Cardiac Autonomic Function in Adults Born Preterm

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Abbreviations: BMI - body mass index, HR - heart rate, HRV - heart rate variability, bpm - beats per minute, rMSSD - root mean square of successive differences, LFP - low frequency power (0.04–0.15 Hz), HFP - high frequency power (0.15–0.4 Hz), VLBW - very low birth weight.

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Abstract

Objective: To evaluate cardiac autonomic function in adults born preterm.

Study design: We studied the association between preterm birth and cardiac autonomic function based on heart rate variability measurements in 600 adults with a mean age of 23.3 years who participated in a geographically based study in Northern Finland. Of these, there were 117 born early preterm (< 34 wk), 207 born late preterm (34–36 full weeks), and 276 born term (controls). Autonomic function was assessed by calculating time and frequency domain heart rate variability measures and by analyzing the data with linear regression.

Results: Compared with controls, mean difference in root mean square of successive differences, indicating cardiac vagal activity, was -12.0% (95% confidence interval -22.2%, -0.5%, adjusted for sex, age, source cohort and season) for the early preterm group and -7.8% (-16.8%, 2.0%) for the late preterm group. Mean differences with controls in low frequency power, an indicator of cardiac vagal activity, which includes some sympathetic- and baroreflex-mediated effects, were -13.6% (-26.7%, 1.8%) for the early preterm group and -16.4% (-27.0%, -4.3%) for the late preterm group. Mean difference in high frequency power, which quantifies cardiac vagal modulation in respiratory frequency, was -19.2% (-36.6%, 2.9%) for the early preterm group and -13.8% (-29.4%, 5.3%) for the late preterm group.

Conclusion: 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.

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 variability (HRV) metrics are commonly used to assess cardiac autonomic function.[11] A substantial proportion of the development of the autonomic nervous system (e.g., 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 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 infants are moderate (32–33 full weeks) or late (34–36 full weeks) preterms. Although many risk factors for cardiometabolic disease found in very preterms are also found in moderate and late preterms, whether these include altered cardiac autonomic function is not known.[4,10] We hypothesized that preterm birth, throughout its whole 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

Participants

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 preterms and randomly selected controls were recruited through the Northern Finland Birth Cohort 1986 (subjects born 1985–1986) or Finnish Medical Birth Register (subjects 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 heart rate monitor. After exclusions (Fig. 1), a total of 117 early preterms (< 34 wk), 207 late preterms (34–36 full weeks),[3] and 276 full term controls with available and sufficient heart rate (HR) data were included in the analysis.

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 SD 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). R-R intervals were recorded at a

spontaneous breathing frequency in a seated position at the beginning of the examination day during a 10–15 min interview conducted by a study nurse.

To quantify cardiac autonomic function, the following measurements were obtained: In the time domain, the geometric mean heart rate (HR) and root mean square of successive differences (rMSSD) were calculated. In the frequency domain, using a fast Fourier transform algorithm, low frequency power (LFP) (0.04–0.15 Hz), high frequency 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 min of data were selected during a calm seated rest period at the beginning of the clinical examination. The most stationary 3–5 min 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 min of adequate stationary data selected for the analysis. Previous studies suggested that 2 min or more of HR data was adequate for spectral analysis and that as little as 1 min of rMSSD data was adequate.[25,29] R-R interval data were visually inspected for artefacts 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 min and a minimum of 90% of accepted R-R intervals were included in the analysis. The geometric mean HR, rMSSD, and frequency domain measures 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 measures 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 1, Table 2, Table 5 and Table 6.

Statistical analysis

Data were analyzed using SPSS Statistics for Windows, Version 24.0 software (SPSS IBM, New York, U.S.A.). Descriptive statistics for the study groups were presented as categorical variables or mean values and standard deviations. Group differences were calculated by an analysis of variance, Pearson's χ^2-test, or the Student's *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,[33] we also 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[30] and engage less in leisure time physical activities[31]. Therefore, BMI and physical activity were included as covariates.

Results

Perinatal, neonatal, sociodemographic and clinical characteristics of the study groups are presented in Table 1. 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=0.05), and the early preterm group had lower self-reported physical activity (P=0.08), although neither difference reached statistical significance in this sample. In the late preterm group, mean LFP was lower (P=0.01) and there were more daily smokers (P=0.01) than in the control group. Otherwise, the sociodemographic and clinical background characteristics of the study groups were similar.

Non-participant analysis

A detailed non-participant 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 the present manuscript. In the present study, there were 12.7% subjects excluded due to 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=0.13). When comparing the background characteristics of the excluded with those included in analysis, among the early preterm group, the mothers of the excluded had more often gestational diabetes (11.7% vs 1.7%, P=0.02). Among the late preterm group, those excluded were younger (Mean age 22.6 vs 23.3 years, P=0.001), were less often part of the NFBC birth cohort (25.7% vs 47.8%, P=0.01) and their mothers had more gestational diabetes (14.3% vs 2.9%, P=0.003) when compared to the non-excluded. In the control population, the excluded were older (23.8 vs 23.5 years, P=0.03), had lower birth weight SD score (-0.24 vs 0.04, P=0.04) and had higher diastolic blood pressure (77.5 vs 75.0, P=0.03). For other characteristics presented in Table 1, there were no differences between the excluded and included participants within any group.

Group differences in autonomic function

Geometric means and standard deviations in HRV measures for the adults born early preterm, late preterm, and term (controls) are presented in Table 1. We first compared these outcomes between the preterm groups and controls, adjusting for age, sex, cohort of recruitment, and season of clinical examination (Fig. 2 and Table 2, Model 1). 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 (P=0.04) and among all preterms (P=0.04) when compared with full term controls. Furthermore, LFP, an additional indicator of cardiac vagal activity that also reflects sympathetic- and baroreflex-mediated effects, was lower for those born late preterm (P=0.01) and among all preterms (P=0.01). The mean HFP, a measure of cardiac vagal modulation in respiratory frequency, was also lower in all preterm groups, although the results were not statistically significant in any group (P=0.09 for early preterms, P=0.15 for late preterms and P=0.06 for all preterms). The LF/HF ratio, a measure 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 2). When adjusted further for daily smoking, BMI, height, and physical activity in Model 3, the results were no longer statistically significant (Table 2). 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 measures. Each one kg/m^2 higher BMI predicted 1.0% lower rMSSD (95% CI -0.1%, 2.1%, P=0.09), 0.9% lower LFP (-2.4%, 6.0%, P=0.2) and 2.1% lower HFP (-0.1%, 4.3%, P=0.06). Each METh/week more physical activity was associated with 0.5% higher rMSSD (0.2%, 0.8%,

P=0.003), 0.6% higher LFP (0.1%, 1.0%, P=0.01) and 0.9% higher HFP (0.3%, 1.6%, P=0.006). 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 measures and blood pressure

Similarly to the previously reported results in the ESTER study[4,10], the current early preterm group had 3.5 mmHg (95% CI 1.2 to 5.8) higher mean systolic and 2.8 mmHg (95% CI 1.1 to 4.6) higher mean diastolic blood pressure when adjusted for sex, age, cohort of recruitment and season of clinical examination (Table 3; online only). Late preterm group had 2.2 mmHg (95% CI 0.3 to 4.1) higher mean systolic- and 1.7 mmHg (95% CI 0.3 to 3.1) higher mean diastolic blood pressure when adjusted for sex, age, cohort of recruitment and season of clinical examination (Table 3; online only). Correlations between HRV measures and blood pressure are shown in (Table 4; online only). 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 3; online only). An exception was in the difference in diastolic blood pressure in the late preterm group, which was 1.3 mmHg (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 5; online only) presents the results separately for women and men. The group differences in HRV measures 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 measures for adults born preterm with a VLBW compared with controls.(Table 6; online only). 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 as compared with those born at term, although the differences were not statistically significant in all comparisons. While the confidence intervals leave some uncertainty specifically as to the difference in cardiac vagal control, overall our results are consistent with altered autonomic regulatory control in adults born preterm, including those born late preterm. This association seemed to be in part mediated by BMI and physical activity.

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 measures. 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.[31] 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 measures.

A number of previous studies provided evidence that altered sympathovagal balance or decreased vagal function were an 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.[32] In the present 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 (e.g. 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.[33] Moreover, when low birth weight is used as an early life indicator, as summarized by a recent review[33], the associations with autonomic nervous system response to stress is stronger among women, while 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 young adults born with a VLBW found no evidence of higher responses in those born with a VLBW as 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.[4,30] 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 measures 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 previously discussed the limitations of the ESTER Preterm Birth Study.[4] As to the present study, first, the 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 measures 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 min. However, the inclusion of findings only from those participants with at least 5 min 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.

Conclusion

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 measures, 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 re-enforce previous suggestions on the importance of health-enhancing physical activity and fitness among individuals born preterm.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

2. 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(4):1240.

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:e1072-81.

4. Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli HM, Miettola S, Hovi P, et al. Cardiometabolic risk factors in young adults who were born preterm. Am J Epidemiol. 2015; 861-73.

5. Kajantie E, Hovi P. Is very preterm birth a risk factor for adult cardiometabolic disease? Semin Fetal Neonatal Med. 2014;19(2):112-7.

6. Luu TM, Katz SL, Leeson P, Thébaud B, Nuyt A. Preterm birth: Risk factor for early-onset chronic diseases. CMAJ. 2016;188(10):736-46.

7. 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(9):1409-37.

8. 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. Hypertension. 2016;68:880-7.

9. 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(4).

10. Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli HM, Martikainen S, Pesonen AK, et al. Ambulatory blood pressure and its variability in adults born preterm. Hypertension. 2015;65(3):615-21.

11. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, FeldmanCL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11):2850-55.

12. 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(9101):478-84.

13. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122-31.

14. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007;74(2):224-42.

15. 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(3):259-69.

16. 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(Pt 1):333-41.

17. Sachis PN, Armstrong DL, Becker LE, Bryan AC. Myelination of the human vagus nerve from 24 weeks postconceptional age to adolescence. J Neuropathol Exp Neurol. 1982;41(4):466-72.

18. 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(3):145-52.

19. 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(2):198-203.

20. 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(3):339-43.

21. 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.

22. Järvelin MR, Hartikainen-Sorri AL, Rantakallio P. Labour induction policy in hospitals of different levels of specialisation. Br J Obstet Gynaecol. 1993;100(4):310-15.

23. Miettola S, Hartikainen AL, Vääräsmäki M, Bloigu A, Ruokonen A, Järvelin MR, et al. Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. Eur J Epidemiol. 2013;28:87-98.

24. Vääräsmäki M, Pouta A, Elliot P, Tapanainen P, Sovio U, Ruokonen A, et al. Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. Am J Epidemiol. 2009;169:1209-15.

25. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043-1065.

26. Eckberg DL. The human respiratory gate. J Physiol (Lond). 2003;548(Pt 2):339-52.

27. Julien C. The enigma of Mayer waves: Facts and models. Cardiovasc Res. 2006;70(1):12-21.

28. Billmann GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol. 2013; 4: 26.

29. Esco MR, Flatt AA. Ultra-short-term heart rate variability indexes at rest and post-exercise in athletes: Evaluating the agreement with accepted recommendations. J Sports Sci Med. 2014;13(3):535-541.

30. Tikanmäki M, Tammelin T, Sipola-Leppänen M, Kaseva N, Matinolli HM, Miettola S, et al. Physical fitness in young adults born preterm. Pediatrics. 2016;137(1).

31. Tikanmäki M, Kaseva N, Tammelin T, Sipola-Leppänen M, Matinolli HM, Eriksson JG, et al. Leisure Time Physical Activity in Young Adults Born Preterm. J Pediatr. 2017;189:135-42

32. Feldt K, Räikkönen K, Eriksson JG, Andersson S, Osmond C, Barker DJ, et al. Cardiovascular reactivity to psychological stressors in late adulthood is predicted by gestational age at birth. J Hum Hypertens. 2007;21(5):401-10.

33. Kajantie E, Räikkönen K. Early life predictors of the physiological stress response later in life. Neurosci Biobehav Rev. 2010;35(1):23-32.

34. Fyfe KL, Yiallourou SR, Wong FY, Horne RSC. The development of cardiovascular and cerebral vascular control in preterm infants. Sleep Med Rev. 2014;18(4):299-310.

35. Wakai RT. Assessment of fetal neurodevelopment via fetal magnetocardiography. Exp Neurol. 2004;190 Suppl 1:65.

36. Kaseva N, Pyhälä R, Wehkalampi K, Feldt K, Pesonen AK, Heinonen K, et al. Adrenalin, noradrenalin and heart rate responses to psychosocial stress in young adults born preterm at very low birthweight. Clin Endocrinol (Oxf). 2014;81(2):231-37.

37. Rossi M, Marti G, Ricordi L, Fornasari G, Finardi G, Fratino P, et al. Cardiac autonomic dysfunction in obese subjects. Clin Sci. 1989;76(6):567-72.

38. Felber Dietrich D, Schindler C, Schwartz J, Barthélémy JC, Tschopp JM, Roche F, et al. Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: Results of the SAPALDIA study. Europace. 2006;8(7):521-29.

39. Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol. 1999;83(8):1242-47.

40. Kiviniemi AM, Perkiömäki N, Auvinen J, Herrala S, Hautala AJ, Ahola R, et al. Lifelong physical activity and cardiovascular autonomic function in midlife. Med Sci Sports Exerc. 2016;48(8):1506-13.

41. Tininenko JR, Measelle JR, Ablow JC, High R. Respiratory control when measuring respiratory sinus arrhythmia during a talking task. Biological Psychology. 2012;89(3):562-569.

42. Bernardi L, Wdowczyk-Szulc J, Valenti C, et al. Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. Journal of the American College of Cardiology. 2000;35(6):1462-1469.

43. Beda A, Jandre FC, Phillips DI, Giannella-Neto Antonio, Simpson DM. Heart-rate and blood-pressure variability during psychophysiological tasks involving speech: Influence of respiration. Psychophysiology. 2007;44(5):767-778.

Figure legends:

Figure 1. Flow chart of the study population. HR, heart rate.

Figure 2. Mean percent difference in heart rate variability measures between early and later preterms as compared with controls born at term, with 95% CIs. HR - heart rate, rMSSD - root mean square of successive differences, LF power - low frequency power (0.04–0.15 Hz), HF power - high frequency power (0.15–0.4 Hz). The presented results are adjusted for age, sex, cohort of recruitment and season of clinical examination.

Table 1. Perinatal and neonatal characteristics of adults born early preterm, late preterm, and term (controls), in addition to current clinical and sociodemographic characteristics.

Characteristic	Early preterm (*n* = 117)					Late preterm (*n* = 207)					Controls (*n* = 276)			
	No.	%	Mean (SD)	Missing	*P* value[a]	No.	%	Mean (SD)	Missing	*P* value[a]	No.	%	Mean (SD)	Missing
Perinatal and neonatal														
Born from multiple pregnancies	30	25.6			<0.001	27	13.4			<0.001	2	0.7		
Maternal hypertension[b]	14	12.0			0.75	30	14.9		5	0.23	30	10.9		1
Maternal preeclampsia[c]	29	24.8			<0.001	23	11.4		5	0.008	13	4.7		1
Maternal gestational diabetes	2	1.7		19	0.85	6	3.2		20	0.22	4	1.5		7
Maternal smoking during pregnancy	18	16.2		6	0.89	42	20.6		3	0.76	44	16.2		5
Gestational age (weeks)			31.8 (2.0)		<0.001			35.8 (0.8)		<0.001			40.1 (1.2)	
Birth weight (g)			1780 (493)		<0.001			2651 (511)		<0.001			3607 (479)	
Birth weight SD score			-0.72 (1.45)		<0.001			-0.68 (1.3)		<0.001			0.04 (1.0)	
Current														
Male sex	58	49.6			0.94	101	48.8			0.79	138	50.0		
Age (years)			23.1 (1.3)		0.003			23.3 (1.3)		0.04			23.5 (1.1)	
Parental education level				1	0.23				4	0.79				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)		0.08			25.3 (14.7)		0.61			26.0 (13.6)	
Season of clinical examination					0.18					0.06				
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			0.14	33	28.2			0.01	59	21.4		
Body mass index (kg/m²)			24.2 (4.5)		0.34			24.5 (4.4)		0.05			23.8 (3.9)	
Height (cm)														
Male			178.9 (6.9)		0.37			177.7 (6.5)		0.87			177.9 (6.9)	
Female			163.4 (4.9)		0.31			164.6 (5.8)		0.73			164.3 (6.0)	
Cohort of recruitment participation	40	34.2			<0.001	99	47.8			0.01	164	59.4		
Clinic systolic BP[d]			119.2 (13.2)		0.03			118.0 (13.6)		0.10			116.0 (12.5)	
Clinic diastolic BP[d]			77.6 (8.9)		0.007			76.6 (8.3)		0.03			75.0 (7.3)	
HR (bpm)[e]			71.8 (1.2)		0.05			70.0 (1.2)		0.46			69.2 (1.2)	
rMSSD (ms)[e]			49.6 (1.8)		0.13			51.1 (1.7)		0.17			54.7 (1.8)	

LFP (ms2)[e]	1563.9 (2.1)	0.10	1507.5 (2.1)	0.01	1788.2 (2.1)
HFP (ms^2)[e]	881.2 (3.1)	0.21	912.8 (2.8)	0.21	1032.9 (3.1)
LF/HF[e]	1.8 (2.0)	0.75	1.7 (1.9)	0.49	1.7 (2.0)

Abbreviations: SD, standard deviation; MET, metabolic equivalent; BP, blood pressure; HR, heart rate; bpm, beats per minute; rMSSD, root mean square of the successive differences in RR intervals; LFP, low frequency power (0.04–0.15 Hz); HFP, high frequency power (0.15–0.4 Hz).

[a] *P* values refer to comparisons between preterm born subjects and controls using the Student's *t*-test or Pearson's x^2 test.

[b] Gestational or chronic hypertension. [c] Includes superimposed preeclampsia. [d] Mean of 3 measurements. [e] Geometric mean.

Table 2. Mean differences (95 CIs) in heart rate variability between early and late preterm adults compared to controls, with a post hoc analysis comparing all adults born preterm to controls.

		Early preterm		Late preterm		Post-hoc analysis of all preterms	
Measurement	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%)	0.06	0.7% (-2.1% to 3.6%)	0.63	1.6% (-1.0% to 4.3%)	0.22
	2	2.0% (-1.8% to 5.9%)	0.31	0.3% (-2.7% to 3.3%)	0.86	0.8% (-2.0% to 3.6%)	0.57
	3	0.8% (-3.0% to 4.7%)	0.68	-0.5% (-3.5% to 2.6%)	0.77	-0.1% (-2.9% to 2.8%)	0.97
rMSSD (Control mean: 54.7 ms)	1	-12.0% (-22.2% to -0.5%)	0.04	-7.8% (-16.8% to 2.0%)	0.12	-9.3% (-17.3% to -0.6%)	0.04
	2	-11.4% (-22.5% to 1.3%)	0.08	-8.4% (-17.7% to 1.9%)	0.11	-9.3% (-17.9% to 0.1%)	0.05
	3	-7.7% (-19.4% to 5.8%)	0.25	-4.5% (-14.4% to 6.5%)	0.40	-5.5% (-14.6% to 4.5%)	0.27
LFP (Control mean: 1788.2 ms^2)	1	-13.6% (-26.7% to 1.8%)	0.08	-16.4% (-27.0% to -4.3%)	0.01	-15.5% (-25.1% to -4.5%)	0.01
	2	-14.6% (-28.5% to 2.0%)	0.08	-16.5% (-27.5% to -3.7%)	0.01	-15.9% (-26.2% to -4.1%)	0.01
	3	-9.8% (-24.7% to 8.2%)	0.27	-12.9% (-24.6% to 0.8%)	0.06	-11.9% (-23.0% to 0.8%)	0.07
HFP (Control mean: 1032.9 ms^2)	1	-19.2% (-36.6% to 2.9%)	0.09	-13.8% (-29.4% to 5.3%)	0.15	-15.7% (-29.6% to 0.9%)	0.06
	2	-19.4% (-38.0% to 5.0%)	0.11	-15.5% (-31.5% to 4.3%)	0.12	-16.7% (-31.4% to 1.2%)	0.07
	3	-12.3% (-32.9% to 14.6%)	0.34	-7.8% (-25.6% to 14.2%)	0.45	-9.3% (-25.6% to 10.7%)	0.38
LF/HF (Control mean 1.7)	1	6.9% (-7.8% to 24.0%)	0.37	-3.1% (-14.2% to 9.5%)	0.61	0.3% (-10.1% to 12.0%)	0.96
	2	5.9% (-9.8% to 24.3%)	0.48	-1.2% (-13.1% to 12.3%)	0.85	1.0% (-10.3% to 13.7%)	0.87
	3	2.9% (-12.6% to 21.2%)	0.73	-5.4% (-17.1% to 7.8%)	0.40	-3.0% (-14.0% to 9.6%)	0.63

Abbreviations: HR, heart rate; rMSSD, root mean square of the successive differences in RR intervals; LFP, low frequency power (0.04–0.15 Hz); HFP, high frequency power (0.15–0.4 Hz).
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, 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.

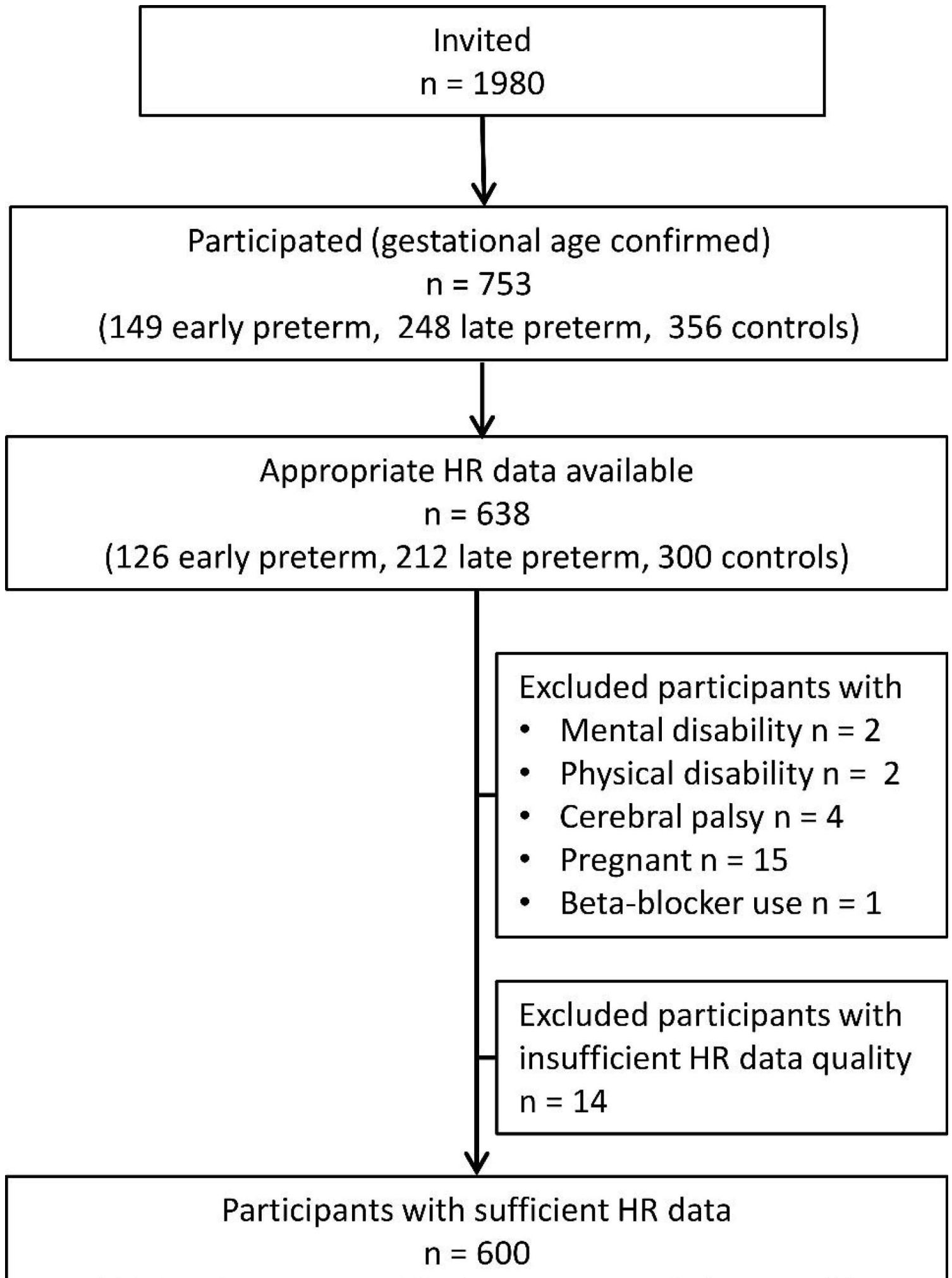
Invited
n = 1980
Participated (gestational age confirmed)
n = 753
(149 early preterm, 248 late preterm, 356 controls)
Appropriate HR data available
n = 638
(126 early preterm, 212 late preterm, 300 controls)
Excluded participants with
• Mental disability n = 2
• Physical disability n = 2
• Cerebral palsy n = 4
• Pregnant n = 15
• Beta-blocker use n = 1
Excluded participants with
insufficient HR data quality
n = 14
Participants with sufficient HR data
n = 600

Table 3. Mean differences (95% CIs) in systolic and diastolic office blood pressure between adults born early preterm and late preterm as compared with controls, adjusted for heart rate variability measures.

		Early preterm		Late preterm	
Measurement	Model	Mean difference in mmHg (95% CI)	*P*-value	Mean difference in mmHg (95% CI)	*P*-value
Systolic blood pressure	1	3.5 (1.2 to 5.8)	0.003	2.2 (0.3 to 4.1)	0.021
	2	3.1 (0.9 to 5.5)	0.006	2.0 (0.2 to 3.9)	0.034
	3	3.3 (1.0 to 5.5)	0.005	2.1 (0.2 to 4.0)	0.032
	4	3.2 (1.0 to 5.5)	0.005	1.9 (0.0 to 3.8)	0.048
Diastolic blood pressure	1	2.8 (1.1 to 4.6)	0.002	1.7 (0.3 to 3.1)	0.020
	2	2.4 (0.7 to 4.1)	0.006	1.4 (0.0 to 2.8)	0.046
	3	2.5 (0.8 to 4.2)	0.004	1.5 (0.1 to 2.9)	0.041
	4	2.5 (0.8 to 4.2)	0.005	1.3 (-0.2 to 2.7)	0.080

Abbreviations: rMSSD, root mean square of the successive differences in RR intervals; HFP, high frequency power (0.15–0.4 Hz); LFP, low frequency power (0.04–0.15 Hz).
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.

Table 4. Correlations between heart rate variability measures and office blood pressure.

Measure	Systolic blood pressure, mean of 3 measurements	*P*-value	Diastolic blood pressure, mean of 3 measurements	*P*-value
Mean HR	0.161	<0.001	0.289	<0.001
rMSSD	-0.144	<0.001	-0.252	<0.001
LFP	-0.146	<0.001	-0.245	<0.001
HFP	-0.127	0.002	-0.232	<0.001
LF/HF	0.046	0.26	0.108	0.008

Abbreviations: HR, heart rate; rMSSD, root mean square of the successive differences in RR intervals; LFP, low frequency power (0.04–0.15 Hz); HFP, high frequency power (0.15–0.4 Hz). The correlations have been calculated from log transformed HRV measures.

Table 5. Mean differences (95% CIs) in autonomic control measures between adults born early preterm and late preterm compared with controls by sex.

			Early preterm	Late preterm
Measurement	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%)

Abbreviations: HR, heart rate; rMSSD, root mean square of the successive differences in RR intervals; LFP, low frequency power (0.04–0.15 Hz); HFP, high frequency power (0.15–0.4 Hz).
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 6. Mean differences (95% CIs) in autonomic control measures between very low birth weight adults compared with controls.

		Very low birth weight (<1500 g) *N* = 28	
Measurement	Model	Mean difference (95% CI)	P-value
Mean HR (Control mean: 69.2 bpm)	1	6.7% (-0.1% to 13.9%)	0.05
	2	3.6% (-4.0% to 11.8%)	0.36
	3	1.4% (-6.2% to 9.7%)	0.72
rMSSD (Control mean: 54.7 ms)	1	-18.1% (-35.6% to 4.1%)	0.10
	2	-15.8% (-36.2% to 11.2%)	0.22
	3	-12.7% (-34.6% to 16.4%)	0.35
LFP (Control mean: 1788.2 ms^2)	1	-25.7% (-45.3% to 0.9%)	0.06
	2	-26.5% (-48.4% to 4.5%)	0.09
	3	-21.6% (-45.8% to 13.3%)	0.19
HFP (Control mean: 1032.9 ms^2)	1	-28.5% (-55.4% to 14.6%)	0.16
	2	-31.1% (-60.1% to 19.0%)	0.18
	3	-26.7% (-58.4% to 29.2%)	0.28
LF/HF (Control mean 1.7)	1	3.9% (-21.7% to 37.8%)	0.79
	2	6.6% (-23.4% to 48.2%)	0.70
	3	6.9% (-24.2% to 50.8%)	0.70

Abbreviations: HR, heart rate; rMSSD, root mean square of the successive differences in RR intervals; LFP, low frequency power (0.04–0.15 Hz); HFP, high frequency power (0.15–0.4 Hz).
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.