE program for 2009–2012 and grants 127437, 129306, 130326, 134791, and 263924 [to E.K.]); University of Oulu Graduate School (to R.K.); the Doctoral Program for Public Health, University of Tampere (to M.S.); the Emil Aaltonen Foundation (to E.K.); Paulo Foundation and the Finnish Foundation for Cardiovascular Research (to A.K.); the European Commission (Framework 5 award QLG1-CT-2000-001643 and Horizon 2020 award 633595 DynaHealth [to M-R.J.]; Horizon2020 award 733280 RECAP Research on Children and Adults Born Preterm [to E.K.]); the Finnish Foundation for Pediatric Research (to E.K.); the Jalmari and Rauha Ahokas Foundation (to E.K.); the Juho Vainio Foundation (to R.K, E.K., M.T., and M.V); the National Graduate School of Clinical Investigation (to M.T.); the Novo Nordisk Foundation (to E.K. and M.V.); the Signe and Ane Gyllenberg Foundation (to E.K.); the Sigrid Jusélius Foundation (to E.K.); and the Yrjö Jahnsson Foundation (to E.K., M.S., and M.V.). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2019.06.056

predict death in a healthy cohort.[24] Early preterm birth has been connected with impaired HRR in adolescents.[25] Although most evidence on cardiovascular risk factors comes from studies on those born very preterm, the risks also are present for those born less preterm.[8] We hypothesized that preterm birth across the range of gestational ages predicts altered HRR after exercise in young adulthood.

Methods

The participants of the current study were a part of Preterm Birth and Early-Life Programming of Adults Health and Disease (ESTER) study. ESTER is a geographically based study in Northern Finland, in which the participants were recruited through the Northern Finland Birth Cohort 1986 (subjects born 1985-1986) or through the Finnish Medical Birth Register (subjects born 1987-1988).[3,9]

The selection criteria are presented in **Figure 1** (available at www.jpeds.com). After exclusions (**Figure 1**), a total of 103 participants born early preterm (<34 weeks), 178 born late preterm (34-36 completed weeks), and 264 controls with adequate HR data were included in the analysis.

Perinatal Data

The perinatal data of the participants recruited through the Northern Finland Birth Cohort has been described.[2] For participants recruited through the Finnish Medical Birth Register, the corresponding data were collected through records at birth hospitals and maternal welfare clinics.[2] Diagnoses of gestational hypertension and maternal gestational diabetes mellitus were confirmed according to prevailing criteria at the time or by reviewing original hospital records.[26] Small for gestation age was defined by birth weight less than −2 SD of the mean according to sex and length of gestation.[27] Very low birth weight (VLBW) vas defined as birth weight <1500 g.

Measurements

Subjects participated in a clinical examination at a mean age of 23.3 years (range: 19.9-26.3 years). At the beginning of examination, all participants were offered a HR monitor (Polar RS800CX and WearLink WIND transmitter, Polar Electro Oy, Kempele, Finland). Beat-to-beat HR (R-R) intervals were recorded during the examination day, including a 4-minute Åstrand−Ryhming[28] step test exercise and the recovery period after the test. During the step test, participants stepped on and off a bench (33 cm high for women and 40 cm for men) repeatedly for 4 minutes at 23 steps per minute, paced by a metronome.[29] Resting HR was recorded at a spontaneous breathing frequency during a calm seated rest position at the beginning of the clinical examination day during a 10- to 15-minute interview conducted by a study nurse. The most stationary 3- to 5-minute R-R interval data period with the lowest mean HR was selected based on a visual inspection and the geometric mean HR was calculated for each group during this period.

Analysis of HRR

As illustrated in **Figure 2**, to assess HRR after the step test, peak HR (bpm) was determined from the HR curve as 10-beat median at the time of step test cessation. Subsequently, the median HR was registered at 30 seconds and 60 seconds after the step test cessation and peak HR - HR at 30 seconds after exercise (HRR_{30s}) and peak HR - HR at 60 seconds after exercise (HRR_{60s}) were calculated (Peak HR – HR at 30 seconds and 60 seconds after exercise, respectively). In addition, the steepest 30-second slope during the first 60 seconds of recovery period (**Figure 2**) was calculated from the median HR data. All HRR measures were calculated using Matlab, version 7.14, software (MathWorks, Natick, Massachusetts).

Statistical Analyses

Data were analyzed using SPSS Statistics for Windows, version 25 software (SPSS IBM Corp, Armonk, New York). Descriptive statistics for the study groups were presented as frequencies of categorical variables or by mean values and SDs. Crude differences were tested by an ANOVA, Person χ^2 test, or the Student t test. Linear regressions were used to analyze differences in continuous or categorical variables. Regression model 1 included age, sex, and cohort of recruitment (Northern Finland Birth Cohort/Finnish Medical Birth Register) as covariates. Regression model 2, aiming to describe the controlled total effect of preterm birth (effect not explained by confounders) on HRR after exercise in young adulthood, included birth weight SD score, maternal gestational diabetes mellitus and maternal hypertensive disorder during pregnancy, parental educational level (describing childhood socioeconomic status), and maternal smoking during pregnancy in addition to the model 1 covariates. Regression model 3, aiming to reflect the direct effect of preterm birth (effect not mediated through current characteristics), included participant's smoking, body mass index (BMI), height, and physical activity in addition to model 2 covariates. Physical activity was evaluated in metabolic equivalent hours per week on the basis of a questionnaire on physical activity.[29]

Results

The perinatal, neonatal, and clinical characteristics including mean values and SDs in HRR measures for the study groups are presented in **Table I**. As previously reported in different subsets of the cohort, those born early preterm had greater systolic blood pressure (119.5 vs 116.6 mm Hg, $P = .04$), greater diastolic blood pressure (77.7 vs 75.6 mm Hg, $P = .03$), and greater resting HR (71.9 vs 68.5 bpm, $P = .03$) when compared with controls born full term.[2,9] Parallel differences were seen for those born late preterm, but the differences were not statistically significant.

HRR

The mean differences in HRR measures between the early and late preterm groups compared with controls are presented in **Table II**. The outcomes were primarily adjusted for age, sex,

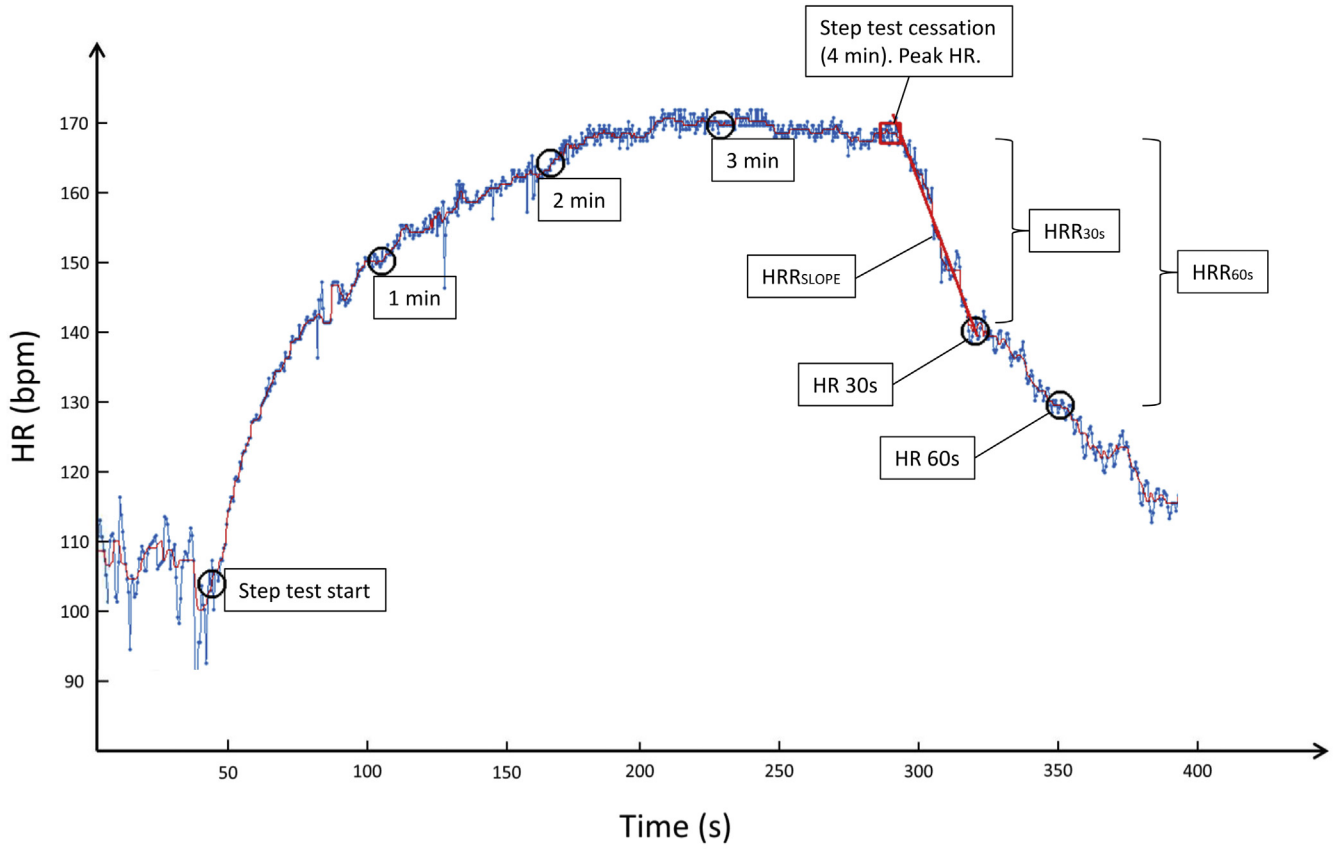

Figure 2. HRR data selection.

and cohort of recruitment (Model 1, **Table II** and **Figure 3** [**Figure 3** available at www.jpeds.com]). The mean HRR during the first 30 seconds immediately after the cessation of step test (HRR_{30s}) was significantly lower for both preterm groups when compared with controls. The mean HRR during the first minute immediately after the cessation of step test (HRR_{60s}) was lower for both preterm groups. The result trended toward statistical significance (P = .059) for those born early preterm. The mean maximum slope in the HRR during the first minute after the cessation of the step test was less steep in the preterm groups when compared with controls, although the result was significant only for those born early preterm. The HRR results are presented as absolute values.

Adjustment for Parental, Prenatal, and Sociodemographic Characteristics

When the regression model 1 was further adjusted for birth weight SD score, gestational diabetes mellitus, gestational hypertension, parental education, and maternal smoking in Model 2 (**Table II**), the differences attenuated only slightly and remained statistically significant. When the regression model 1 was adjusted for parental history of myocardial infarction. the differences remained (not shown).

Adjustment for Current Characteristics

When regression Model 2 was supplemented by adjusting additionally for current smoking, BMI, height, and physical activity in model 3, the differences remained statistically significant for HRR_{30s} in the early preterm group and for HRR_{60s} in the late preterm group. For other comparisons, the differences were attenuated to nonsignificance. BMI and physical activity appeared to be affecting most between group differences in HRR.

Sensitivity Analysis

In sensitivity analysis, we adjusted the models for lean body mass and body fat percent instead of height and BMI. In addition, we adjusted for asthma (asthma diagnosis, use of inhalable glucocorticoids, or self-reported medical reimbursement for asthma medication) and use of bronchodilation during the clinical visit day which may affect HR. We also repeated the analyses after excluding participants born from multiple pregnancies and after exclusion of those born small for gestational age (birth weight < −2SD). Any of these aforementioned adjustments had only minor effect to the results (not shown).

The Associations of Sex and VLBW with HRR

There was no statistically significant sex interaction found in HRR differences between the groups. However, to allow comparability with previous literature, we calculated differences separately for early and late preterm born women and men (**Table III**; available at www.jpeds.com). Although there was no consistent pattern of larger differences in either

Table I. Perinatal, neonatal, and current characteristics of participants born early and later preterm and controls born at term

	Early preterm (n = 103)					Late preterm (n = 178)					Controls (n = 264)			
Characteristics	**No.**	**%**	**Mean (SD)**	**Missing**	***P* Value***	**No.**	**%**	**Mean (SD)**	**Missing**	***P* Value***	**No.**	**%**	**Mean (SD)**	**Missing**
Perinatal and neonatal characteristics														
Born from multiple pregnancy	25	24.3%			<.001	26	14.6%			<.001	1	0.4%		
Maternal gestational or chronic hypertension	13	12.6%			.58	26	14.6%		5	.21	28	10.6%		2
Maternal preeclampsia†	22	21.4%			<.001	21	11.8%		5	.008	13	4.9%		2
Maternal gestational diabetes	1	1.0%		18	.69	5	2.8%		17	.35	4	1.5%		4
Maternal smoking during pregnancy	17	16.5%		4	.90	38	21.3%		3	.26	45	17.0%		3
History of myocardial infarction in the mother	1	1.0%		6	.48	1	0.6%		7	.78	1	0.4%		12
History of myocardial infarction in the father	4	3.9%		6	.81	11	6.2%		8	.17	9	3.4%		13
Small for gestational age	17	16.5%			<.001	26	14.6%			<.001	5	1.9%		
Gestational age, wk			31.9 (1.9)		<.001			35.8 (0.8)		<.001			40.1 (1.2)	
Birth weight, g			1808 (485)		<.001			2637 (514)		<.001			3611 (472)	
Birth weight SD score			−0.71 (1.43)		<.001			−0.70 (1.28)		<.001			0.04 (0.98)	
Current														
Male sex	52	50.5%			.91	91	51.1%			1.00	135	51.1%		
Age, y			23.1 (1.4)		.004			23.2 (1.3)		.006			23.5 (1.2)	
Parental education level				1	.57				3	.94				1
Basic or less or unknown	8	7.8%				12	6.7%				15	5.7%		
Secondary	61	59.2%				104	58.4%				158	59.8%		
Lower-level tertiary	10	9.7%				23	12.9%				38	14.4%		
Upper-level tertiary	23	22.3%				36	20.2%				52	19.7%		
Self-reported physical activity (MET, h/wk)			25.2 (13.8)		.58			25.5 (14.9)		.64			26.1 (13.9)	
Daily smoking	29	28.2%			.21	41	23.0%			.79	58	22.0%		
BMI, kg/m^2			24.4 (4.8)		.30			24.6 (4.2)		.08			23.9 (4.0)	
Height, cm														
Male			178.7 (7.2)		.30			177.8 (6.5)		.72			177.5 (6.8)	
Female			163.3 (5.4)		.36			164.2 (6.0)		.87			164.1 (5.7)	
Cohort of recruitment participation	36	35.0%			<.001	72	40.4%			<.001	154	58.3%		
Office systolic blood pressure‡			119.5 (13.0)		.04			118.5 (13.4)		.13			116.6 (12.4)	
Office diastolic blood pressure‡			77.7 (8.6)		.03			76.8 (8.4)		.15			75.6 (7.4)	
Resting HR, bpm§			71.9 (1.2)		.03			69.8 (1.2)		.37			68.5 (1.2)	
Peak HR			159.5 (15.5)		.16			157.8 (14.7)		.56			157.0 (14.7)	
HR_{30s}, bpm			132.1 (20.4)		.01			129.4 (19.2)		.11			126.4 (19.4)	
HR_{60s}, bpm			114.5 (23.0)		.05			113.2 (19.5)		.08			109.8 (20.4)	
HRR_{SLOPE}, bpm/s			1.07 (0.30)		.03			1.10 (0.31)		.09			1.16 (0.36)	
HRR_{30s}, bpm			27.3 (8.3)		.003			28.4 (8.5)		.02			30.6 (9.8)	
HRR_{60s}, bpm			45.0 (12.0)		.11			44.6 (9.7)		.01			47.3 (12.5)	

HR, resting heart rate, geometric mean of 3-5 minutes seated rest period, geometric mean SD; HRR_{SLOPE}, maximum 30s slope of heart rate recovery during 1 min after step test cessation; *MET*, metabolic equivalent; *Peak HR*, 10-beat median at the time of step test cessation.

**P* values refer to comparisons between subjects born preterm and controls using the Student *t* test or Pearson χ^2 test.

†Includes superimposed preeclampsia.

‡Mean of 3 measurements.

§Geometric mean.

sex, women born late preterm had lower mean differences in HRR than men.

When we compared those born with VLBW (**Table IV**; available at www.jpeds.com) with controls, the VLBW group had a gentler mean maximum slope in the HRR (0.23 beats/s [0.07-0.39]), lower HRR_{30s} (−7.38 bpm [−11.76 to −3.00]), and lower HRR_{60s} (−7.36 bpm (−12.91 to −1.83]) compared with controls, when adjusted for age, sex, and cohort of recruitment. When further adjusted for birth weight SD score, gestational diabetes mellitus, gestational hypertension, parental education and maternal smoking, BMI, height, and physical activity, the results attenuated and were no longer statistically significant.

Discussion

We hypothesized that preterm birth, early or late, is associated with altered HRR after exercise in young adulthood. The results revealed lower HRR after exercise for adults born preterm when compared with controls, although not all individual comparisons were statistically significant. Overall, our results suggest an altered HRR in young adults

Table II. Mean differences (95% CIs) in HRR measures between adults born early and late preterm compared with control group

Measurements	Model	Early preterm Mean difference (95% CI)	Early preterm *P* value	Late preterm Mean difference (95% CI)	Late preterm *P* value
HRR_{SLOPE}, beats/s (control mean: −1.16)	1	0.095 (0.019 to 0.171)	.014	0.061 (−0.003 to 0.124)	.060
	2	0.096 (0.015 to 0.178)	.021	0.062 (−0.004 to 0.128)	.067
	3	0.078 (−0.002 to 0.158)	.057	0.049 (−0.016 to 0.114)	.142
HRR_{30s}, bpm (control mean 30.6)	1	−3.16 (−5.23 to −1.08)	.003	−2.06 (−3.79 to −0.34)	.019
	2	−3.09 (−5.32 to −0.86)	.007	−1.94 (−3.75 to −0.13)	.036
	3	−2.60 (−4.81 to −0.40)	.021	−1.51 (−3.30 to 0.28)	.098
HRR_{60s}, bpm (control mean 47.3)	1	−2.50 (−5.10 to 0.09)	.059	−2.77 (−4.93 to −0.60)	.012
	2	−1.87 (−4.68 to 0.95)	.194	−2.35 (−4.64 to −0.06)	.044
	3	−1.49 (−4.34 to 1.37)	.306	−2.33 (−4.64 to −0.02)	.048

Model 1 (N = 545): age, sex, and cohort of recruitment. Model 2 (N = 545): Model 1 + birth weight SD score, gestational diabetes mellitus, gestational hypertension, parental education, maternal smoking. Model 3 (N = 531): Model 2 + smoking, BMI, height, and physical activity.

born preterm, including those born late preterm. Greater BMI[30] and lower physical activity[31] in adults born preterm seem to mediate in part the association.

There is extensive evidence for increased cardiovascular risk in children and adults born preterm.[1-6] Studies report on elevated blood pressure, greater blood pressure variability, and altered autonomic control.[7-9] Recent literature has connected preterm birth to increased risk of early heart failure,[32] reduced myocardial functional reserve during exercise,[33,34] and to ventricular structural differences in adulthood.[35,36] Birth at VLBW or at extremely low birth weight has been associated with impaired glucose regulation and obstructive airflow.[1,30,37] Previous literature suggested that decreased vagal function is an independent risk factor for all-cause mortality and an underlying factor for cardiovascular disease.[16,18,20] Attenuated HRR immediately after the cessation of exercise has been considered an independent and powerful predictor of overall mortality.[22,23] Abnormal HRR after submaximal exercise has also been reported to predict death in a healthy cohort.[24]

The mechanisms by which preterm birth is connected to increased cardiovascular risks such as elevated blood pressure are not clear. The third trimester of gestation is important to the development of the autonomic nervous system. Myelination of the vagus nerve, baroreflex sensitivity, and HR variability all undergo substantial maturation during the third trimester.[10,11] Although pregnancy is interrupted by preterm birth in second or third trimester, altered autonomic control may be one mechanism linking preterm birth with cardiovascular risk factors in adulthood.

Previous studies have led to the conclusion that the HR regulation during mild levels of exercise is mainly controlled by withdrawal of the parasympathetic activity whereas the activation of sympathetic tone is primary in more strenuous exercise.[20] The decrease in HR immediately after cessation of exercise is considered to result from reactivation of the vagal (parasympathetic) system.[21] A previous study reported that the initial HR recovery within 30 seconds after cessation of exercise was mediated primarily by cardiac vagal control, almost independently of exercise intensity or sympathetic blockade.[21] In the current study, we found that HRR_{30s} after submaximal exercise was significantly lower for adults born early or late preterm, suggesting that altered cardiac vagal modulation for those born preterm extends at least to young adulthood.

For infants, those born at lower gestational age have reduced cardiac parasympathetic control.[12,38] Altered cardiac control in neonates born preterm is suggested to relate to preterm birth per se rather than other pregnancy complications.[39] A recent study on 13-year-old children reported on lower exercise tolerance and slower HRR after maximal exercise on 13-year-old children born preterm with VLBW.[25] Moreover, young adults born preterm with extremely low birth weights had lower parasympathetic regulatory capacity as measured by HR variability when compared with those with normal weight at birth.[13,15] There is also evidence on premature decline in the cardiac parasympathetic function on adults born with extremely low birth weights.[15] Our previous study on cardiac autonomic function in this cohort was also consistent with lower parasympathetic cardiac control, at least in relation to sympathetic activity across the range of preterm births, but there was a degree of uncertainty in this finding. The current study reinforces this finding and provides additional evidence for reduced parasympathetic control in adults born preterm. The results were particularly clear for adults born preterm with VLBW had altered HRR after exercise compared with controls.

A previous study on low birth weight adults suggested that autonomic control varied by sex.[40] We did not find statistically significant sex interactions in HRR after exercise. However, we found that women born late preterm had lower mean HRR than men, which is aligned with previous findings suggesting that the association between preterm birth and adult office blood pressure is stronger among women than men.[4] This finding is also aligned with previous reports on the association of stronger autonomic nervous system response to stress in women with low birth weight than in men.[40]

Children and adults born preterm undertake less physical activity,[6,31] have lower cardiorespiratory[6,41] and muscular

fitness,[6,29] and more obstructive airflow[6,42] than those born at term, although there is some controversy on whether these findings extend to those born late preterm.[29,31,43] Adults born very preterm tend to be leaner probably because of lower lean body mass,[4] but across the whole range of prematurity a greater BMI and body fat percentage prevail.[2] All this could contribute to reduced cardiac parasympathetic control. When we adjusted our results for physical activity and BMI, the results attenuated but remained statistically significant. Additional proportion of variance in the full model was mainly explained by adding BMI and physical activity, suggesting that lower physical activity and adiposity might in part mediate the association of preterm birth and altered HRR. Adding daily smoking or current height had minor effect on the results. We also adjusted for several parental and prenatal confounders associated with preterm birth, which did not explain the associations between preterm birth and altered HRR.

We have discussed previously the limitations of ESTER preterm birth study.[2] A limitation in the current study is that we did not use a maximal exercise test and the exercise stimulus was not personalized to maximum HR. However, HRR evaluated after submaximal exercise provides prognostic information that is comparable with HRR quantified after maximal exercise test.[24] The step test protocol used was similar for all participants. However, as the physical fitness of the participants varied, relative exercise load experienced by the individual participants was different. As the load of exercise may affect to HRR, this could potentially confound the results. To avoid this, we adjusted for physical activity and the differences remained statistically significant for HRR_{30s} in the early preterm group and for HRR_{60s} in the late preterm group. Also, there was no difference in self-reported physical activity between the study groups in this sample. Therefore, it is possible, but unlikely that the results could be explained only by the differences in participant's physical fitness. Although we were able to adjust for a number of confounding factors, residual confounding cannot be excluded. In addition, usable HR data could not be obtained from a number of participants and thus the sample size was limited, which might lead to more conservative estimates.

Autonomic function may be addressed, in addition to HR variability, with alternative methods such as plasma catecholamine level measurements or measurement of pre-ejection period by impedance cardiography. In this study, we did not have these measurements available. They would make an interesting topic for future studies and might further verify the findings in this study.

We found that young adults born preterm, early or late, have altered HRR from exercise. This suggests that preterm birth is associated with altered parasympathetic postexercise reactivation of the autonomic nervous system. This may be one mechanism increasing the cardiovascular risks for those born preterm. Our finding further highlights the importance of health-enhancing physical activity and fitness for children and adults born preterm. ■

Submitted for publication Nov 7, 2018; last revision received May 15, 2019; accepted Jun 24, 2019.

Reprint requests: Risto Karvonen, MD, Department of Chronic Disease Prevention, National Institute for Health and Welfare, PO Box 310, 90101 Oulu, Finland. E-mail: risto.karvonen@thl.fi

References

1. Parkinson JRC, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics 2013;131:1240.
2. Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli H, Miettola S, Hovi P, et al. Cardiometabolic risk factors in young adults who were born preterm. Am J Epidemiol 2015;181:861-73.
3. Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Hovi P, Miettola S, Ruokonen A, et al. Cardiovascular risk factors in adolescents born preterm. Pediatrics 2014;134:1072.
4. Kajantie E, Hovi P. Is very preterm birth a risk factor for adult cardiometabolic disease? Semin Fetal Neonatal Med 2014;19:112-7.
5. Luu TM, Katz SL, Leeson P, Thébaud B, Nuyt A. Preterm birth: risk factor for early-onset chronic diseases. CMAJ 2016;188:736-46.
6. Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr 2017;106:1409-37.
7. Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, et al. Blood pressure in young adults born at very low birth weight: adults born preterm international collaboration. Hypertension 2016;68:880-7.
8. Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli H, Martikainen S, Pesonen A, et al. Ambulatory blood pressure and its variability in adults born preterm. Hypertension 2015;65:615-21.
9. Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, et al. Cardiac autonomic function in adults born preterm. J Pediatr 2019;208:103.e4.
10. Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PFF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. J Physiol (Lond) 2005;568:333-41.
11. Van Leeuwen P, Lange S, Bettermann H, Grönemeyer D, Hatzmann W. Fetal heart rate variability and complexity in the course of pregnancy. Early Hum Dev 1999;54:259-69.
12. Yiallourou SR, Witcombe NB, Sands SA, Walker AM, Horne RSC. The development of autonomic cardiovascular control is altered by preterm birth. Early Hum Dev 2013;89:145-52.
13. Mathewson KJ, Van Lieshout RJ, Saigal S, Boyle MH, Schmidt LA. Reduced respiratory sinus arrhythmia in adults born at extremely low birth weight: evidence of premature parasympathetic decline? Int J Psychophysiol 2014;93:198-203.
14. Rakow A, Katz-Salamon M, Ericson M, Edner A, Vanpée M. Decreased heart rate variability in children born with low birth weight. Pediatr Res 2013;74:339-43.
15. Mathewson KJ, Van Lieshout RJ, Saigal S, Morrison KM, Boyle MH, Schmidt LA. Autonomic functioning in young adults born at extremely low birth weight. Glob Pediatr Health 2015;2. 2333794X15589560.
16. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94:2850-5.
17. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351:478-84.
18. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141:122-31.
19. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007;74:224-42.
20. Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ, et al. Modulation of cardiac autonomic activity during and immediately after exercise. Am J Physiol 1989;256:H141.

21. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yuokohama H, et al. Vagally mediated heart-rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart-failure. J Am Coll Cardiol 1994;24:1529-35.
22. Cole CR, Blockstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart rate recovery immediately after exercise as a predictor of mortality. Herz Kreislauf 2000;32:156.
23. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000;284:1392-8.
24. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med 2000;132:552-5.
25. Haraldsdottir K, Watson AM, Goss KN, Beshish AG, Pegelow DF, Palta M, et al. Impaired autonomic function in adolescents born preterm. Physiol Rep 2018;6:e13620.
26. Miettola S, Hartikainen A, Vääräsmäki M, Bloigu A, Ruokonen A, Järvelin M, et al. Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. Eur J Epidemiol 2013;28:87-98.
27. Pihkala J, Hakala T, Voutilainen P, Raivio K. Characteristic of recent fetal growth curves in Finland. Duodecim 1989;105:1540-6.
28. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 1954;7:218-21.
29. Tikanmäki M, Tammelin T, Sipola-Leppänen M, Kaseva N, Matinolli H, Miettola S, et al. Physical Fitness in Young Adults Born Preterm. Pediatrics 2016;137(1).
30. Saarenpaa H, Tikanmaki M, Sipola-Leppanen M, Hovi P, Wehkalampi K, Siltanen M, et al. Lung function in very low birth weight adults. Pediatrics 2015;136:642-50.
31. Tikanmaki M, Kaseva N, Tammelin T, Sipola-Leppanen M, Matinolli HM, Eriksson JG, et al. Leisure time physical activity in young adults born preterm. J Pediatr 2017;189:142.e2.
32. Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy A. Preterm birth and risk of heart failure up to early adulthood. J Am Coll Cardiol 2017;69:2634-42.
33. Huckstep OJ, Williamson W, Telles F, Burchert H, Bertagnolli M, Herdman C, et al. Physiological stress elicits impaired left ventricular function in preterm-born adults. J Am Coll Cardiol 2018;71:1347-56.
34. Goss KN, Beshish AG, Barton GP, Haraldsdottir K, Levin TS, Tetri LH, et al. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018;198:1549-58.
35. Lewandowski AJ, Bradlow WM, Daniel A, Davis EF, Jane F, Atul S, et al. Right ventricular systolic dysfunction in young adults born preterm. Circulation 2013;128:713-20.
36. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013;127:197-206.
37. Morrison KM, Ramsingh L, Gunn E, Streiner D, Van Lieshout R, Boyle M, et al. Cardiometabolic health in adults born premature with extremely low birth weight. Pediatrics 2016;138.
38. Patural H, Barthelemy JC, Pichot V, Mazzocchi C, Teyssier G, Damon G, et al. Birth prematurity determines prolonged autonomic nervous system immaturity. Clin Auton Res 2004;14:391-5.
39. Aye CYL, Lewandowski AJ, Oster J, Upton R, Davis E, Kenworthy Y, et al. Neonatal autonomic function after pregnancy complications and early cardiovascular development. Pediatr Res 2018;84:85-91.
40. Kajantie E, Räikkönen K. Early life predictors of the physiological stress response later in life. Neurosci Biobehav Rev 2010;35:23-32.
41. Svedenkrans J, Henckel E, Kowalski J, Norman M, Bohlin K. Long-term impact of preterm birth on exercise capacity in healthy young men: a national population-based cohort study. PLoS One 2013;8:e80869.
42. Gibson AM, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. Semin Fetal Neonatal Med 2014;19:105-11.
43. Kajantie E, Strang-Karlsson S, Indredavik Evensen KA, Haaramo P. Adult outcomes of being born late preterm or early term—what do we know. Semin Fetal Neonat Med 2019;24:66-83.

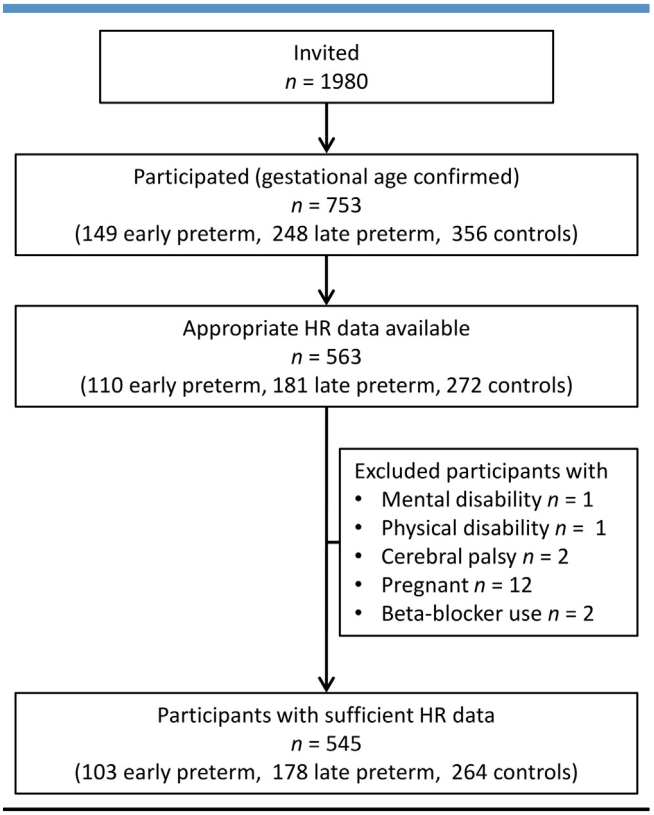

Figure 1. Flow chart of the study population.

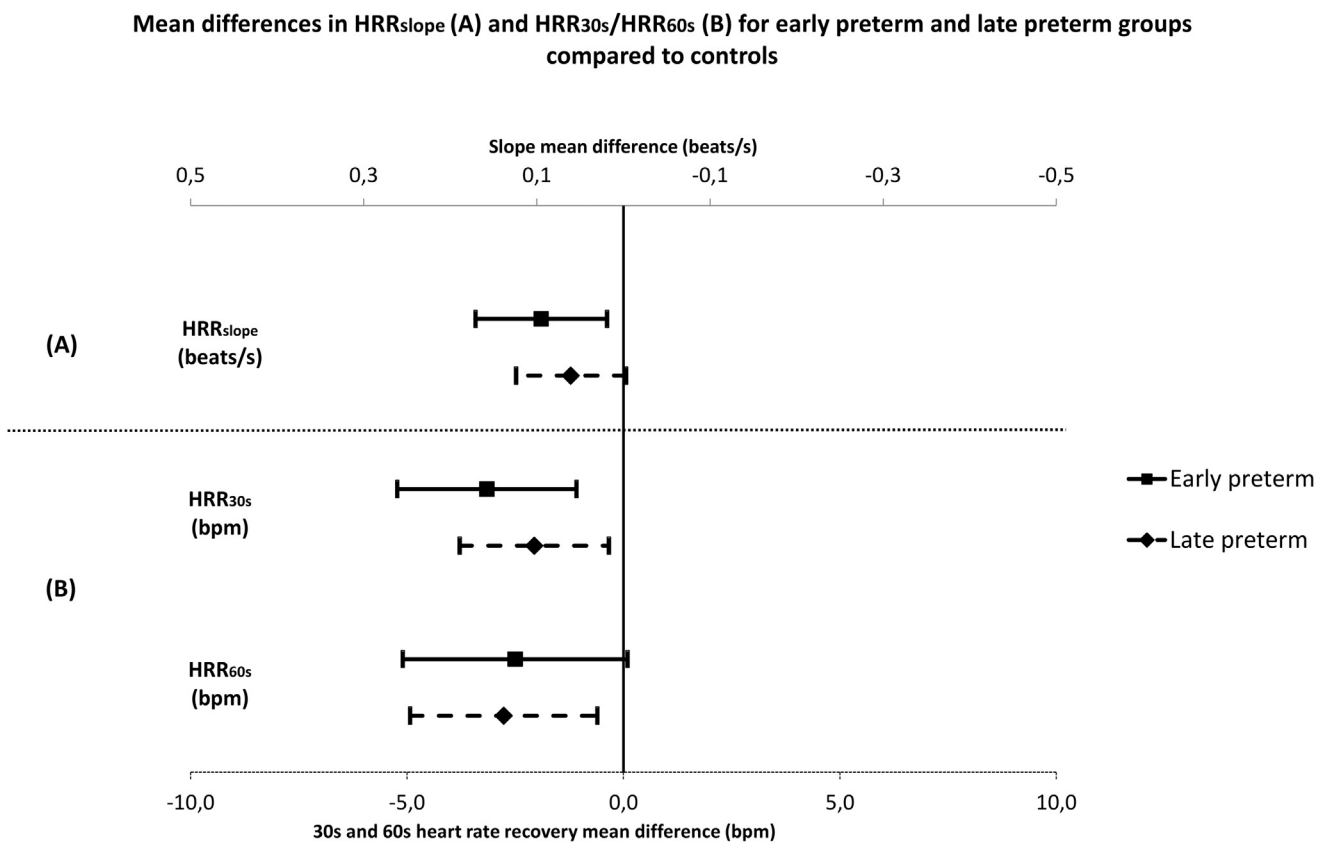

Figure 3. Mean difference in HRR measures for early preterm and late preterm groups compared with controls, with 95% CIs.

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

Measurements	Sex	Model	Early preterm	Late preterm
			Mean difference (95% CI)	Mean difference (95% CI)
HRR_{SLOPE} (beats/s) (control mean: −1.25 beats/s)	Women	1	0.105 (−0.011 to 0.222)	0.095 (−0.002 to 0.192)
		2	0.116 (−0.015 to 0.246)	0.091 (−0.011 to 0.193)
		3	0.073 (−0.054 to 0.200)	0.077 (−0.022 to 0.176)
HRR_{SLOPE} (beats/s) (control mean: *P* value 1.07 beats/s)	Men	1	0.086 (−0.012 to 0.185)	0.028 (−0.054 to 0.109)
		2	0.070 (−0.035 to 0.175)	0.026 (−0.062 to 0.114)
		3	0.066 (−0.040 to 0.173)	0.013 (−0.077 to 0.102)
HRR_{30s} (bpm) (control mean: 32.9 bpm)	Women	1	−3.027 (−6.211 to 0.157)	−3.015 (−5.675 to −0.355)
		2	−2.878 (−6.446 to 0.690)	−2.428 (−5.223 to 0.367)
		3	−1.754 (−5.247 to 1.738)	−2.168 (−4.893 to 0.556)
HRR_{30s} (bpm) (control mean: 28.4 bpm)	Men	1	−3.309 (−6.001 to −0.617)	−1.149 (−3.384 to 1.086)
		2	−2.991 (−5.858 to −0.124)	−1.151 (−3.537 to 1.234)
		3	−2.950 (−5.851 to −0.048)	−0.643 (−3.088 to 1.801)
HRR_{60s} (bpm) (control mean: 50.3 bpm)	Women	1	−2.186 (−6.095 to 1.723)	−4.105 (−7.370 to −0.840)
		2	−2.126 (−6.549 to 2.297)	−3.737 (−7.202 to −0.272)
		3	−1.572 (−6.047 to 2.904)	−3.538 (−7.029 to −0.049)
HRR_{60s} (bpm) (control mean: 44.4 bpm)	Men	1	−2.872 (−6.322 to 0.578)	−1.488 (−4.352 to 1.375)
		2	−1.496 (−5.218 to 2.225)	−0.563 (−3.659 to 2.534)
		3	−1.254 (−5.077 to 2.570)	−0.718 (−3.939 to 2.503)

Model 1 (Women: N = 267, Men: N = 278): age, sex, and cohort of recruitment. Model 2 (Women: N = 267, Men: N = 278): Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and maternal smoking. Model 3 (Women: N = 260, Men: N = 271): Model 2 plus smoking, BMI, height, and physical activity. All group means are geometric means.

Table IV. Mean differences (95% CIs) in HRR between adults with VLBW compared with controls

		VLBW (<1500 g) N = 22	
Measurements	**Model**	**Mean difference (95% CI)**	***P* value**
HRR_{SLOPE} (beats/s) (control mean: −1.16 beats/s)	1	0.23 (0.07 to 0.39)	.005
	2	0.19 (0.01 to 0.38)	.036
	3	0.15 (−0.04 to 0.34)	.113
HRR_{30s} (bpm) (control mean: 30.6 bpm)	1	−7.38 (−11.76 to −3.00)	.001
	2	−5.22 (−10.24 to −0.19)	.042
	3	−3.65 (−8.78 to 1.48)	.163
HRR_{60s} (bpm) (control mean: 47.3 bpm)	1	−7.37 (−12.91 to −1.83)	.009
	2	−5.36 (−11.73 to 1.02)	.099
	3	−4.43 (−11.12 to 2.27)	.194

Model 1 (N = 286): Age, sex, and cohort of recruitment. Model 2 (N = 286): Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal preeclampsia, parental education, and maternal smoking. Model 3 (N = 279): Model 2 plus smoking, BMI, height, and physical activity.
All group means are geometric means.