OULU 2021
D 1619

ACTA UNIVERSITATIS OULUENSIS

Risto Karvonen

PRETERM BIRTH AND CARDIOVASCULAR RISK FACTORS IN YOUNG ADULTHOOD

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

ACTA UNIVERSITATIS OULUENSIS
D Medica 1619

RISTO KARVONEN

PRETERM BIRTH AND CARDIOVASCULAR RISK FACTORS IN YOUNG ADULTHOOD

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 12 of the Department of Paediatrics, on 11 June 2021, at 12 noon

UNIVERSITY OF OULU, OULU 2021

Acta Univ. Oul. D 1619, 2021

Supervised by
Professor Eero Kajantie
Doctor Marika Paalanne

Reviewed by
Professor Anne Monique Nuyt
Docent Jaana Pihkala

Opponent
Doctor Adam Lewandowski

ISBN 978-952-62-2951-5 (Paperback)
ISBN 978-952-62-2952-2 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

PUNAMUSTA
TAMPERE 2021

Karvonen, Risto, Preterm birth and cardiovascular risk factors in young adulthood.
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; National Institute for Health and Welfare
Acta Univ. Oul. D 1619, 2021
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Adults born preterm (birth before 37 weeks of gestation) have several increased risk factors of cardiovascular disease, including higher blood pressure compared with peers born at term. Although more than 80% of preterm births are late preterm (34 to 36 completed weeks of gestation), it is not clear to what extent the elevated risks are present in individuals with a history of late preterm birth. The mechanisms by which preterm birth is associated with elevated risks of cardiovascular disease, such as higher blood pressure, are unclear.

The aim of this study was to investigate the association of between preterm birth, throughout its gestational age range, with blood pressure and cardiac autonomic regulation in young adulthood in three cohort studies: the ESTER Preterm Birth study, the Helsinki Study of Very Low Birth Weight Adults and the McMaster Cohort.

Adults born preterm had higher office-measured blood pressure, higher 24-hour ambulatory blood pressure, higher blood pressure variability, lower cardiac parasympathetic- and higher sympathetic autonomic regulation and slower heart rate recovery after exercise than their peers born at term. The higher blood pressure, increased blood-pressure variability, changes in cardiac autonomic regulation and slower post-exercise heart rate recovery seemed to be partially associated with unfavorable body composition, reduced physical activity and female sex.

Those with a history of preterm birth have higher levels of risk factors of cardiovascular disease than their peers born at term. As most of the risk factors, such as body composition and physical activity are modifiable, adults born preterm may especially benefit from promotion of healthy lifestyles and primary prevention.

Keywords: autonomic regulation, blood pressure, cardiovascular risk factor, heart rate recovery, heart rate variability, parasympathetic, preterm birth, sympathetic

Karvonen, Risto, Ennenaikainen syntymä ja sydän- ja verisuonitautien riskitekijät nuorilla aikuisilla.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Terveyden ja hyvinvoinnin laitos
Acta Univ. Oul. D 1619, 2021
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Ennenaikaisesti (ennen 37. raskausviikkoa) syntyneillä aikuisilla on todettu kohonneita sydän- ja verisuonisairauksien riskitekijöitä täysiaikaisena syntyneisiin verrokkeihin nähden. Ennenaikainen syntymä on yhteydessä muun muassa aikuisiän kohonneeseen verenpaineeseen. Mekanismeja, joilla ennenaikainen syntymä on yhteydessä lisääntyneisiin sydän- ja verisuonisairauksien riskitekijöihin ei tunneta. Vaikka yli 80 % keskosista syntyy lievästi ennenaikaisena (34–36 raskausviikoilla), valtaosa aiemmista keskostutkimuksista on tehty hyvin tai erittäin ennenaikaisesti syntyneillä. Sitä, ovatko sydän- ja verisuonisairauksien riskitekijät koholla myös lievästi ennenaikaisena syntyneiden ryhmässä, on tutkittu vähemmän.

Väitöskirjatutkimuksessa selvitettiin, miten eriasteinen ennenaikainen syntymä on yhteydessä aikuisiän kohonneeseen verenpaineeseen ja sydämen autonomiseen säätelyyn kolmessa eri kohorttitutkimuksessa: Pohjoissuomalaisessa ESTER-tutkimuksessa, Helsingin Pikku-K tutkimuksessa ja kanadalaisessa McMaster-tutkimuksessa.

Ennenaikaisesti syntyneillä aikuisilla todettiin korkeampi verenpaine, korkeampi 24 tunnin ambulatorinen verenpaine, suurempi verenpaineen vuorokausivaihtelu, vähentynyt parasympaattinen- ja lisääntynyt sympaattinen sydämen säätely sekä hitaampi rasituksen jälkeinen sykepalautuma. Kohonneet riskitekijät vaikuttivat olevan yhteydessä epäedulliseen kehonkoostumukseen, vähentyneeseen fyysiseen aktiivisuuteen ja naissukupuoleen.

Ennenaikaisesti syntyneillä aikuisilla on verrokkeihin nähden korkeampia sydän- ja verisuonisairauksien riskitekijöitä. Näitä riskejä on mahdollista ehkäistä, joten ennenaikaisesti syntyneet aikuiset voivat erityisesti hyötyä terveellisistä elämäntavoista.

Asiasanat: autonominen säätely, parasympaattinen, sydän- ja verisuonitaudit, sykepalautuma, sykevaihtelu, sympaattinen, verenpaine

To my family

Acknowledgements

This dissertation study was carried out at the National Institute for Health and Welfare (THL), University of Oulu Graduate School and the PEDEGO Research Unit at the University of Oulu, Faculty of Medicine from 2013 to 2021. The study is part of Northern Finland Birth Cohort 1986 (NFBC 1986) study, the ESTER Preterm Birth Study, the Helsinki Study of Very Low Birth Weight adults (HeSVA) and the McMaster cohort study. I am grateful to the participants in these studies for their valuable contribution, which was an imperative for this work.

I want to thank the Director General of THL Markku Tervahauta, Ph.D., former directors of THL, Professors Pekka Puska and Juhani Eskola, and Professors Terhi Kilpi, Tiina Laatikainen, Erkki Vartiainen and Markku Peltonen, and Kati Kristiansson, Ph.D., for providing excellent research facilities. I am grateful to the current and former heads of the PEDEGO Research Unit Professors Kaisa Tasanen-Määttä and Mika Rämet, and Professors Marjo Renko and Matti Uhari for providing excellent graduate school training.

The major part of this study was supported financially by the Health and Biosciences Doctoral Programme at the University of Oulu, to which I want to express my gratitude. I also want to thank Juho Vainio Foundation, Signe and Ane Gyllenberg Foundation, The Finnish Medical Foundation and Sigrid Juselius Foundation who have supported this thesis. I am also grateful to the Foundation for Pediatric Research, the Academy of Finland, the Emil Aaltonen Foundation, the Diabetes Research Foundation, and the Yrjö Jahnsson Foundation, who have supported the ESTER study.

I have had the privilege to work with two extraordinary supervisors, Professor Eero Kajantie and Marika Paalanne, Ph.D., to whom I express my deepest gratitude for their highly professional, motivational and excellent guidance. Eero, I truly admire your enormous knowledge, diligence and enthusiasm in science. I have learned from the best. Marika, your pioneering work in ESTER has been really inspirational and paved the road for the rest of us.

I warmly thank the members of my thesis follow-up group; Docent Minna Ruddock, Professor Kaisa Tasanen-Määttä and Merja Kallio, Ph.D., for their kind guidance. I also want to warmly acknowledge Professor Riitta Veijola for being my degree supervisor. I am indebted to Professor Anne Monique Nuyt and Docent Jaana Pihkala for careful pre-review of my thesis. I also thank Nick Bolton, Ph.D., for revising the English language of the thesis. I am honoured that Dr. Adam Lewandowski accepted the invitation to be my opponent.

I want to express my gratitude to the professionals in NFBC 1986, ESTER, HeSVA and McMaster Cohorts, whose amazing work before me has enabled this dissertation; Professors Johan Eriksson, Marjo-Riitta Järvelin, Katri Räikkönen, Sture Andersson, Katherine Morrison, Louis Schmidt, Saroj Saigal, Mikko Tulppo and Docent Marja Vääräsmäki. I wish to acknowledge all the hard-working scientists and research personnel in these studies; specifically my dear co-authors Ph.D.s Marjaana Tikanmäki, Karen Mathewson, Antti Kiviniemi, Petteri Hovi, Hanna-Maria Matinolli, Riikka Pyhälä, Ryan Van Lieshout, and Elizabeth Gunn, M.Sc.. I particularly wish to thank you Marjaana for your warm-hearted peer support and friendship and for the countless times you have rescued me with your superb research skills. I also want to express my deepest gratitude to you Karen for your and your family's extraordinary hospitality during my research visit to Canada, for the vast amount of work you have done and the for advice you have given to me. Your professionalism is truly inspiring.

My dear study-group fellows; Pieta Näsänen-Gilmore, Suvi Alenius, Maiju Mikkonen, Julia Suikkanen, Markku Nurhonen, Elina Keikkala, Anna Pulakka, Peija Haaramo, Johan Björkqvist and others – my warmest thanks for all your support and friendship home and away. I am grateful for the unforgettable moments I have had the pleasure to experience with you in our conference tours. I also want to thank Sarianna Vaara and all other colleagues in the Kastelli Research Center for your help and support during these years.

Finally, my deepest gratitude goes to my family. My dear sister Raisa, "The docent on duty", without your wisdom and everlasting kind support in practical research problems I would have been lost. I also want to take this opportunity to thank you and your family for the vital support you gave to help me navigate through the difficult times in my personal life. My mother Kristiina, your help and support in taking care of my sons has been crucial and you were always there when needed. My father Jaakko, I wish to thank you for your guidance and encouragement throughout the process. My beloved Eeva, I wish to express my deepest love and gratitude to you for your patience and continuous support during these years. Lastly, my warmest thanks go to my clever and talented sons Vili, Riku and Jere. Although you have probably been exposed to the early-life adversity of a father struggling with his thesis, I am confident that you all have bright futures ahead in whatever you want to do!

Kajaani, February 2021 Risto Karvonen

Abbreviations

ABP	Ambulatory blood pressure
AGA	Appropriate for gestational age
ANS	Autonomic nervous system
AV	Atrioventricular
BMI	Body mass index
BP	Blood pressure
BRS	Baroreflex sensitivity
CI	Confidence interval
CO	Cardiac output
CVD	Cardiovascular disease
CVLM	Caudal ventrolateral medulla
DBP	Diastolic blood pressure
DoHAD	Developmental origins of health and disease
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EDR	ECG-derived respiration
ELBW	Extremely low birth weight
EMD	Electromechanical delay
EPT	Early preterm
ESTER	Preterm Birth and Early-Life Programming of Adult Health and Disease study
FFT	Fast Fourier transformation
FGR	Fetal growth restriction
FMBR	Finnish Medical Birth Register
GA	Gestational age
HeSVA	The Helsinki Study of Very Low Birth Weight Adults
HF	High frequency
HFnu	High frequency in normalized units
HFP	HF power
HR	Heart rate
HRR	Heart rate recovery
HRR30s	Peak HR – HR at 30 seconds after exercise
HRR60s	Peak HR – HR at 60 seconds after exercise
HRRslope	Maximum 30s HRR slope during 60s recovery period
HRV	Heart rate variability

ICT	Isovolumic contraction time
LBW	Low birth weight
LF	Low frequency
LFnu	Low frequency in normalized units
LF/HF	The ratio between LF and HF
LFP	LF power
lnHF	Natural logarithm of high frequency power
lnLF	Natural logarithm of low frequency power
LPT	Late preterm
LV	Left ventricle
M	Men
NA	Nucleus ambiguous
NBW	Normal birth weight
NFBC	Northern Finland Birth Cohort
NN50	Number of NN interval differences greater than 50ms
NR	Not reported
NS	Not statistically significant
NTS	Nucleus of the solitary tract
N.U.	Normalized unit
P	P-value
PDS	Power spectral density
Peak HR	Mean HR at the time of step test cessation
PEP	Pre-ejection period
pNN50	Proportion of NN50 divided by total number of NN intervals
PNS	Parasympathetic nervous system
PSD	Power spectral density
Ptot	Total power
rMSSD	Root mean square of successive differences
RR, RRI	Cardiac R-wave interval (heart period)
RSA	Respiratory sinus arrythmia
RVLM	Rostral ventrolateral medulla
SA	Sinoatrial
SBP	Systolic blood pressure
SD	Standard deviation
SDNN	Standard deviation of the NN intervals
SES	Socioeconomic status
SGA	Small for gestational age

SI	Stress index
SNS	Sympathetic nervous system
SV	Stroke volume
TINN	Baseline width of the RR interval histogram
VLBW	Very low birth weight
VLF	Very low frequency
W	Women
WHO	World Health Organization

Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Sipola-Leppänen M*, Karvonen R*, Tikanmäki M, Matinolli HM, Martikainen S, Pesonen A, Räikkönen K, Järvelin M, Hovi P, Eriksson JG, Vääräsmäki M, Kajantie E. (2015). Ambulatory blood pressure and its variability in adults born preterm. *Hypertension,* 65(3), 615-621.

II Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, Tulppo M, Vääräsmäki M, Kajantie E. (2019). Cardiac autonomic function in adults born preterm. *The Journal of Pediatrics,* 208, 96-103.

III Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, Tulppo M, Vääräsmäki M, Kajantie E. (2019). Post-exercise heart rate recovery in adults born preterm. *The Journal of Pediatrics,* 214, 89-95.

IV Karvonen R, Mathewson KJ, Pyhälä R, Gunn E, Tikanmäki M, Kiviniemi A, Hovi P, Andersson S, Räikkönen K, Van Lieshout R, Schmidt L, Saigal S, Morrison K, Kajantie E. Sex-specific differences in cardiac and blood pressure regulation in very and extremely low birth weight survivors: A 10-year multi-center study. (Manuscript submitted).

*Equal contribution.

Contents

1 Introduction

Each year, roughly 15 million live-born infants, one out of nine, are born preterm throughout the world (Blencowe *et al.* 2012, Chawanpaiboon *et al.* 2019). Many advances in neonatal care in recent decades have greatly improved survival of the smallest infants born preterm. These advances have introduced a new cohort of adults born preterm to the world. These individuals born preterm, or preterm at very or extremely low birth weights are exposed to multiple adversities in early life. Compared with their peers born at term, developed in a natural fetal environment, preterm infants continue their early development in a substantially different environment, such as in neonatal intensive care. Earlier research has shown that these early adversities may bear long-lasting effects on later health among those born preterm. Early programming has been proposed to lead to permanent changes in body composition, body function and metabolism, contributing to adult disease (Barker *et al.* 2007).

Preterm birth, and preterm birth at very low birth weight have been associated with several increased risks of cardiometabolic disease in adulthood and with increased rates of manifest cardiovascular disease such as hypertension, heart failure, type 2 diabetes, metabolic syndrome and ischaemic heart disease (Parkinson *et al.* 2013, Kajantie *et al.* 2014, Sipola-Leppänen *et al.* 2014 and 2015, Luu *et al.* 2016, Crump *et al.* 2019, Lewandowski *et al.* 2020). Though the majority of preterm births are late preterm, most of the earlier research has focused on adults born with extremely or very low birth weight or born very preterm. High blood pressure is the leading risk factor globally as regards death and cardiovascular disease, accounting for more than 10 million deaths annually (Lim *et al.* 2010, Stanaway *et al.* 2018). The mechanisms that lead to elevated blood pressure in those born preterm are not clear. Impaired autonomic regulation, an important risk factor of cardiovascular morbidities, may be one mechanism contributing to elevated blood pressure and other cardiovascular risk factors (Tsuji *et al.* 1996, La Rovere *et al.* 1998, Thayer & Lane 2007).

The goal of this thesis was to evaluate the association between preterm birth, across its whole range, and risk factors of cardiovascular disease in three cohorts of healthy adults. We evaluated blood pressure, blood pressure variability, autonomic sympathetic and parasympathetic regulation of the heart, and heart rate recovery after exercise among those born preterm. We also evaluated whether the associations between preterm birth and elevated risks for cardiovascular disease could be explained by body composition, reduced physical activity or sex.

2 Review of the literature

2.1 Preterm birth

2.1.1 Prevalence of preterm birth

Approximately 15 million infants (11% of all live births) are born preterm globally each year (Blencowe *et al.* 2012, Chawanpaiboon *et al.* 2019). The number of preterm births varies substantially by region: in 2010, in Northern European countries the preterm birth rate was around 5%, while it was 18% in some African countries, and over 60% of all preterm infants were born in South Asia and sub-Saharan Africa (Blencowe *et al.* 2012).

2.1.2 Definition of preterm birth

The World Health Organization (WHO 1977) categorizes births into three gestational-age groups according to completed gestational age:

1. Pre-term birth: < 37 completed weeks (less than 259 completed days) of gestation
2. Term birth: 37 to 41 completed weeks (259 to 293 days) of gestation
3. Post-term birth: 42 or more completed weeks of gestation

Preterm birth may be further divided into the following subcategories by gestational age (Engle *et al.* 2007, Blencowe *et al.* 2012):

1. Extremely preterm (< 28 completed weeks)
2. Very preterm (28 to < 32 completed weeks)
3. Moderately preterm (32 to ≤ 36 completed weeks)

However, as the majority of preterm births occur between 34 to 36 gestational weeks, moderately preterm birth may be further split into a late-preterm group (34 to 36 completed weeks) and to a group born at weeks 32 – 33, which also can be referred to as moderately preterm (Engle *et al*. 2007). In 2010, 84% of preterm-born individuals were born moderately or late preterm, 10% were born very preterm and 5% extremely preterm (Blencowe *et al.* 2010). In this thesis, the categorization of preterm births follows that used in recruiting participants of the ESTER cohort study (Sipola-Leppänen 2015):

1. Early preterm (< 34 completed weeks)
2. Late preterm (34 to < 36 completed weeks)
3. Term (37 or more completed weeks)

Subgroups of infants born preterm can also be defined on the basis of their birth weight:

1. Extremely low birth weight (ELBW; < 1000 g)
2. Very low birth weight (VLBW; < 1500 g)
3. Low birth weight (LBW; < 2500 g)

However, a weight-based definition of preterm birth does not take into account gestational age at the time of birth or other aspects which might affect weight, such as intrauterine growth restriction. Therefore the small-for-gestational-age criteria (SGA; more than two standard deviations below the mean, or < 10^{th} percentile) are commonly evaluated when weight-based categorization is applied. SGA is defined on the basis of birth-weight curves, which might vary significantly depending on the referred standard which may be based either on measured birth weights or fetal weights estimated by fetal ultrasound measurements. In this thesis birth weight SD scores were calculated according to Finnish standards (Pihkala *et al.* 1979).

2.1.3 Aetiology and risk factors of preterm birth

As illustrated in Figure 1, obstetric precursors with their approximate shares of preterm births can be categorised in three groups (Goldenberg *et al.* 2008).
The most common indications for induced preterm labour include pre-eclampsia or eclampsia and intrauterine growth restriction (IUGR), while the preterm births initiated spontaneously or by preterm premature rupture of the membranes (PPROM) are the result of multiple causes such as infection, inflammation, uteroplacental ischaemia, decidual senescence, cervical or vascular disease, breakdown of maternal-fetal tolerance, stress, uterine overdistension and unknown reasons (Romero *et al.* 2014, Goldenberg *et al.* 2008). The aetiology is not perfectly understood and the precise causal mechanisms often cannot be defined; therefore, risk factors associated with preterm birth have been sought (Goldberg *et al.* 2008).

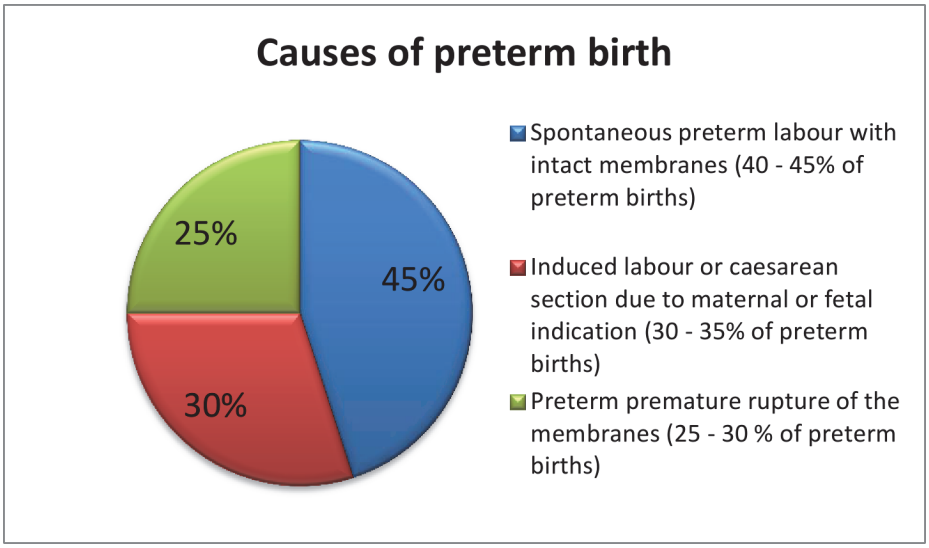


Fig. 1. Obstretic precursors of preterm birth. Modified from Goldenberg et al. 2008

The most common maternal, pregnancy-related and medical conditions elevating the risk of preterm delivery are listed below. Many of these conditions may be present at the same time and preterm birth may be the outcome of several risks interacting.

Risk factors of preterm birth:

- Maternal risk factors
  - Ethnic background
  - Single marital status
  - Close temporal proximity of previous delivery
  - Low socioeconomic and educational status
  - Low and high maternal age
  - Hard physical labour under stressful conditions
  - Previous preterm delivery
  - Obesity
  - Low BMI
  - High levels of psychosocial stress
  - Smoking

  - Heavy alcohol use
  - Use of cocaine and heroin
- Pregnancy-related risk factors:
  - Multiple pregnancy
  - Placenta praevia
  - Placental abruption
  - Polyhydramnios and oligohydramnios
- Maternal medical conditions:
  - Abdominal surgery during 2nd or 3rd trimester
  - Thyroid disease
  - Asthma
  - Diabetes
  - Hypertension
  - Depression

  (Goldberg et al. 2008, Blencove et al. 2012, Romero et al. 2014)

2.2 Developmental origins of health and disease (Dohad)

In the 1980s, epidemiologist David Barker and colleagues introduced the theory that undernutrition in the womb was an important early origin of adult cardiac and metabolic disorders as a result of fetal programming, which leads to permanent changes in body composition, function and metabolism and contributes to adult disease (Barker 2007). "Barker's hypothesis" emerged from earlier epidemiological findings in birth- and death-record studies, which revealed geographic correlation between infant mortality and certain causes of adult death when the surviving infants were adults; there was a connection between prenatal nutrition and late-onset coronary artery disease and a connection between size at birth with rates of adult death from ischaemic heart disease (Barker 1986, Barker *et al.* 1989, Barker *et al.* 1993). "Barker's hypothesis" was then expanded to cover the long-term effects of the length of gestation, in addition to birth weight only.

Later on, "Barker's hypothesis" was strengthened with mounting evidence and has been extended to the widely accepted Developmental Origins of Health and Disease (DOHaD) theory. The DOHaD theory suggests that prevailing conditions during sensitive early developmental periods program human tissues

and organs in a way that leads to altered function throughout life when adjusting to prevailing environmental conditions (Barker 1998, Gluckmann 2008, Kajantie *et al.* 2014). This altered function may then appear as an increased risk of chronic disease.

The DOHaD field has since further expanded to cover the effects of gestational age, in addition to birth weight, on later disease. Research has indeed shown that those born preterm at very low birth weight have a higher incidence of cardiovascular disease (Barker *et al.* 1989, Barker *et al.* 2005, Osmond *et al.* 1993, Kajantie *et al.* 2014 , Markopoulou *et al.* 2019, Lewandowski *et al*. 2020), a higher risk of ischaemic heart disease (Crump *et al.* 2019), higher rates of impaired glucose regulation (Hovi *et al*. 2007, Morrison *et al.* 2016, Markopoulou *et al.* 2019), a higher risk of early heart failure (Carr *et al.* 2017), higher all-cause mortality in young adulthood (Crump *et al*. 2011a), higher blood pressure and more hypertension (Sipola-Leppänen *et al.* 2015, Hovi *et al.* 2016. Crump *et al.* 2011b). In women born preterm, higher rates of pre-eclampsia, gestational diabetes and gestational hypertension have been reported (Boivin *et al.* 2012).

2.3 Cardiovascular disease

2.3.1 Epidemiology, pathophysiology and significance

Cardiovascular diseases (CVDs) are the leading cause of death globally, causing up to 17 million (37%) premature deaths in 2015 (World Health Organization 2017). CVDs are disorders affecting the heart and blood vessels and can be divided into two groups (Mendis *et al.* 2011):

1. CVDs due to atherosclerosis:
   - Ischaemic heart disease or coronary artery disease (heart attack)
   - Cerebrovascular disease (stroke) and
   - Diseases of the aorta and arteries (including hypertension and peripheral vascular disease)
2. Other CVDs:
   - Congenital heart disease
   - Rheumatic heart disease and
   - Cardiomyopathies and cardiac arrhythmias

In addition to these, the WHO also considers deep vein thrombosis and pulmonary embolism as CVDs (World Health Organization 2017). 85% of CVD deaths are caused by heart attack or stroke. The most important behavioural, metabolic and intermediate risks (those affected by behavioural choices) and other risk factors of heart attack and stroke are presented below. Of these risks, hypertension is the leading risk factor as regards death and disease in adults, accounting for up to 13% of global deaths, followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight or obesity (5%) (Mendis *et al.* 2011, Lewington *et al.* 2002, Lim *et al.* 2012). Most deaths associated with these risks are due to CVDs. Atherosclerosis is one of the main underlying processes leading to coronary artery disease and stroke, and atherosclerotic cardiovascular disease starts early, even in childhood, with the severity of the disease increasing with the number of cardiovascular risks listed below (Mendis *et al.* 2011, Berenson *et al.* 2008). The current study is focused on the aetiology of CVDs related to atherosclerosis and on the risks and mechanisms by which these risks, especially high blood pressure, are affected by preterm birth.

Risk factors of cardiovascular disease:

- Behavioural
  - Unhealthy diet
  - Physical inactivity
  - Tobacco smoking
  - Harmful use of alcohol
- Metabolic or intermediate risks
  - High blood pressure
  - Raised blood glucose
  - Raised blood lipids
  - Overweight and obesity
- Other
  - Poverty and low educational status
  - Advancing age
  - Gender (Male)
  - Inherited disposition

– Psychological factors (stress, depression)
– Air pollution
– Other risk factors

(Berenson *et al.* 2008, Mendis *et al.* 2011, Lim *et al.* 2012, World Health Organization 2017)

2.3.2 Blood pressure and blood pressure variability

High blood pressure is globally the leading single risk factor of death and cardiovascular disease, which accounted for 9.4 million (95% CI 8.6 to 10.1) deaths in 2010 and 10.4 million (95% CI 9.4 to 11.5) deaths in 2017 (Lim *et al.* 2010, Stanaway *et al.* 2018). In 2010, 31.1% (95% CI 30.0% – 32.2%) of the world's adults had hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or use of antihypertensive medication) (Mills *et al.* 2016). High blood pressure is strongly and directly related to vascular (and overall) mortality at levels down to at least 115/75 mmHg, with no evidence of a threshold (Lewington *et al*. 2002).

Blood pressure variability has been identified as an independent risk factor of cardiovascular disease: increased short-term (ambulatory) variability in daytime SBP has been associated with increased all-cause mortality (hazard ratio 1.10, 95% CI 1.04 to 1.16) (Stevens *et al.* 2016, Zawadzki *et al.* 2017). 24-Hour BP variability and awake SBP variability independently predict organ damage, and 24-hour BP variability predicts atherosclerosis (Frattola *et al.* 1993, Tatasciore *et al.* 2007, Mancia *et al.* 2010). Enhanced night-time SBP variability has been associated with an excess risk of cardiac events in hypertensive patients (Verdeccia *et al.* 1994, Verdeccia *et al.* 2007). Loss of nocturnal blood-pressure decline (non-dipping) has been shown to predict organ damage and cardiovascular mortality independently of blood pressure (Ohkubo *et al.* 2002, Salles *et al.* 2016).

2.4 Cardiac regulation

2.4.1 Blood pressure regulation

Cardiac output is the product of heart rate (HR) and stroke volume (SV), describing the amount of blood the heart pumps in a minute. Mean arterial pressure (MAP) is a product of cardiac output and total peripheral resistance.

Cardiac output and peripheral resistance are under the control of arterial baroreflex and autonomic control system. At rest, heart rate is mainly controlled by the parasympathetic vagus nerve, and vascular tone is sympathetically mediated (Wehrwein *et al.* 2013). Heart rate is an outcome of interplay between the sympathetic and parasympathetic nervous systems, where sympathetic activation of the autonomic nervous system increases the heart rate, and parasympathetic (vagal) activity decreases it. Heart rate is mainly controlled by the autonomic nerves, but it is also regulated by baroreceptors, chemoreceptors, pulmonary inflation, atrial receptors, and ventricular receptor reflexes. Myocardial performance (e.g. contractility and heart rate) is also regulated by several hormones, such as epinephrine, adrenocortical steroids, thyroid hormones, insulin, glucagon, and anterior pituitary hormones. Alterations in blood O_2, CO_2 and H^+ concentrations also alter cardiac function directly by ion channels and by reflex pathways via central and peripheral chemoreceptors (Pappano & Wier 2013). While the autonomic nervous system controls heart rate and thus blood pressure in the short term (within seconds), the renin-angiotensin-aldosterone system (RAAS) controls blood pressure in the longer term (minutes to days), contributing to changes in extracellular fluid volume and blood pressure homeostasis by adjusting the amount of renin in the circulation (Carey *et al.* 2018). Renin, angiotensin II and aldosterone act together to elevate arterial pressure by way of sodium and water reabsorption in the kidneys (increasing blood volume) and by increasing vascular tone (Fountain & Lappin 2020). Blood pressure regulation is a highly integrated and complex system with multiple overlapping systems acting simultaneously. In the present study, the focus is on the autonomic control part of blood pressure regulation.

2.4.2 Autonomic cardiac regulation

Autonomic nervous system

The autonomic nervous system is the primary mechanism for controlling human ‘fight or flight’ and ‘rest and digest’ responses. Autonomic control is largely operated unconsciously and it regulates heart rate, digestion, respiration, the pupillary response, urination, and sexual functions. The autonomic nervous system can be divided in two branches; sympathetic (SNS) and parasympathetic (PNS) nervous systems, which operate simultaneously and commonly have

opposite effects in target organs. Heart rate is mainly controlled by the autonomic nervous system and the discussion in the present study is restricted to autonomic control of the heart rate.

Sympathetic nerves emerge from the spinal-cord roots from thoracic segment T_1 to lumbar segment L_2 and enter the paravertebral chain of ganglia. Sympathetic preganglionic nerves are rather short and synapse mainly in stellate and middle cervical ganglia, from which relatively long postganglionic nerves lead to the heart and other target organs. The sympathetic postganglionic neurotransmitter is norepinephrine, which acts on β_1 receptors on the sinoatrial (SA) node and increases Ca^{++} current in the SA action potential, eventually accelerating firing in the SA node, the natural pacemaker region of the heart.

Parasympathetic nerves enter or originate in the spinal cord in cranial segments III, VII, IX and X and in sacral segments S_2 – S_4. Parasympathetic regulation of the heart originates in the medulla oblongata, from where preganglionic nerve fibres pass through the neck as the cervical vagus nerves; they pass through the mediastinum and synapse with postganglionic nerves on the epicardial surface or within the heart. Most of the cardiac parasympathetic ganglia are located near the SA node or atrioventricular (AV) connective tissue. Vagal stimulation depresses or even stops the SA node from firing for several seconds and inhibits AV conduction by release of the neurotransmitter acetylcholine. Muscarinic acetylcholine receptors react by increasing cardiac cell membrane K^+ conductance, enabling a rapid vagal effect on SA and AV nodal function (latency time 50 to 100 ms). Therefore, when vagal nerves are stimulated, the heart rate decreases fast, attaining a steady-state value as rapidly as in 1-2 cardiac cycles. Similarly, the heart rate returns quickly to its basal level when vagal activation is discontinued. The sympathetic response on the other hand, due to the neurotransmitter norepinephrine, decays more gradually (Schmidt & Thews 1989, Noble *et al.* 2010, Pappano & Wier 2013).

Although sympathetic and vagal modulations interact constantly, under resting conditions, vagal tone is more prominent and variations in heart rate are mostly dependent on vagal activity (Levy 1971, Chess *et al.* 1975). Parasympathetic effects overcome sympathetic influences as a result of two independent mechanisms: cholinergic effects induce a reduction of norepinephrine released in response to sympathetic activity, and there is cholinergic attenuation of the norepinephrine stimulus (Task Force 1996).

Autonomic dysregulation and cardiovascular disease

The connection between altered cardiac autonomic control and increased risks of cardiometabolic disease, increased morbidity and increased overall mortality has been consistently observed in a number of studies. Altered cardiac control has been connected with an increased risk of new cardiac events (angina pectoris, myocardial infarction, coronary heart disease death, or congestive heart failure) (Tsuji *et al.* 1996, Dekker *et al.* 2000), increased mortality in patients with recent myocardial infarction (Kleiger *et al.* 1987, Bigger *et al.* 1992, Bigger et al.1996, La Rovere *et al.* 1998, Dekker *et al.* 2000, Huikuri *et al.* 2000), increased mortality in patients with chronic heart failure (James *et al.* 1998), increased mortality in patients without a history of cardiovascular complications (Kiviniemi *et al.* 2014), and all-cause mortality (Bigger *et al.* 1992, Tsuji *et al.* 1994, Dekker *et al.* 2000, Gerritsen *et al.* 2001 Thayer *et al.* 2010).

Autonomic dysfunction may be especially hazardous for patients already at an elevated risk of cardiovascular disease (diabetics, hypertensive patients, patients with a history of CVD) (Gerritsen *et al.* 2000) Furthermore, evidence suggests that autonomic imbalance is associated with increased CVD risk factors (Thayer *et al.* 2010), such as hypertension (Liao *et al.* 1996, Sighn *et al.* 1998, Schroeder *et al.* 2003), diabetes (Liao *et al.* 1995, Sighn *et al.* 2000, Carnethon *et al.* 2003), high cholesterol (Kupari *et al.* 1993, Christensen *et al.* 1999), smoking (Hayano *et al.* 1990, Yotsukura *et al.* 1998, Minami *et al.* 1999), physical inactivity (Rossy & Thayer 1998, Rennie *et al.* 2003, Sloan *et al.* 2003), obesity (Pertetta *et al.* 1995, Karason *et al.* 1999) and work stress (Kang *et al.* 2004, Hintsanen *et al.* 2007).

Heart rate recovery (HRR)

At the onset of physical exercise, the increase in heart rate results primarily from withdrawal of the parasympathetic nervous control, and sympathetic activation progresses and maintains exercise tachycardia more gradually when the exercise reaches more vigorous levels (Arai *et al.* 1989, Pierpont *et al.* 2013, Kluess *et al.* 2000). After the cessation of exercise, parasympathetic reactivation and sympathetic withdrawal both contribute to heart rate recovery (HRR), but the relative contributions from each arm are not fully clear (Pierpont *et al.* 2013). An earlier study by Savin *et al*. suggested that sympathetic withdrawal plays a bigger role in immediate HRR after peak exercise, with the parasympathetic arm having

an effect later during HRR (Savin *et al.* 1982). However, Imai *et al.* found that HRR 30 seconds after exercise was almost solely due to parasympathetic reactivation and the finding was supported by Perini *et al.*, who found plasma epinephrine peaks 1 min after high-level exercise, consistent with high levels of sympathetic activity remaining in the early phases of exercise recovery (Imai *et al.* 1994 & Perini *et al.* 1989).

Heart rate remaining higher after exercise (decreased HRR), a likely indicator of decreased parasympathetic activity, is an independent and powerful predictor of cardiovascular disease, heart failure and overall mortality (Cole *et al.* 1999, Nishime *et al.* 2000, Watanabe *et al.* 2001, Bilsel *et al.* 2006, Qui *et al.* 2017). Abnormal HRR, even after submaximal exercise, has been shown to predict death in an otherwise healthy cohort (Cole *et al.* 2000).

2.4.3 Baroreflex and baroreflex sensitivity

The baroreceptor reflex is the most important regulating mechanism as regards short-term arterial blood pressure and heart rate. It helps to maintain blood pressure at nearly constant levels during changes in posture, exercise, emotion, and other conditions (Benarroch 2008, Adriessen *et al.* 2005, Lanfranchi & Somers 2002). The baroreflex reacts to sudden changes in systemic blood pressure by adapting heart rate and vascular resistance via autonomic nervous system regulation: heart rate is mediated by both parasympathetic (vagal) and sympathetic modulation and vascular resistance is mainly mediated by the sympathetic nervous system (Adriessen *et al.* 2005).

As illustrated in Figure 2, the sensors in the baroreflex are located mainly in the aortic arch and in the carotid artery sinuses. Baroreceptors are mechanoreceptors that respond to stretching of the blood vessels caused by a change in arterial pressure and they transduce the stretch into an electrical signal in the afferent nerves connected to the medulla. The afferent aortic depressor nerve and the carotid sinus nerve synapses in the nucleus of the solitary tract (NTS). The parasympathetic baroreflex synapses in the nucleus ambiguous (NA) before entering the sinoatrial node of the heart via the vagus nerve. The sympathetic side of the baroreflex goes through the caudal ventrolateral medulla (CVLM), continues through the rostral ventrolateral medulla (RVLM) before entering the interomediolateral cell column in the spinal cord before finally reaching heart and blood vessels (Wehrwein & Joyner 2013).

The afferent discharges initiated by the baroreceptors due to changes in arterial pressure trigger reflex adjustments that buffer or oppose the changes in blood pressure: when arterial pressure is increased, the baroreflex initiates higher parasympathetic activation and inhibits sympathetic activation, resulting in deceleration of heart rate, decreased heart contractility, lower vascular resistance and venous return. Vice versa, a decrease in arterial pressure leads to deactivation of baroreceptors and thus enhanced sympathetic activity and vagal inhibition, leading to accelerated heart rate, increased cardiac contractility, elevated vascular resistance and increased venous return (Lanfranchi & Somers 2002, La Rovere *et al.* 2008). There are significant differences in the time delay mediated by the parasympathetic and sympathetic efferents: a rapid rise in arterial pressure produces an immediate parasympathetic reaction (within 200 to 600ms), whereas the reaction to sympathetic activation occurs after a 2-3s delay (La Rovere *et al.* 2008). Therefore, the baroreflex ability to control rapid changes in blood pressure is due to parasympathetic (vagal) but not sympathetic activity (La Rovere *et al.* 2008).

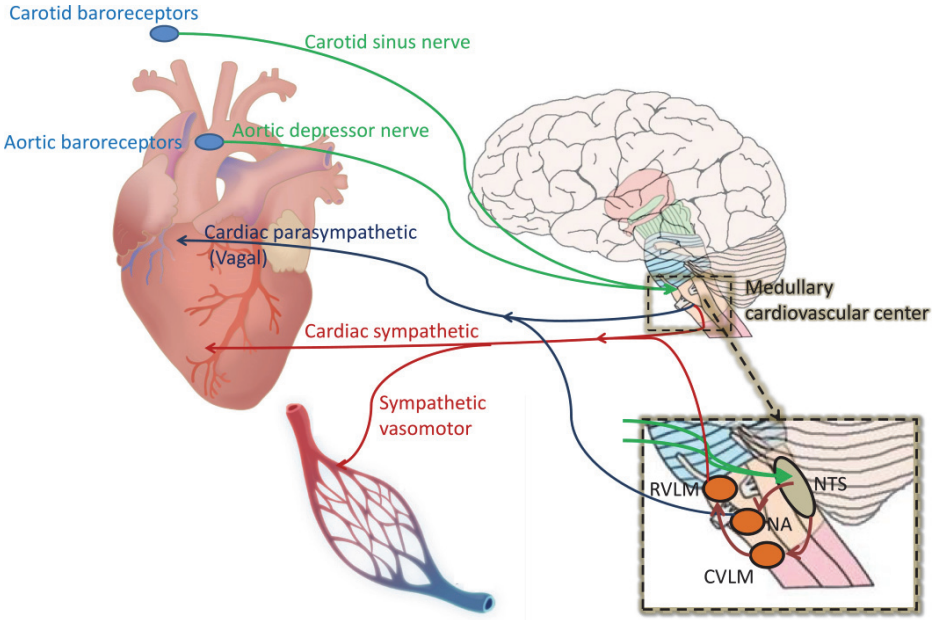


Fig. 2. Simplified illustration of the baroreflex mechanism. Abbreviations: CVLM, caudal ventrolateral medulla; NA, nucleus ambiguous; NTS, nucleus of the solitary tract; RVLM, rostral ventrolateral medulla. Modified from Wehrwein & Joyner 2013.

Baroreflex sensitivity (BRS) is used as a measure of the cardiovascular autonomic system. It is classically defined as the slope of the blood pressure vs. beat-to-beat relationship: beat-to-beat interval change (ms) per blood pressure change (mmHg), plotted during a change in blood pressure induced by the administration of adrenaline or sodium nitroprusside (Smyth *et al*. 1969, Korner *et al.* 1974, Fritsch *et al.* 1989). However, spectral analyses have offered the opportunity to use spontaneous changes in blood pressure and beat-to-beat intervals to create a power spectrum without the need of pharmacological intervention: cross-spectral analysis of blood pressure and beat-to-beat interval fluctuations in the low-frequency band (LF; 0.04 to 0.15 Hz) have been shown to be useful in creating an estimate of BRS (Andriessen *et al.* 2005, de Boer *et al.* 1987, Robbe *et al.* 1987, Honzíková *et al.* 1992, Head *et al.* 2001). Low BRS has been associated with an increased risk of cardiac mortality in patients with prior myocardial infarction (La Rovere *et al.* 1998) and among individuals without any history of major cardiovascular complications (Kiviniemi *et al.* 2014).

2.4.4 Measurements of cardiac autonomic control

Heart rate variability

Cardiac autonomic control can be noninvasively assessed through analysing the oscillation between consecutive heart beats, known as heart rate variability (HRV). HRV can be analysed from uncontrolled long-term (24-hour) ECG recordings or from laboratory-controlled short-term (2 – 5 min) recordings. HRV measurements can be divided into time-domain methods, frequency-domain methods and geometric methods. This study is focused on the analysis of short-term HRV analysis in time and frequency domains. Geometric methods were out of the scope of this study due to the fact that they would have required long-term (24-hour) ECG recordings for appropriate analysis (Task Force 1996).

Time-domain methods

In time-domain methods, each QRS complex is detected from continuous ECG records and the intervals between successive normal-to-normal (NN intervals) are determined. The simplest way to evaluate time-domain HRV is to calculate the standard deviation of the NN intervals (SDNN). However, SDNN is dependent on

the length of the ECG recording and thus other measures have been developed. The most commonly used time-domain variables are: the root mean square of successive NN interval differences (rMSSD); NN50, the number of NN interval differences greater than 50ms; and pNN50, the proportion of instances of NN50 divided by the total number of NN intervals. All of these time-domain measures are highly correlated with each other. Out of these, calculation of rMSSD is the recommended method for analysing short-term components of HRV and thus was selected as a time-domain measure in this study (Task Force 1996).

Frequency domain

Various spectral methods have been introduced for analysing heart rate variability: power spectral density (PSD) analysis provides an estimate of how variance is distributed as a function of frequency. Spectral HRV analysis provides information on how power (variability) is distributed as a function of frequency. PSD can be evaluated by parametric and non-parametric algorithms, and one of the most common methods used is non-parametric fast Fourier transformation (FFT). As illustrated in Figure 3, spectral analysis by fast Fourier transformation divides the total power of HRV into specific frequency components, representing different underlying rhythms that the HRV signal is assumed to reflect. The power spectrum of HRV can be divided into two main spectral components reflecting the contributions from the two branches of the autonomic nervous system: oscillations of low frequency (LF; 0.04 – 0.15 Hz) are attributed to baroreflex-mediated influences and reflect both sympathetic and parasympathetic activity, and oscillations of high frequency (HF; 0.15 – 0.4 Hz) are attributed to respiratory-related changes (sinus arrhythmia) reflecting vagal (parasympathetic) efferent activity to the heart (Pomeranz *et al.* 1985, Pagani *et al.* 1986, deBoer *et al.* 1987, Task force 1996, Schaffer *et at.* 2014, Yiullarou *et al.* 2017). The LF/HF ratio has traditionally been considered to be a marker of sympathovagal balance (Pagani *et al.* 1986, Malliani *et al.* 1991), though the validity of this marker has been challenged (Billman *et al.* 2013). An illustration of time-domain and frequency-domain results calculated by using Kubios heart rate analysis software (version 3.3.1. https://www.kubios.com) is presented in Figure 4. A selection of time-domain and frequency-domain variables is evaluated in this thesis, and their descriptions and normal values are presented in Table 1 (Task Force 1996, Shafer *et al.* 2014).

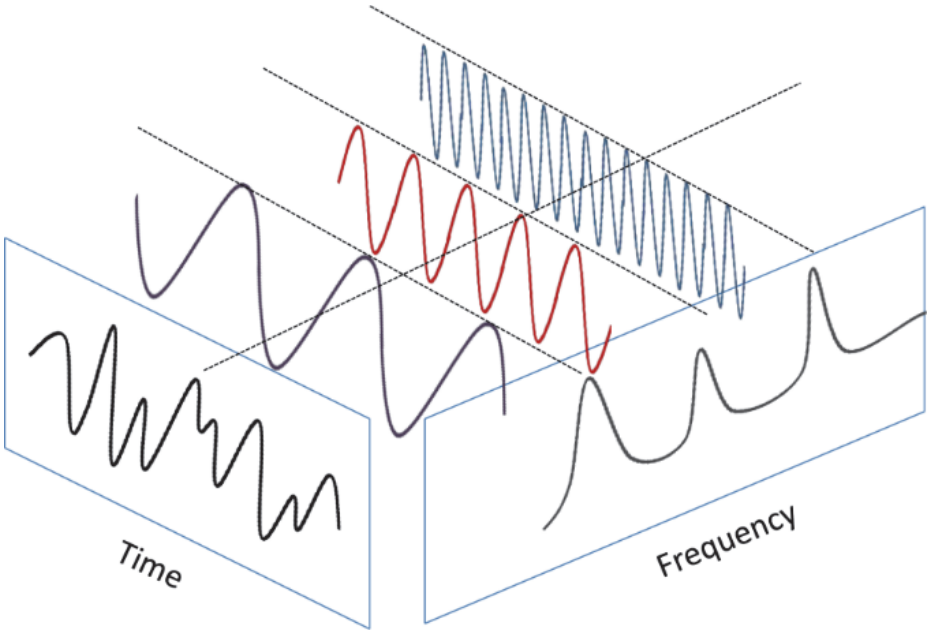
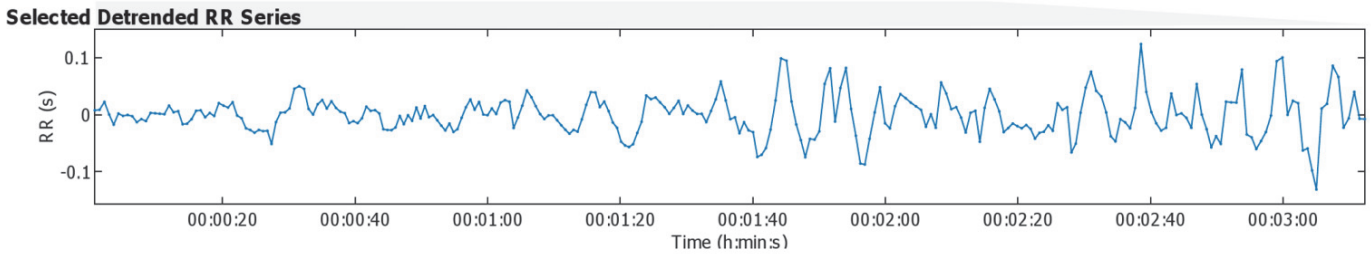


Fig. 3. A simplified illustration of a signal distributed into time- and frequency-domain components (modified from Wikimedia Commons 2021). In this thesis the fast Fourier transformation method was applied in spectral analysis. Spectral analysis divides the total power of HRV into components with different frequencies and amplitudes. The HRV frequency ranges applied are: very low frequency (VLF ≤ 0.04 Hz), low frequency (LF 0.04 – 0.15 Hz) and high frequency (HF 0.15 – 0.40 Hz).

Table 1. Selected time- and frequency-domain HRV measures, their descriptions, normal values and physiological correlates. Modified from Task Force 1996 & Schaffer et al. 2014.

Variable	Unit	Description	Normal values (Mean ± SD)	Physiological correlates in short term HRV recordings
Time domain				
rMSSD^	ms	The square root of the mean of the sum of squares of differences between adjacent NN intervals	27 ± 12	Parasympathetic activity
Frequency domain				
LF	ms^2, %, n.u.	Power in LF range (0.04 – 0.15 Hz)	1170 ± 416	Parasympathetic activity, sympathetic activity and effects mediated by baroreflex.
HF^	ms^2, %, n.u.	Power in HF range (0.15 – 0.4 Hz)	975 ± 203	Parasympathetic activity, heart rate variations related to the respiratory cycle.
LF/HF		Ratio LF [ms^2]/HF[ms^2]	1.5 – 2.0	Sympathovagal balance? Controversial interpretation.

^ HF is an approximate frequency domain correlate of rMSSD



Time-Domain Results

Variable	Units	Value
Mean RR*	(ms)	702
Mean HR*	(bpm)	85
Min HR	(bpm)	74
Max HR	(bpm)	98
SDNN	(ms)	34.2
RMSSD	(ms)	31.7
NN50	(beats)	27
pNN50	(%)	9.89
RR triangular index		7.21
TINN	(ms)	186.0
Stress Index (SI)		12.1

Frequency-Domain Results (FFT spectrum)

Variable	Units	VLF	LF	HF
Frequency band	(Hz)	0.00-0.04	0.04-0.15	0.15-0.40
Peak frequency	(Hz)	0.033	0.110	0.150
Power	(ms^2)	38	806	375
Power	(log)	3.636	6.693	5.926
Power	(%)	3.11	66.08	30.70
Power	(n.u.)		68.20	31.69

Total power	(ms^2)	1220		
Total Power	(log)	7.107		
LF/HF ratio		2.152		
EDR	(Hz)	-		

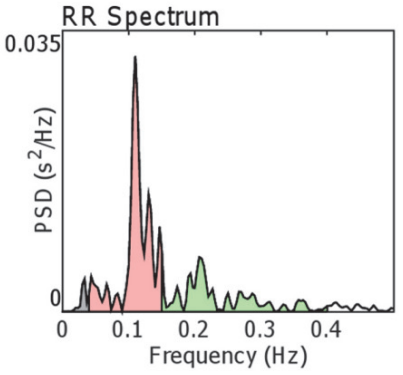


Fig. 4. Illustration of time-domain and frequency-domain HRV variables calculated with Kubios software.

Pre-ejection period (PEP).

Heart rate variability measures are not perfectly equipped to capture sympathetic nervous system activity, mainly due to the simultaneous influence of vagal components (Table 1; Task Force 1996). Pre-ejection period measurement is a non-invasive method to assess cardiac sympathetic activity: under stable cardiac preload and afterload conditions, changes in PEP reflect heart contractility influenced by sympathetic, but not parasympathetic regulation (Larkin and Kasprowicz 1986, Schächinger *et al.* 2001). PEP can be evaluated via thoracic impedance cardiography and is defined as the time elapsed between the electrical initiation of the heartbeat (Q wave in ECG) and the rapid rise of left ventricular pressure up to the level of diastolic aortic pressure, when the aortic valve opens (Figure 5).

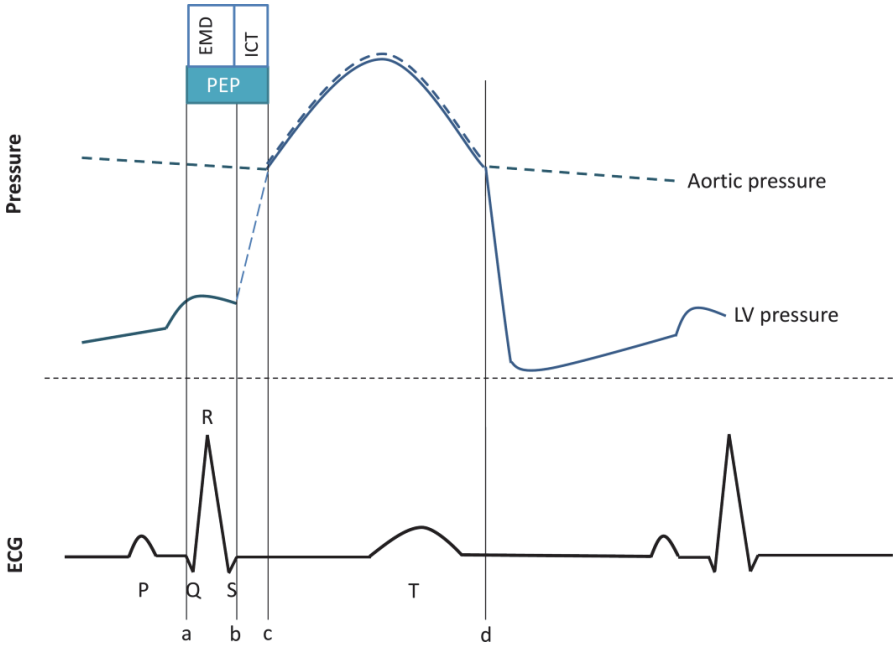


Fig. 5. Simplified illustration of the pre-ejection period: PEP is initiated at Q-wave onset, including electromechanical delay (EMD; a-b), followed by isovolumic contraction time (ICT; b-c). PEP ends with opening of the aortic valve when left ventricular pressure reaches aortic pressure (c). (d) Denotes aortic valve closure. Figure modified from Krohova *et al.* 2017.

2.5 Long-term cardiovascular consequences of being born preterm

The care of preterm neonates has undergone very considerable development in recent decades: assisted ventilation was introduced in the late 1960s, the use of antenatal and postnatal corticosteroids was started in the 1970s, and in the 1980s the use of exogenous surfactant was introduced (Philip 2005). In addition to neonatal resuscitation, current key measures for improving the survival of infants born preterm include thermal care, breastfeeding support and management and prevention of infections (Howson 2012). These advances have changed the prognosis of infants born at ~1kg birth weight in high-resource settings from 95% mortality to 95% survival in 50 years (Philip 2005). This development has introduced a whole new cohort of individuals with a history of very preterm birth at very low birth weight who have now entered into adulthood. The health of these preterm individuals who have now reached adulthood needs to be evaluated, as we still do not know very much about the consequences of preterm birth in adulthood. These individuals were exposed to early adversity in many forms due to preterm birth, which may have had several have long-lasting consequences in later life.

One of the most studied long-term outcomes of preterm birth is related to risk factors of cardiovascular disease. Following list presents some of the main findings concerning long-term consequences of preterm birth related to cardiovascular disease risk:

- Biochemical risk factors
  - Impaired glucose regulation
  - More atherogenic lipid profile
- Behavioural risk factors
  - Lower physical activity and less exercise
  - Increased preference for fatty foods
  - Lower intake of vegetables, fruit and milk products
- Risk factors associated with body composition and function
  - Higher body-fat percentage
  - Lower lean body mass
  - Lower fitness
  - Elevated blood pressure

  - Altered autonomic control
- Cardiovascular remodelling
  - Reduced cardiac reserve
  - Smaller cardiac left and right ventricular volumes
  - Decreased vascularity and increased vascular stiffness
  - Higher pulmonary and systemic vasculature pressure
  - Reduced descending-aorta diameter
  - Lower carotid and brachial arterial distensibility
- Manifest disease
  - Increased rate of hypertension
  - Increased rate of early heart failure
  - Increased rate of metabolic syndrome
  - Higher risk of type 2 diabetes
  - Higher risk of ischaemic heart disease
  - Higher risk of pulmonary vascular disease

  (Lewandowski *et al.* 2020, Hovi P *et al.* 2007, Morrison *et al.* 2016, Mathewson *et al.* 2014, Sipola-Leppänen *et al.* 2014, Sipola-Leppänen *et al.* 2015, Kajantie *et al.* 2004, Kajantie *et al.* 2010b, Kajantie *et al.* 2014, Hovi *et al.* 2007, Kaseva *et al.* 2013, Svedenkrans *et al.* 2013, Parkinson *et al.* 2013 Tikanmäki *et al.* 2014, Luu *et al.* 2016, Carr *et al.* 2017, Raju *et al.* 2017, Matinolli *et al.* 2018, Bates *et al.* 2020, Flahaut *et al.* 2020).

2.5.1 Cardiometabolic outcomes of preterm birth

Preterm birth or preterm birth at ELBW/VLBW has been associated with several increased risks of cardiometabolic disease in adulthood (Parkinson *et al.* 2013, Kajantie *et al.* 2014, Sipola-Leppänen *et al.* 2014, Sipola-Leppänen *et al.* 2015, Luu *et al.* 2016, Raju *et al.* 2017, Markopoulou *et al.* 2019, Lewandowski *et al.* 2020), including impaired glucose regulation (Hovi *et al.* 2007, Morrison et al. 2016), increased rates of type 1 and type 2 diabetes (Crump *et al.* 2019), increased adiposity (Morrison *et al.* 2016, Makopoulou *et al.* 2019), more early heart failures (Carr *et al.* 2017) and increased rates of metabolic syndrome (Sipola-Leppänen *et al.* 2015). Previous research has connected preterm birth with altered myocardial structural and functional differences, reductions in systolic and diastolic function and in altered cardiac right-ventricular ejection

fraction and stroke volume in adulthood (Lewandowski *et al*. 2013a, Lewandowski *et al*. 2013b). In a recent review it was concluded that preterm birth occurring during an important period of fetal cardiovascular development leads to an early physiological shift to a relatively hyperoxic environment with increased systemic and decreased pulmonary vascular resistance, associated with reduced cardiac reserve, smaller cardiac left and right ventricular volumes, decreased vascularity, increased vascular stiffness and higher pulmonary and systemic pressure in later life (Lewandowski *et al.* 2020). Another recent register study showed the first evidence of a link between preterm birth and a higher risk of ischaemic heart disease in adulthood (Crump *et al.* 2019). Probably the most extensively investigated risk factor associated with preterm birth is higher blood pressure (Hovi *et al* 2007, Kajantie *et al.* 2014, Sipola-Leppänen *et al.* 2015), which will be addressed in more detail below.

2.5.2 Office blood pressure in adults born preterm

Office blood pressure refers to blood pressure measured during a clinical visit, commonly carried out by a nurse or a doctor using an automated or auscultatory device. The association between preterm birth and elevated office blood pressure in later life has been established in several studies (Table 2). An accumulating number of studies on adults born preterm or with low or extremely low birth weight have shown higher office SBP in preterm-born individuals when compared with term controls (Irving *et al.* 2000, Kistner *et al.* 2000, Doyle *et al.* 2003, Järvelin *et al.* 2004, Hack *et al.* 2005, Johansson *et al.* 2005, Dalziel *et al.* 2007, Hovi *et al.* 2007, Rotteveel *et al.* 2008, Indredavik Evensen *et al.* 2009, Keijzer-Veen 2010, Lazdam *et al.* 2010, Thomas *et al.* 2011, Kerkhof *et al.* 2012, Lewandowski *et al.* 2013, Tauzin *et al.* 2014, Sipola-Leppänen *et al.* 2015, Juonala *et al.* 2015, Morrison *et al.* 2016, Skudder-Hill *et al.* 2019).

An association between higher office DBP in adulthood and preterm birth has also been reported in many studies (Doyle *et al.* 2003, Johansson *et al.* 2005, Hovi *et al.* 2007, Lazdam *et al.* 2010, Thomas *et al.* 2011, Lewandowski *et al.* 2013, Tauzin *et al.* 2014, Sipola-Leppänen *et al.* 2015, Juonala *et al.* 2015 Morrison *et al.* 2016, Skudder-Hill *et al.* 2019), whereas others have not observed differences in DBP (Kistner *et al.* 2000, Hack *et al.* 2005, Indredavik Evensen *et al.* 2009, Keijzer-Veen 2010). In a meta-analysis covering 10 studies in children and adults (mean age 17.8 years) born preterm at a mean gestational age of 30.2 weeks a 2.5 mmHg (95% CI 1.7 – 3.3) higher office-measured level of SBP was

observed among preterm-born individuals vs. controls (de Jong *et al.* 2012). In a recent individual-participant meta-analysis covering nine VLBW cohorts with a total of 1571 adolescents or young adults born VLBW and 777 controls it was reported that adults born VLBW had 3.4 mmHg (95% CI 2.2 – 4.6) higher systolic blood pressure and 2.1 mmHg (95% CI 1.3 – 3.0) higher diastolic blood pressure, and the differences were more pronounced in women (Hovi *et al.* 2016).

Juonala *et al.* (2015) studied 41-year-old adults born preterm and SGA and found 7.2 mmHg (95% CI 2.3 – 12.1) higher SBP in adults born preterm and SGA compared with adults born preterm and AGA, and 7.3 mmHg (95% CI 5.2 – 9.4) higher SBP in adults born preterm and SGA compared with controls born at term, whereas there were no significant differences in blood pressure between adults born preterm and AGA compared with adults born at term, suggesting that elevated blood pressure is associated with intrauterine growth restriction rather than prematurity *per se.* However, Hovi *et al.* (2016) showed that blood pressure differences between adults born VLBW and controls were associated with maternal pre-eclampsia, but the differences were similar regardless of fetal growth disturbance, multiple birth, maternal smoking or postnatal complications within the VLBW group.

A recent Swedish register study on 18-year-old military conscripts also showed elevated systolic blood pressure and an increased risk of hypertension in subjects born preterm, especially women (Skudder-Hill *et al.* 2019). Another recent meta-analysis covered 20 studies on preterm-born adults (< 37 weeks of gestation) and it was reported that prematurity was associated with 4.2 mmHg (95% CI 3.0 – 5.5) higher systolic blood pressure and 2.3 mmHg (95% CI 1.2 to 3.3) higher diastolic blood pressure (Markopoulou *et al.* 2018). In a large Swedish cohort of individuals born in 1973 – 1979 and followed to ages 25.5 – 37.0, it was shown that individuals born preterm were more likely to be prescribed antihypertensive medication than their peers born at term (Crump *et al.* 2011).

Ambulatory blood pressure in adults born preterm

As presented in Table 3, the association between preterm birth at ELBW/VLBW and elevated 24-hour systolic and diastolic ambulatory blood pressure (ABP) in adulthood has been reported in several studies (Doyle *et al.* 2003, Hovi *et al.* 2010, Roberts *et al.* 2014, Lewandowski *et al.* 2015, Haikerwal *et al.* 2020). Significant differences are observed in both awake and sleep time ambulatory blood pressure (Doyle *et al.* 2003, Roberts *et al.* 2014, Lewandowski *et al.* 2015,

Paquette *et al.* 2018, Haikerwal *et al.* 2020). In a recent meta-analysis covering six studies evaluating ambulatory blood pressure measurements revealed 4.6 mmHg (95% CI 2.0 – 7.2) higher mean 24-hour systolic ABP and 1.7 mmHg (95% CI 0.9 – 2.5) higher 24-hour diastolic ABP in adults born prematurely (Markopoulou *et al.* 2018).

Hovi *et al.* found that blood pressure point estimates on the association between VLBW and 24-hour blood pressure were greater among women than men born VLBW, though the interaction of sex and birth weight group predicting 24-hour BP was statistically significant only for 24-hour diastolic pressure. (Table 3, Hovi *et al.* 2010). Similar observations were made in a later meta-analysis which revealed 3.5 mmHg (95% CI 1.4 to 5.6) higher systolic ABP, and 1.6 mmHg (95% CI 0.04 to 3.1) higher diastolic 24-hour ABP in women born preterm, but no such elevation in men (Parkinson *et al*. 2013). More recently, Haikerwal *et al.* also reported more evident mean differences in ABP among females than males (Haikerwal *et al.* 2020).

2.5.3 Blood pressure variability in adults born preterm

Although elevated systolic blood pressure variability has been connected with increased overall mortality (Stevens *et al.* 2016), progression of organ damage (Frattola *et al.* 1993), triggering of vascular events (Clement *et al.* 2003), and hypertensive left ventricular hypertrophy (Parati *et al.* 2006), blood pressure variability has been less-well studied among preterm-born individuals. Hovi *et al.* (2010) reported 1.1 mmHg higher systolic daytime blood pressure standard deviation in VLBW men compared with term-born men.

Table 2. Mean differences in office blood pressure in adults born preterm compared with controls born at term.

Authors and publication year	Cohort location	Birth years	Cases + controls	Mean age / range (years)	Exposure	Mean difference (mmHg)	
						SBP (95% CI or P)	DBP (95% CI or P)
Irving *et al*. 2000	Edinburgh, UK	1973 – 1975	19 + 27	24	< 2000g	7 (P < 0.001)	5 (NR)
Kistner *et al*. 2000	Stockholm, Sweden	1966 – 1974	15 + 17	26	< 32 weeks	13 (P < 0.001)	5 (P = 0.155)
Doyle *et al*. 2003	Melbourne, Australia	1977 – 1982	156 + 38	18	VLBW	8.6 (3.4 to 13.9)	4.3 (1.0 to 7.6)
Järvelin *et al*. 2004	Northern Finland	1966	273 + 4356	31	< 37 weeks	W: 2.7 (P = 0.015)	W: 1.0 (P = 0.25)
						M: 1.0 (P = 0.59)	M: 0.0 (P = 0.96)
Hack *et al*. 2005	Cleveland, USA	1977 – 1979	195 + 208	20	VLBW	1.9 (-0.2 to 4.1)	0.4 (-1.4 to 2.1)
Johansson *et al*. 2005	Sweden	1973 – 1981	14192 + 275895	18	24 - 28 weeks	1.9 (1.3 – 2.7)	1.9 (0.5 – 7.9)
					29 – 32 weeks	1.4 (1.3 – 1.6)	1.8 (1.1 – 3.0)
					33 – 36 weeks	1.2 (1.2 – 1.3)	1.3 (1.0 – 1.5)
Dalziel *et al*. 2007	Auckland, New Zealand	1969 – 1974	311 + 147	30	< 37 weeks	3.5 (0.9 to 6.1)	NR
Hovi *et al*. 2007	Helsinki, Finland	1978 – 1985	166 + 172	22	VLBW	4.0 (1.5 to 6.5)	3.5 (1.7 to 5.3)
Rotteveel 2008	Netherlands	1983	29 + 30	20	< 32 weeks	W: 9	W: 6
						M: 19 (P < 0.001)	M: 9 (P = 0.002)
Cooper *et al*. 2009	1958 British cohort	1958	279 + 2177	44 – 45	< 37 weeks	NR	2.4 (1.0 to 3.8)
Indredavik Evensen *et al*. 2009	Trondheim, Norway	1986 – 1988	37 + 63	18	VLBW	6.5 (P < 0.01)	2.2 (NS)
Keijzer-Veen *et al*. 2010	Netherlands	1983	29 +30	20	< 32 weeks	8.4 (4.1 to 12.7)	2.0 (-1.9 to 5.9)
Lazdam *et al*. 2010	United Kingdom	1982 – 1985	52 + 32	22 – 26	< 37 weeks	6.7 (P = 0.006)	5.5 (P < 0.001)
Thomas *et al*. 2011	United Kingdom	NR	19 +18	18 – 27	≤ 33 weeks	6.5 (2.2 to 10.8)	5.9 (1.8 to 10.1)
Kerkhof *et al*. 2012	Netherlands	NR	163 + 243	18 – 24	< 36 weeks	2.3 (P < 0.01)	-2.8 (P < 0.001)
Lewandowski *et al*. 2013	United Kingdom	1982 – 1985	102 + 102	23 – 28	< 1850g	8.4 (P < 0.001)	4.2 (P < 0.001)
Tauzin *et al*. 2014	France	1984 – 1985	16 +15	21	< 37 weeks	10 (P < 0.05)	4 (P < 0.05)

Authors and publication year	Cohort location	Birth years	Cases + controls	Mean age / range (years)	Exposure	Mean difference (mmHg)	
						SBP (95% CI or P)	DBP (95% CI or P)
Sipola-Leppänen *et al*. 2015	Northern Finland	1985 – 1989	376 + 344	23	< 34 weeks 34 – 36 weeks	EPT: 3.0 (0.9 to 5.1) LPT: 1.7 (-0.1 to 3.4)	EPT: 2.6 (0.9 to 4.2) LPT: 1.2 (-0.1 to 2.5)
Juonala *et al.* 2015	Finland	1962 – 1977	P-AGA: 87 P-SGA: 39 Term: 1630	40 – 41	< 37 weeks SGA (-1 SD)	P-AGA: -0.6 (P = 0.91) P-SGA: 7.2 (P < 0.001)	P-AGA: 0.4 (P = 0.57) P-SGA: 4.3 (P = 0.004)
Morrison *et al*. 2016	Ontario, Canada	1977 – 1982	94 + 88	31	ELBW	4.9 (P = 0.004)	3.2 (P = 0.02)
Skudder-Hill *et al.* 2019	Sweden	1973 – 1988	W: 299 + 4933 M: 18320 + 348079	18	< 37 weeks	W: 3.8 (P < 0.001) M: 1.5 (1.4 to 1.7)	W: 1.1 (P = 0.026) M: 0.4 (0.2 to 0.5)
Haikerwal *et al.* 2020	Victoria, Australia	1991 – 1992	297 + 260	25	< 28 weeks / <1000g	5.7 (3.7 to 8.4)	4.3 (2.4 to 6.3)

Abbreviations: DBP, diastolic blood pressure; ELBW, extremely low birth weight < 1000g; EPT, early preterm (< 34 weeks); LPT late preterm (34-36 weeks); M, men; NR, not reported; NS, not statistically significant; P-AGA, preterm appropriate birth weight (>1 SD z score); P-SGA, preterm with low birth weight (≤ - 1 SD z score); SBP, systolic blood pressure; SD, standard deviation; VLBW, very low birth weight < 1500g; W, women.

Table 3. Mean differences in ambulatory blood pressure in adults born preterm compared with controls born at term.

Authors and year	Cases + controls	Mean age / range (years)	Exposure	Mean difference in mmHg (95% CI or P)					
				24-hour SBP	24-hour DBP	Awake SBP	Awake DBP	Sleep SBP	Sleep DBP
Kistner *et al.* 2000	15 + 17	26	< 32 weeks	4 (P = 0.23)	1 (P = 0.26)	5 (P = 0.12)	3 (P = 0.26)	1 (P = 0.92)	2 (P = 0.31)
Doyle *et al.* 2003	156 + 38	18	< 1500g	4.7 (1.4 to 8.0)	1.1 (-1.2 to 3.5)	5.9 (2.8 to 9.1)	1.3 (-1.2 to 3.8)	3.8 (0.4 to 7.2)	0.7 (-1.9 to 3.3)
Hovi *et al.* 2010	118 + 120	18 – 27	< 1500g	W: 3.1 (P = 0.03) M: -0.4 (P = 0.81)	W: 1.8 (P = 0.05) M: -1.2 (P = 0.30)	W: 2.6 (P = 0.05) M: 0.6 (P = 0.78)	W: 1.4 (P = 0.10) M: 1.1 (P = 0.38)	W: 2.7 (P = 0.05) M: -0.3 (P = 0.84)	W: 1.8 (P = 0.08) M: 0.2 (P = 0.92)
Roberts *et al.* 2014	136 + 120	18	< 28 weeks	3.2 (0.1 to 6.4)	2.0 (0.3 to 4.0)	5.1 (1.9 to 8.4)	2.7 (0.7 to 4.8)	3.0 (-0.4 to 6.4)	1.2 (-0.8 to 3.3)
Lewandowski *et al.* 2015	30 + 60	23 – 28	< 1850g	10.5 (P < 0.001)	2.5 (P = 0.02)	9.7 (P < 0.001)	2.6 (P = 0.05)	9.2 (P < 0.001)	2.6 (P = 0.04)
Paquette *et al.* 2018	92 + 92	23	< 37 weeks	5.1 (P = 0.001)	2.6 (P = 0.004)	4.6 (P = 0.002)	1.9 (P = 0.079)	3.8 (P = 0.018)	1.9 (P = 0.10)
Haikerwal *et al.* 2020	151 + 119	25	< 28 weeks / <1000g	4.5 (1.2 to 7.7)	3.4 (1.5 to 5.2)	4.9 (1.6 to 8.4)	3.7 (1.7 to 5.8)	6.1 (2.5 to 9.6)	4.2 (2.2 to 6.3)

Abbreviations: DBP, diastolic blood pressure; M, men; NS, not statistically significant; SBP, systolic blood pressure; W, women.

2.5.4 Cardiac autonomic control in adults born preterm

Human autonomic nervous system development

A significant proportion of autonomic nervous system development occurs during the 3rd trimester of pregnancy and this development is interrupted by preterm birth (Sachis *et al.* 1982, Van Leeuven *et al.* 1999, Andriessen *et al.* 2005). The interruption of gestation by preterm birth may have far-reaching consequences in later autonomic regulation. Preterm birth has been connected with several adverse outcomes in preterm infants' cardiovascular and central nervous system functions, such as higher heart rate, reduced blood pressure, lower parasympathetic autonomic control, and reduced baroreflex function (Gournay *et al.* 2002, Patural *et al.* 2004, Andriessen *et al.* 2005, Longin *et al.* 2006, Witcombe *et al.* 2012 and Fyfe *et al.* 2014). These disturbances may be attributed to altered development of these systems following preterm birth (Fyfe *et al.* 2014). Fetal autonomic nervous system function goes through significant maturation during the course of pregnancy (Kimura *et al.* 1996, Tsukasa *et al.* 1999, Fyfe *et al.* 2015): the sympathetic branch is developed mainly in the 1st trimester, whereas short-term heart rate variability, an index of parasympathetic autonomic control, increases later during pregnancy (Van Leeuwen *et al.* 1999 and Wakai *et al.* 2004).

The heart rate in a human fetus increases to 175 pbm by the 9th gestational week and declines thereafter to about 150 bpm by the 16th gestational week and further to about 140 bpm at term (Van Lith *et al.* 1992, Van Leeuwen *et al.* 1999). It is assumed that the decrease in heart rate in the 3rd trimester of pregnancy is mediated by an increase in autonomic parasympathetic activity which overrides the accelerating influence of sympathetic tone (Van Leeuwen *et al.* 1999). Indeed, whereas the sympathetic branch of the autonomic nervous system appears to develop more rapidly in the 1st trimester of pregnancy, parasympathetic control becomes more prominent later during fetal development and increases further during the 3rd trimester (Wakai *et al.* 2004, Fyfe *et al.* 2014). This assumption is supported by the findings of Sachis *et al.* 1982, who found that the total number of myelinated vagal (parasympathetic) fibres increased linearly with postconceptional age, leading to fewer total myelinated vagal fibres in infants born preterm compared with full-term infants or adolescents.

Infants born preterm have shown lower heart rate variability compared with term-born infants, with parasympathetic activity primarily affected (Clairbault *et al.* 1992, Longin *et al.* 2006, Patural *et al.* 2004, Fyfe *et al.* 2015). Preterm birth

seems to reduce parasympathetic function at least to term-equivalent age (Eiselt *et al.* 1993, Patural *et al.* 2008) and this continues at least up to 5 – 6 months post-term, when compared with infants born at term (Yiallourou *et al.* 2013).

Preterm birth and autonomic control in later life

Though the connection between preterm birth and reduced autonomic control in preterm infants has been clearly established, it is less-well known how these disturbances persist to adolescence and adulthood. It has been unknown whether autonomic function differs between preterm-born adults and those born at term and to what extent these possible alterations are due to parasympathetic and/or sympathetic parts of the autonomic regulation.

Table 4 presents a summary of studies examining the association of preterm birth with alterations in autonomic control in adolescence and adulthood. De Rogalski Landrod *et al.* studied preterm-born children in the neonatal period, at age 2 – 3 years and again at age 6 – 7 years and found decreased sympathetic activity and more substantially decreased parasympathetic activity in the preterm-born group compared with controls in the neonatal period, but at ages 2 – 3 and ages 6 – 7 the differences had attenuated, suggestive of ANS function recovery to a level similar to that in term-born controls in the first two years of life (De Rogalski Landrod *et al.* 2007). In contrast, Haraldsdottir *et al.* found that 12- to 14-year-old children born preterm had lower rMSSD values and reduced HRR after maximal exercise, suggesting reduced parasympathetic activity in those born preterm compared with controls (Haraldsdottir *et al.* 2018). Rakow et al. studied children born preterm and children born term but small for gestational age compared with normal-birth-weight controls, and found that ANS function was significantly lower in both of the exposure groups compared with the normal-birth-weight controls, suggesting that low body weight, whether due to preterm birth or intrauterine growth restriction, affected ANS function at the age of 9 – 10 years (Rakow *et al.* 2013). However, Yiallourou *et al.* found that fetal growth restriction was not associated with autonomic control at nine years of age, but, surprisingly, appropriate for gestational age (AGA) preterm birth alone was associated with elevated high-frequency HRV, suggesting more powerful parasympathetic response to blood pressure swings in AGA preterms compared with term controls (Yiallourou *et al.* 2017).

Whether the autonomic impairment reported in children born preterm remains in adulthood is less-well studied. Mathewson *et al.* found that parasympathetic

regulatory capacity (HF) may be reduced in adults born at ELBW compared with normal-birth-weight controls (Mathewson *et al.* 2015). Whereas the evidence on autonomic control in children born preterm remains scattered, these studies suggest that early adversity due to preterm birth may have an impact on autonomic functioning in adolescence.

Two more recent studies concerned reduced heart rate recovery after maximal exercise, an indicator of parasympathetic activity, in adults born VLBW (Haraldsdottir *et al.* 2019) and in adults born preterm (Huckstep *et al.* 2020). Impaired myocardial reserve seems to underlie reduced exercise capacity and heart rate recovery in young adults born preterm (Huckstep *et al.* 2020). These findings suggest that preterm birth and preterm birth at VLBW may be associated with impaired parasympathetic regulation in adulthood. However, whether these alterations exist in the preterm-born population and especially in the later preterm-born population is not known. Additionally, to our knowledge, the association of preterm birth with alterations in the sympathetic modulation of the heart has not been reported. In the current study we aimed to explore further whether these alterations seen in autonomic control and blood pressure regulation persist in adulthood in those born preterm, and whether the alterations are seen in those born late preterm.

Table 4. Summary of studies assessing autonomic control in adolescents and adults born preterm.

Authors and publication year	Cohort location	Birth years	Cases + controls	Mean age / range (years)	Exposure	Main finding on autonomic control	Conclusion
De Rogalski 2007	France	1999 - 2004	30 + 14	2 – 3 6 – 7	25 – 37 weeks	No differences in Ptot, VLF, LF, HF, LF/HF ratio, LFnu, HFnu between the preterm and term-born groups at ages 2 – 3 or 6 - 7 years.	Preterm-born children had recovered from autonomic impairment and had similar ANS activity as the full-term group, suggesting fast ANS maturation in prematures during the two first years of life, especially in the parasympathetic arm.
Rakow 2013	Sweden	1990 - 1993	31 preterm 27 SGA 28 controls	9	< 32 weeks	All frequency and time domain components tested were lower in preterm group / SGA group vs. controls.	Autonomic control appears to be affected in 9-year-old children born LBW despite their gestational age.
Yiallourou 2017	Australia	2001 - 2010	18 preterm FGR 15 preterm AGA 20 term AGA controls	9	Preterm AGA Preterm FGR	Preterm-born children had higher HF heart rate variability and higher blood pressure variability compared with term controls during sleep.	Preterm birth alone is associated with increased parasympathetic activation and blood pressure changes related to respiration. FGR combined with preterm birth did not alter autonomic control at 9y.

Authors and publication year	Cohort location	Birth years	Cases + controls	Mean age / range (years)	Exposure	Main finding on autonomic control	Conclusion
Haraldsdottir 2018	Wisconsin, USA	2003 - 2004	21 + 20	13	< 36 weeks	Preterm group had lower SDRR (SDNN), lower rMSSD, higher LF variability accompanied by lower HRR after maximal exercise than term controls.	Results suggest autonomic dysfunction in healthy adolescents born preterm at 12 – 14 years.
Mathewson 2014	Ontario, Canada	1977 - 1982	30 + 47	22 – 26 30 – 35	< 1000g	LF (RSA) was lower in ELBW vs. controls	Parasympathetic decline in smallest birth weight ELWB adults.
Haraldsdottir 2019	Wisconsin and Iowa, USA	1988 - 1991	12 + 16	26	< 1500g	Lower 1-minute and 2-minute HRR after maximal exercise compared with controls in normoxia and hypoxia.	Adults born premature may lack typical cardiovascular risk factors yet present with autonomic dysfunction reflected by slower HRR following maximal exercise.
Huckstep 2020	United Kingdom	NR	47 + 54	23	32.8 ± 3.2 weeks	Similar 1-minute HRR and lower 2-minute HRR with preterm group vs. term controls.	Impaired myocardial functional reserve underlies reduction in HRR in young adults born preterm.

Abbreviations: AGA, appropriate for gestational age; ANS, autonomic nervous system; ELBW, extremely low birth weight (< 1000g); HF, high frequency; HFnu, high frequency normalized units; HRR, heart rate recovery; LF, low frequency; LFnu, low frequency normalized units; LBW, low birth weight (< 1500g); NR, not reported; Ptot, total power; LF/HF ratio, ratio between LF and HF; rMSSD, root mean square of successive differences; RSA, respiratory sinus arrhythmia; SDRR, standard deviation of R-R intervals; VLF, very low frequency.

3 Aims and hypothesis

The overarching aim of this thesis was to clarify the association between preterm birth with blood pressure and cardiac autonomic regulation in adulthood. We hypothesized that preterm birth, across its entire range, is associated with elevated ambulatory blood pressure, higher blood pressure variability, impaired autonomic control (reduced HRV and shorter PEP) and reduced heart-rate recovery after exercise. We also hypothesized that impaired cardiac autonomic regulation is associated with higher blood pressure in adults born preterm. For this purpose, we studied the ESTER cohort, the McMaster cohort and the HeSVA cohort. The specific aims were:

1. Using ESTER, McMaster and HeSVA cohorts, to investigate whether adults born preterm, compared with term-born controls, have increased risks of elevated ambulatory blood pressure, higher blood pressure variability, impaired cardiac autonomic control and reduced recovery after exercise. (I-IV)
2. To study, in the ESTER cohort, whether these risks are present and similar in adults born early preterm (< 34 weeks) and late preterm (34 to < 37 weeks) vs. term. (I-III)
3. To investigate, in the HeSVA and McMaster cohorts, whether the risks of elevated blood pressure and impaired autonomic regulation are present in adults born at very low birth weight (VLBW, ≤ 1500 g) or at extremely low birth weight (ELBW, ≤ 1000 g) compared with normal-birth-weight (NBW) controls. (IV)
4. To evaluate, in the ESTER, McMaster and HeSVA cohorts, whether the observed associations could be explained by sex, unfavorable body composition, reduced physical activity, perinatal factors or childhood socioeconomic status. (I-IV)
5. To see if the observed associations are replicable in another cohort with preterm birth at very or extremely low birth weight as the exposure. (IV)

4 Subjects and methods

We examined the relationship between preterm birth and cardiovascular risk factors on the basis of data from three different cohort studies: 1) the ESTER Preterm Birth Study (I, II, III), 2) the Helsinki Study of Very Low Birth Weight Adults (IV), and 3) the McMaster Cohort (IV).

4.1 The ESTER Study (I, II, III)

4.1.1 Study population

The ESTER study ("Preterm birth and early life programming of adult health and disease") is a geographically based birth cohort study in Northern Finland carried out in 2009 to 2011 (Sipola-Leppänen, 2015). The cohort study was established to evaluate the effects of preterm birth and maternal pregnancy disorders on adulthood health and wellbeing. The ESTER study has two sub-studies: 1; ESTER Preterm Birth Study and 2; Maternal Pregnancy Disorders and Child's Health in Adulthood. In the current study, only subjects in the ESTER Preterm Birth Study are included. The ESTER study was conducted as a joint effort by the National Institute for Health and Welfare, the Institute of Health Science at the University of Oulu, the Northern Ostrobothnia Hospital District and the University of Helsinki. The study participants born in 1985 to 1986 were recruited from the Northern Finland Birth Cohort (NFBC) and participants born in 1987 to 1989 in Northern Finland were selected from the Finnish Medical Birth Register (FMBR) (Sipola-Leppänen, 2015). All those in the NFBC 1986 cohort that were born preterm (< 37 weeks of gestation), exposed to maternal gestational hypertension, pre-eclampsia or gestational diabetes were selected in the study. From the FMBR, all individuals born before 34 weeks of gestation were selected. Additionally, subjects fulfilling similar criteria (preterm birth, maternal gestational hypertension, pre-eclampsia or gestational diabetes) were selected randomly from the FMBR. Control subjects were selected randomly from both the NFBC and the FMBR. In total, 2920 individuals were invited to join the cohort, and in the present study, the data used concerned 149 participants born early preterm, 248 participants born late preterm and 356 full-term controls (Figure 6).

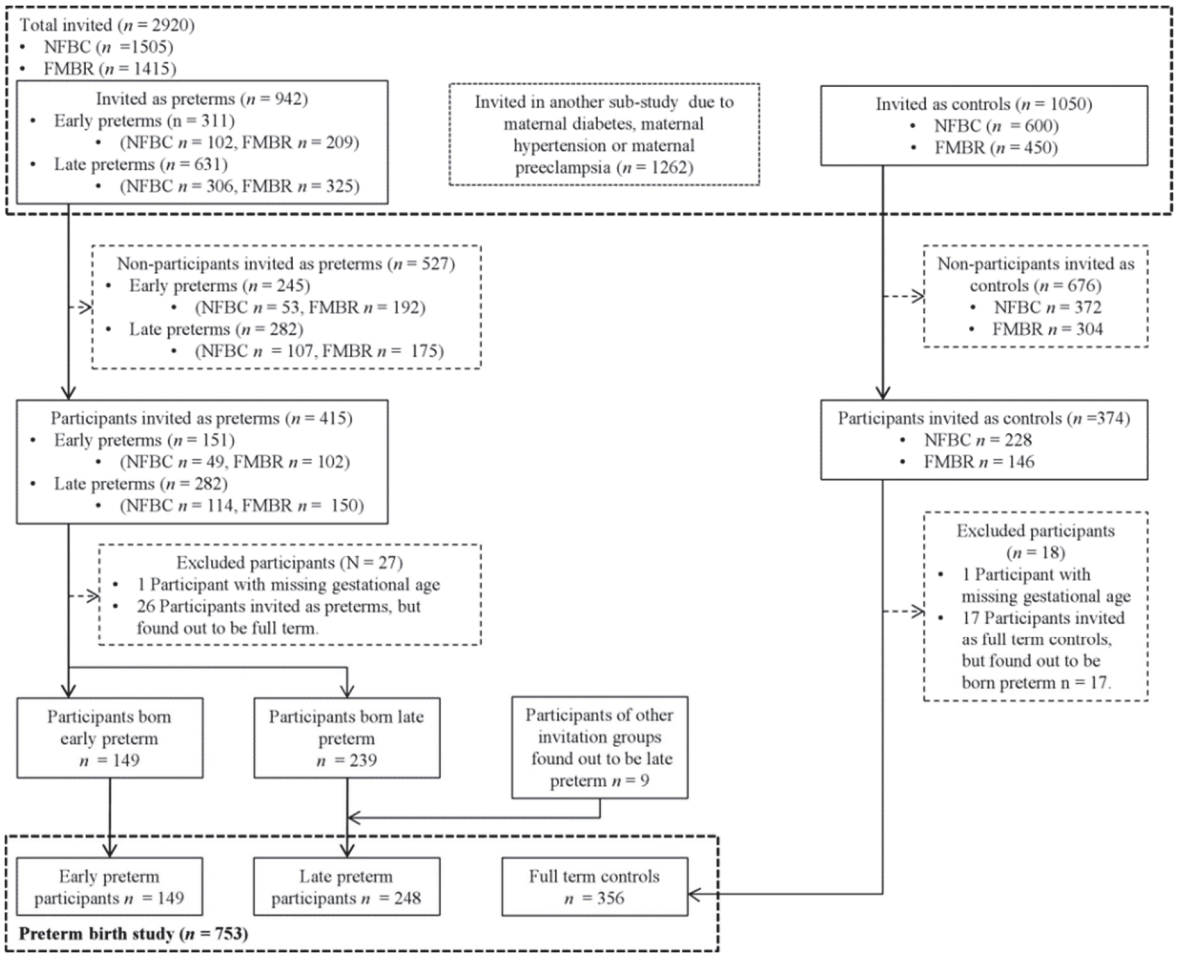


Fig. 6. Outline of selection of the ESTER preterm birth study participants. (Articles I, II, III). Modified from Tikanmäki 2018.

4.1.2 Perinatal and neonatal data

Perinatal and neonatal data was collected from birth hospitals, maternal welfare clinics and questionnaires. Gestational age was determined by reviewing original hospital records. As the present work concentrates on the effects of preterm birth in relation to cardiovascular risk factors, we included those born preterm and their randomly selected controls in the study. In all ESTER studies, including those included in this study (Articles I, II, III), the subjects were categorized into three groups based on their gestational age:

1. Those born before 34 weeks of gestation (early preterm group, n = 149),
2. Those born from 34 to < 37 weeks of gestation (late preterm group, n = 248),
3. Those born at ≥ 37 weeks of gestation (controls, n = 356)

Maternal gestational disorders (gestational diabetes, chronic or gestational hypertension, and pre-eclampsia) were determined according to prevailing medical guidelines. Birth weight SD scores were calculated according to Finnish standards (Pihkala *et al.* 1979). Small for gestational age was defined as more than two standard deviations (SDs) below the mean.

4.1.3 Questionnaire

The participants were requested to complete an electronic questionnaire prior to the clinical visit or on paper during or after the visit. The questionnaire included questions on lifestyle, medication, medical history and socioeconomic status (SES). Parental educational attainment was chosen as an indicator of childhood SES. Self-reported physical activity, daily smoking and the amount of weekly alcohol doses were also recorded.

4.1.4 Clinical examination

The subjects participated in clinical examinations at a mean age of 23.3 years at clinics in Oulu, Kemi, Kuusamo, Raahe, Rovaniemi and Ylivieska (Sipola-Leppänen 2015 and Tikanmäki 2018). The participants had fasted overnight prior to the clinical visit. Blood pressure was measured by an experienced study nurse with the participants in a seated position. After a five-minute rest period BP was measured from the participant's upper right arm, using an automatic oscillometric blood pressure monitor (Intellisense M10-IT, cuff size 22-42 cm; Omron

Healthcare Co., Ltd., Kyoto, Japan). A mean value was recorded from three successive measurements. Height (cm) was measured three times by using a portable stadiometer and the mean value was recorded. Body composition (weight, lean body mass, fat mass and body fat percentage) was measured by segmental multi-frequency bioelectrical impedance analysis (InBody 3.0, Biospace Co., Seoul, Korea). BMI was calculated the basis of height and weight. The participants were offered a heart rate monitor (RS800CX and WearLink WIND transmitter, Polar Electro Oy, Kempele, Finland) at the beginning of the examination and R-R intervals were recorded throughout the examination day.

4.1.5 Ambulatory measurements (I)

To enable 24-hour blood pressure assessment, volunteer subjects were given ambulatory blood pressure (ABP) monitors (Spacelabs 90207, Spacelabs Medical, Inc., WA, U.S.A.) after the clinical examination day. The subjects wore a cuff on the non-dominant upper arm for 24 hours and blood pressure was measured every 20 minutes during the day (7:00 to 22:00 h) and every 30 minutes at night (22:00 to 07:00 h). Sleep-wake rhythm was measured with an accelerometer (GT1M; ActiGraph, Inc., Pensacola, FL) worn in the wrist simultaneously with ABP measurement. The subjects were instructed to keep a sleep log reporting bedtimes and wake-up times. The participants returned the ABPs and accelerometers after the 24-hour recording period for data download. The accuracy of the sleep log was visually inspected against the raw accelerometry data and night-time data was removed when inconsistent against the accelerometry data or if the bedtime information was missing. When the reported wake-up time was inconsistent or missing, it was estimated from the accelerometry data. The time of sleep onset was estimated by using ActiLife software (ActiLife 5.10.0; ActiGraph Pensacola, FL, U.S.A.) using the Sadeh algorithm (Sadeh *et al.* 1994). For those who had no accelerometry data available (60 subjects) BP when sleeping was defined as that between 01:00 and 07:00 h, and awake BP was defined as that between 09:00 and 23:00 h. Those with less than 15 BP measurements when awake, or less than eight measurements when sleeping, were excluded from the respective awake/sleep and 24-hour analyses. As described in Figure 7 (Article I), those who used antihypertensive medication, were pregnant or had insufficient or no ABP data available were also excluded from the analysis. After these exclusions the mean ABPs (mmHg) and BP standard deviations (mmHg, indicator of BP variability) were calculated for the subjects' 24-hour, awake- and sleep times.

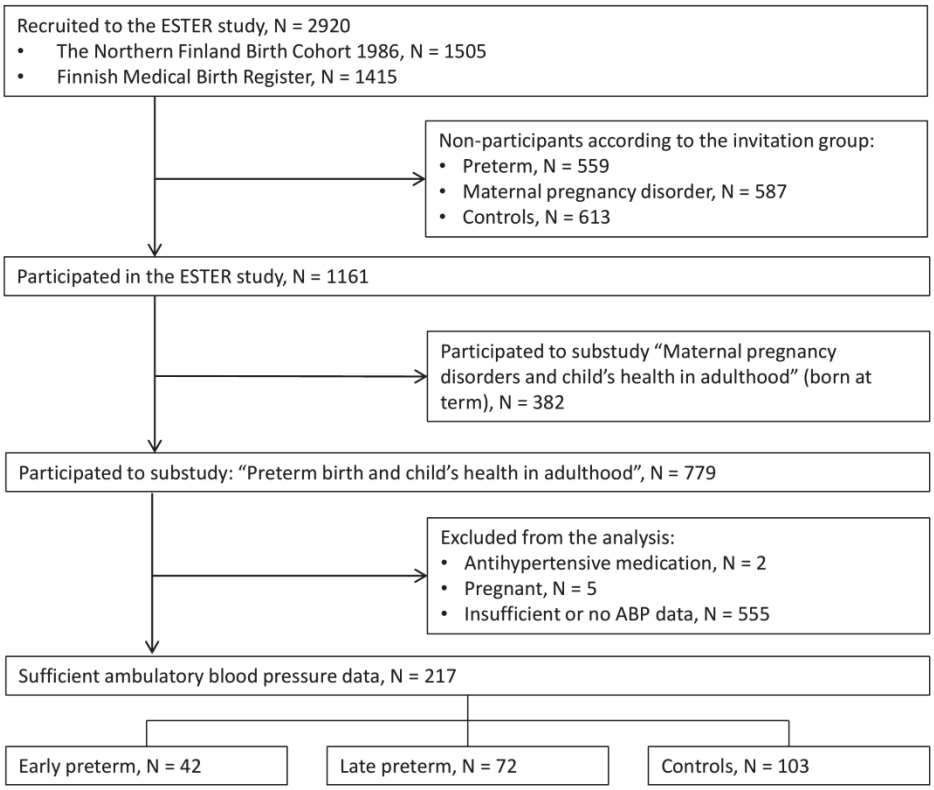


Fig. 7. Flowchart of the study population (Article I). Modified from Sipola-*Leppänen et al. 2015*

4.1.6 Autonomic control measurements (II)

Resting cardiac autonomic control was addressed in Articles II and IV. Article III focused on the reactivation of the parasympathetic nervous system after exercise stimulus. Beat-to-beat heart rate intervals were recorded throughout the clinical examination day, but we visually selected most stationary 3 – 5 min R-R periods with the lowest mean HR for analysis at the beginning of the examination day (Article II). The data used was recorded during a 10- to 15-minute interview conducted by a study nurse, with the subject in a seated position while breathing at spontaneous breathing frequency (Article II). R-R intervals were visually inspected for artifacts and ectopic beats and replaced with local averages where

necessary. Sequences with more than 10 consecutive ectopic beats or noise were deleted. R-R intervals over at least three minutes and a minimum 90% of acceptable R-R intervals were included in the analysis.

In the time domain we calculated geometric mean HR and root mean square of successive differences (rMSSD) and in the frequency domain, using a fast Fourier transformation 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 calculated using Hearts software (Hearts 1.2 software, University of Oulu, Oulu, Finland). HFP and rMSSD were considered as measures of autonomic parasympathetic activity (Task Force 1996) and variation in HFP was considered to quantify the amplitude of variation in respiratory frequency (0.20-025 Hz) (Ekberg *et al.* 2003). LFP was also considered as a measure of parasympathetic activity, but it was considered to include some influence from sympathetic- and baroreflex-mediated effects (Task Force 1996, Julien *et al*. 2006). The LF/HF ratio was calculated as a marker of sympathovagal balance, though there was some controversy as to its interpretation (Billman *et al.* 2013). The outcome measures were skewed and thus transformed into natural logarithms (ln) prior to analysis, and were subsequently transformed back again and reported in a untransformed form. Prior to the analysis we excluded those who had mental or physical disabilities, had reported cerebral palsy, were pregnant or used beta blocker medication (Figure 8).

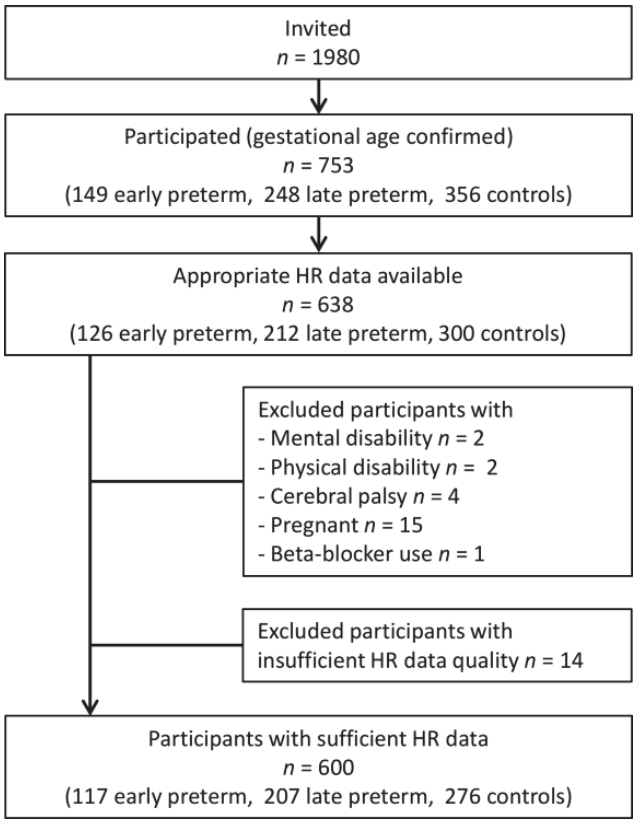


Fig. 8. Flowchart of the study population (Article II). Modified from Karvonen *et al.* 2019a.

4.1.7 Heart rate recovery measurements (III)

The subjects underwent an Åstrand-Ryhming (Åstrand-Ryhming 1954) step-test exercise, during which they stepped on and off a bench (33 cm high for women and 40 cm for men) repeatedly for four minutes at a pace of 23 steps per minute, paced by a metronome (Article III). Peak heart rate (HR) was determined by calculating the 10-beat median at the time of test cessation. Subsequently we recorded median HR at 30 seconds and 60 seconds after test cessation. Heart rate recovery (HRR) was calculated as peak HR – HR at 30 seconds after exercise cessation (HRR30s) and as peak HR – HR at 60 seconds after exercise cessation

(HRR60s). We also calculated the steepest 30-second slope during the first 60 seconds of the recovery period from the median HR data. Matlab software, version 7.14 (MathWorks, Natick, Massachusetts), was used for calculating all HRR measures. The HRR measures selection procedure is presented in Figure 9.

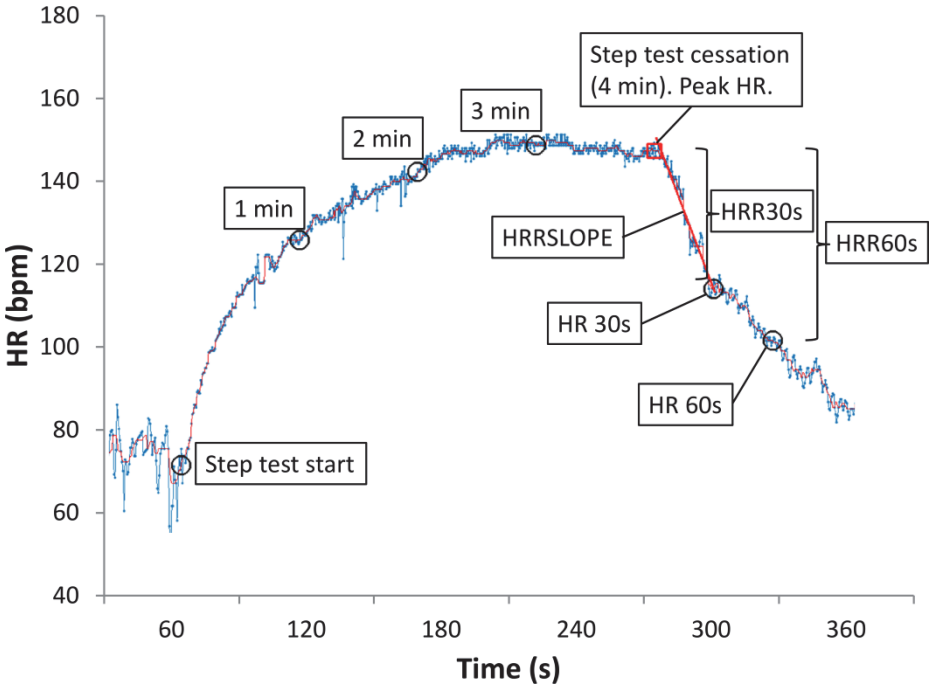


Fig. 9. HRR data selection. Modified from Karvonen *et al.* 2019b.

The study population selection process is presented in Figure 10. After excluding those with mental or physical disabilities, who had reported cerebral palsy, were pregnant or used beta blocker medication, 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.

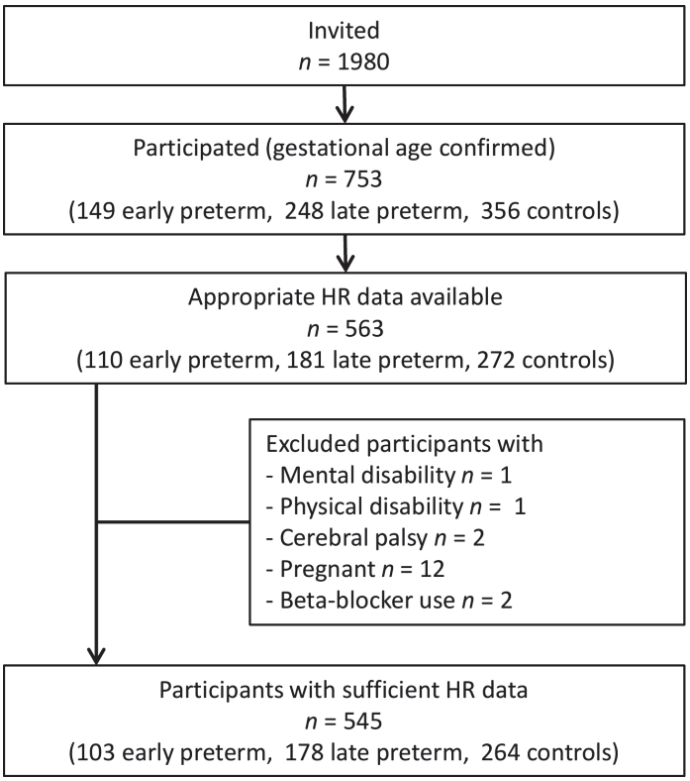


Fig. 10. Flowchart of the study population (article III). Modified from Karvonen *et al.* 2019b.

4.2 The Helsinki Study of Very Low Birth Weight Adults (IV)

4.2.1 The study population

The Helsinki Study of Very Low Birth Weight Adults (HeSVA) is a longitudinal birth cohort study aiming to assess the effects of preterm birth at VLBW on health and wellbeing in adulthood (Hovi *et al.* 2007). The original HeSVA study cohort was comprised of 335 VLBW infants born between 1978 and 1985 who were treated at the intensive care unit of the Children's Hospital, Helsinki University Central Hospital, Finland. Controls in the HeSVA cohort were selected in 2004 to 2005 from the birth hospital records by choosing the next available singleton

term-born infant of the same sex, and birth weight appropriate for its gestational age (normal birth weight; NBW) (Hovi *et al.,* 2007). A total of 255 VLBW subjects and 314 NBW control subjects living in the greater Helsinki area were contacted utilizing the Population Register Centre of Finland. Out of those contacted, 166 VLBW subjects and 172 NBW controls, group-matched for sex, age and birth hospital agreed to participate (Hovi *et al.* 2007). From these, a random sample of 56 VLBW subjects and 44 NBW controls were invited to take part in clinical examinations and ECG recordings in 2005.

4.2.2 Clinical examination and measurements

Participants in the HeSVA cohort attended a clinical visit at the Department of Psychology, University of Helsinki, Finland (Pyhälä *et al.* 2009, Mathewson *et al.* 2015, Hovi *et al.* 2009). Their heights and weights were measured. Heart rate and office blood pressures were measured two times from the subjects' right arm via an automatic sphygmomanometer (Omron HEM-773-E, Omron Healthcare Europe, Hoofddorp, the Netherlands) and mean values were calculated (Hovi *et al.* 2007). The participants were standing alone in a closed laboratory room when a 5-minute ECG recording was collected using a modified lead II configuration. Pre-ejection period (PEP) was recorded simultaneously with the ECG via four external impedance electrodes on the front and back of the torso. R-R interval data was assessed using Biopac Acknowledge 3.8.1 software (Santa Barbara, CA). Indices of autonomic control (high frequency power (lnHF), low frequency power (lnLF) and PEP) and blood pressures (SPB and DBP) were calculated offline from the 5-min resting ECG recording in its entirety, using WinCPRS software (Absolute Aliens Oy, Turku, Finland). Blood pressure was monitored by a Finometer (FMS, Amsterdam, the Netherlands), a non-invasive, beat-to-beat finger photoplethysmograph, which was validated against mercury sphygmomanometers (Pyhälä *et al*. 2009).

4.3 The McMaster Cohort (IV)

4.3.1 The study population

The McMaster Cohort comprised 397 ELBW subjects born weighing 501 to 1000g, whose gestational age ranged between 23 to 34 weeks. They were

recruited at birth between 1977 and 1982 from a geographically defined region in southwestern Ontario, Canada. Age-, sex- and socioeconomically matched NBW (birth weight ≥ 2500g) controls were selected at eight years of age. ELBW subjects were assessed at ages 3, 5, 8, 14, 22 to 26 and 30 to 35 years. At young adulthood assessment (22-26 years), 142 ELBW subjects participated and ECG data was successfully recorded in 67 ELBW and 80 NBW control subjects. In the adult (30 to 35 years) visit, appropriate ECG data was recorded in 55 ELBW subjects and 56 NBW controls.

In Article IV we addressed questions concerning the effects of preterm birth and sex on autonomic and blood pressure regulation. Young adult participants born at VLBW in Finland (HeSVA) and at ELBW in Canada (McMaster cohort) were combined with their respective controls to form the FinCan cohort (Mathewson *et al.* 2014). Autonomic and blood pressure regulation was examined again in the Canadian participants a decade later, at age 30-35 years.

4.3.2 Clinical examination and measurements

At the McMaster cohort young-adulthood assessment (22-26 years), the participants sat quietly in a comfortable chair while resting ECG was recorded for two minutes via two disposable ECG electrodes placed on the medial forearms. R-R interval data was analysed offline and autonomic measures (RRI, lnHF and lnLF) were calculated using IBI Analysis software (James Long Company, Caroga Lake, NY). Blood pressures were collected during the same assessment using an ambulatory blood pressure monitor. At the McMaster adulthood assessment (30-35 years), resting ECG measurements were recorded for six minutes using a Finometer (Finapres Medical Systems BV, Arnhem, the Netherlands) with electrodes placed below the right clavicle and on the lower left rib area in a modified lead II configuration. Autonomic measures (RRI, lnHF and lnLF) were calculated from the Finometer data. At the adult assessment, blood pressures (SBP and DBP) were measured in a seated position using a BpTRU device (BpTRU Medical Devices, Coquitlam, BC, Canada). Body composition was assessed in the mature adult assessment via dual-energy radiograph absorptiometry on a GE Lunar Prodigy Advance scanner (Model #8743, GE Healthcare, Mississauga, Ontario, Canada).

4.4 Statistical methods

Data were analysed using SPSS for Windows software, versions 22.0, 24.0 and 25.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). We presented descriptive statistics for the study groups as frequencies of categorial variables or as mean values and SDs. Group differences were tested using analysis of variance, Pearson's $\chi 2$ test, or Student's *t* test. Data normality was tested via histograms and the measurements were transformed to natural logarithms (ln) prior to analysis but were transformed back again and reported in untransformed form when necessary. To assess differences between the exposure groups (early preterm / late preterm / VLBW / ELBW) and controls we used linear regression models to adjust for covariates, as described in Table 5. We based our estimates of study power in clinical studies on our previous studies and existing literature. For example, with a power of 0.80 and an alpha value of 0.05, two-way comparisons of SBP, DPB, rMSSD, HFP and LFP (Article II) allowed us to detect a 0.31 SD difference between the early preterm group (N = 117) and the control group (N = 276). With a power of 0.90 and an alpha value of 0.01, the corresponding difference is 0.43 SD.

Covariates used in linear regression models assessing the association between preterm birth vs. ambulatory blood pressure and its variability in adults born preterm (I) were:

- Model 1: Age and sex. Additionally, models for BP when awake/asleep included the variable of whether or not sleep was assessed by accelerometry.
- Model 2: Model 1 plus parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, pre-eclampsia, gestational diabetes mellitus, and birth weight SD score.
- Model 3: Model 1 plus parental educational attainment, height, BMI, physical activity, and smoking.

Covariates in linear regression models assessing the association between preterm birth and cardiac autonomic control in adults born preterm (II):

- Model 1: Age, sex, cohort of recruitment, and season of clinical examination.
- Model 2: Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, maternal pre-eclampsia, parental education, and parental smoking.
- Model 3: Model 2 plus smoking, BMI, height, and physical activity.

Covariates in linear regression models assessing the association between preterm birth and postexercise heart rate recovery in adults born preterm (III):

- Model 1: Age, sex, and recruitment cohort.
- Model 2: Model 1 plus birth weight SD score, gestational diabetes mellitus, gestational hypertension, parental education, maternal smoking.
- Model 3: Model 2 plus smoking, BMI, height, and physical activity.

Covariates in linear regression models assessing sex-specific differences in cardiac autonomic and blood pressure regulation in low-birth-weight survivors at the young adult (22-26 years) assessment (IV):

- Model 1: Age, sex and cohort.
- Model 2: Model 1 variables plus highest parental educational level (as an estimate of childhood socioeconomic status) and maternal smoking during pregnancy.
- Model 3: Model 2 variables plus height.
- Model 4: Model 3 variables plus BMI.

Covariates in linear regression models assessing sex-specific differences in cardiac autonomic and blood pressure regulation in low-birth-weight survivors at the adult (30-35 years) assessment (IV):

- Model 1: Age and sex.
- Model 2: Model 1 variables plus parental educational level and maternal smoking.
- Model 3: Model 2 plus height and percentage body fat.

Table 5. Study design and cohorts in Articles I – IV.

Variable	Study I	Study II	Study III	Study IV		
	ESTER	ESTER	ESTER	HeSVA	McMaster young adult assessment (22-26 years)	McMaster adult assessment (30 - 35 years)
Predictors	Early preterms (<34 wk) Late preterms (34 to 36 wk) GA at birth	Early preterms (<34 wk) Late preterms (34 to 36 wk)	Early preterms (<34 wk) Late preterms (34 to 36 wk)	VLBW (< 1500 g)	ELBW (< 1000 g)	ELBW (< 1000 g)
Controls	≥ 37 weeks	≥ 37 weeks	≥ 37 weeks	NBW (≥ 2500 g)	NBW (≥ 2500 g)	NBW (≥ 2500 g)
Main outcome variables						
Blood pressure	Means and SDs of 24-hour, awake and sleep systolic- and diastolic ABP	Mean systolic- and diastolic office blood pressure	Mean systolic- and diastolic office blood pressure	Mean systolic- and diastolic office blood pressure (standing)	Mean systolic- and diastolic office blood pressure (seated)	Mean systolic- and diastolic office blood pressure (seated)
Autonomic measures	-	Mean HR, rMSSD, LFP, HFP, LF/HF ratio	HRRSlope, HRR30s, HRR60s	RRI, lnHF, lnLF and PEP	RRI, lnHF and lnLF	RRI, lnHF and lnLF
Mediators/modifiers	Height, BMI, self-reported physical activity, daily smoking.	Height, BMI, self-reported physical activity, daily smoking.	Height, BMI, self-reported physical activity, daily smoking.	Height and weight		Height and body fat percentage

Variable	Study I	Study II	Study III	Study IV		
	ESTER	ESTER	ESTER	HeSVA	McMaster young adult assessment (22-26 years)	McMaster adult assessment (30 - 35 years)
Confounders	Age, sex, use of accelerometry, parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, pre-eclampsia (including superimposed), gestational diabetes and birth weight SD score	Age, sex, recruitment cohort, parental educational level, season of clinical examination, birth weight SD score, gestational diabetes, gestational hypertension, maternal pre-eclampsia and maternal smoking	Age, sex, recruitment cohort, parental educational level, season of clinical examination, birth weight SD score, gestational diabetes, gestational hypertension, maternal pre-eclampsia and maternal smoking	Age, sex and recruitment cohort, parental educational level and maternal smoking		Age, sex and recruitment cohort, parental educational level and maternal smoking
Additional analyses	Exclusion of subjects exposed to maternal hypertensive pregnancy or born SGA	Sex differences and VLBW	Sex differences and VLBW			

Abbreviations: ESTER, Preterm birth and early life programming of adult health and disease; HeSVA, The Helsinki Study of Very Low Birth Weight Adults; SD, standard deviation; GA, gestational age; ABP, ambulatory blood pressure; BMI, body mass index; SGA, small for gestation age; HR, heart rate; LFP, low frequency power; HFP, high frequency power; LF/HF ratio, the ratio between LF and HF; VLBW, very low birth weight (< 1500g); NBW, normal birth weight (≥ 2500 g); PEP, pre-ejection period.

4.5 Ethics

The ESTER Study (I-III) was approved by the Ethics Committees at Helsinki and Uusimaa, and Northern Ostrobothnia Hospital Districts. HeSVA (IV) was approved by the Ethics Committee of the Department of Children's and Adolescents' Diseases and Psychiatry at Helsinki University Central Hospital. The McMaster cohort (IV) laboratory procedures were approved by the participating university and hospital research ethics boards.

5 Results

5.1 Background characteristics (I-IV)

The neonatal and current characteristics of the ESTER, HeSVA and McMaster cohort's participants are presented in Table 6. As expected, in each cohort, the exposure-group participants (early- or late preterms, ELBWs or VLBWs), in addition to shorter gestational age and lower birth weight, were more often born small for their gestational age than controls born at term. As presented in Table 6, preterm-born participants were younger than controls in the ESTER study and in the combined HeSVA and McMaster young-adult cohort. The VLBW/ELBW participants were also shorter in the young-adult assessment and in the McMaster adult assessment. ELVW/VLBW women were also lighter than control women in the HeSVA study and McMaster young-adult assessment. Women and men born preterm or with ELBW/VLBW had similar BMI as their peers born at term in all three cohorts.

5.2 Office blood pressure (I-IV)

The association between preterm birth or preterm birth at ELBW/VLBW and office blood pressure in adulthood was reported in all four articles (I – IV). In the ESTER study (Article II), adults born early preterm had 3.5 mmHg higher office SBP and 2.8 mmHg higher office DBP compared with controls born at term, when adjusted for age, sex, recruitment cohort, and season of clinical examination (model 1, Table 7, Figure 11). Adults born late preterm had 2.2 mmHg higher office SBP and 1.7 mmHg higher office DBP when compared with controls (model 1, Table 7, Figure 11). In the combined HeSVA and McMaster young-adult subset (age 19-26 years) SBP and DBP were similar in the ELBW/VLBW group and controls (Table 7). However, a decade later, in the McMaster adult assessment (age 29-35 years), those born with ELBW had 5.4 mmHg higher SBP and 3.9 mmHg higher DBP, when adjusted for age and sex (Table 7). As illustrated in Figure 11, the differences in blood pressure tended to be more prominent with increasing exposure (shorter gestational age or lower birth weight) and with increased chronological age.

Table 6. Neonatal and current characteristics in the ESTER, HeSVA and McMaster Cohorts.

Cohort	ESTER			HeSVA & McMaster young-adult assessment (19–27 years)		McMaster adult assessment (30–35 years)	
	Early Preterm (n = 117)	Late Preterm (n = 207)	Controls (n = 276)	VLBW/ELBW (n = 127)	Controls (n = 127)	ELBW (n = 55)	Controls (n = 56)
Neonatal							
Gestational age (weeks)	31.8 (2.0)	35.8 (0.8)	40.1 (1.1)	28.3 (2.4)	Term	27.2 (2.4)	Term
Birth weight (g)	1780 (493)	2651 (408)	3607 (479)	970	3462 (472)	834 (215)	3384 (44)
SGA, n (%)	11 (26.2%)***	5 (6.9%)***	1 (1.0%)	48 (37.8%)***	0 (0%)	18 (32.7%)***	0 (0%)
Current							
Male sex, n (%)	58 (49.6%)	101 (48.8%)	138 (50.0%)	57 (44.9%)	52 (40.9%)	19 (34.5%)	23 (41.1%)
Age (years)	23.1 (1.3)**	23.3 (1.3)**	23.5 (1.1)	23.1 (1.7)*	23.6 (1.4)	32.0 (1.6)	32.3 (1.4)
Body mass index (kg/m^2)							
Men	24.2 (4.1)	25.3 (4.5)	24.4 (3.5)	24.1 (4.7)	24.1 (3.8)	26.0 (5.0)	25.7 (3.8)
Women	24.2 (4.8)	23.8 (4.2)	23.2 (4.3)	23.1 (5.2)	25.1 (6.8)	26.2 (6.5)	25.7 (4.7)
Height (cm)							
Men	178.9 (6.9)	177.7 (6.5)	177.9 (6.9)	172.9 (8.6)**	178.0 (7.7)	175.9 (8.2)*	182.4 (8.2)
Women	163.4 (4.9)	164.6 (5.8)	164.3 (6.0)	161.0 (8.0)**	164.4 (6.6)	159.7 (7.5)*	163.9 (6.3)
Weight (kg)							
Men	77.6 (15.1)	79.8 (14.3)	77.2 (12.7)	71.7 (13.6)	76.3 (12.1)	80.1 (14.4)	85.9 (14.3)
Women	64.7 (13.9)	64.5 (12.0)	62.5 (11.6)	60.1(13.6)**	68.1 (20.5)	66.9 (16.7)	69.4 (14.0)

Abbreviations: SGA, small for gestational age (>2 SD); VLBW, very low birth weight (< 1500 g); ELBW, extremely low birth weight (< 1000 g). P values for the differences compared with controls: * P < 0.05; ** P < 0.01; *** P < 0.001. (P-values not presented for gestational age and birth weight). Values presented as exact numbers or group means and SDs in parentheses.

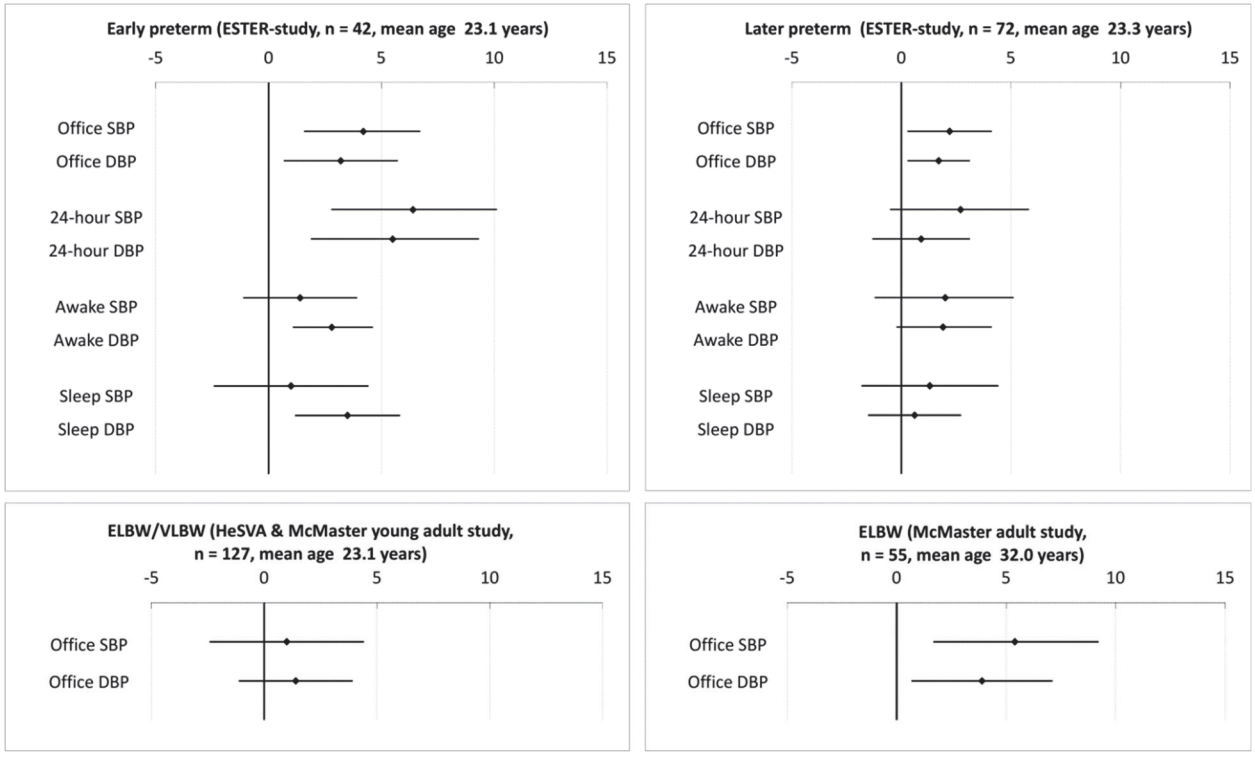


Fig. 11. Mean differences in office and ambulatory blood pressures, with 95% confidence intervals, in adults born early preterm, later preterm or at extremely or very low birth weight compared with controls (zero line), adjusted for age, sex and cohort (and for season of clinical examination in the HeSVA study).

Table 7. Office blood pressures in the ESTER, HeSVA and McMaster cohorts.

	Office SBP (mmHg)		Office DBP (mmHg)	
Cohort	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)
ESTER				
Early preterm (n = 117)	119.2 (13.2)	3.5 (1.2, 5.8)[a]	77.6 (8.9)	2.8 (1.1, 4.6)[a]
Late preterm (n = 207)	118.0 (13.6)	2.2 (0.3, 4.1)[a]	76.6 (8.3)	1,7 (0.3, 3.1)[a]
Controls (n = 276)	116.0 (12.5)	-	75.0 (7.3)	-
Combined HeSVA & McMaster young adult assessment				
ELBW/VLBW (n= 127)	119.7 (14.1)	1.0 (-2.4, 4.4)[b]	72.8 (10.7)	1.4 (-1.1, 3.9)[b]
Controls (n = 127)	118.3 (13.9)	-	70.6 (10.1)	-
McMaster adult assessment				
ELBW (n = 55)	113.0 (11.9)	5.4 (1.7, 9.2)[c]	74.1 (10.1)	3.9 (0.7, 7.1)[c]
Controls (n = 56)	108.3 (10.4)	-	70.4 (7.4)	-

Abbreviations: ELBW, extremely low birth weight (< 1000 g); VLBW, very low birth weight (< 1500 g).

[a] Mean differences (95% CI) when adjusted for age, sex, recruitment cohort (NFBC or FMBR) and season of clinical examination.

[b] Mean differences (95% CI) when adjusted for age, sex and recruitment cohort (HeSVA or McMaster).

[c] Mean differences (95% CI) when adjusted for age and sex.

5.3 Ambulatory blood pressure and blood pressure variability (I)

5.3.1 Mean ambulatory blood pressure

Ambulatory blood pressure and blood pressure variability in adults born preterm were analysed in the ESTER study and reported in Article I. We found that adults born early preterm had 5.5 mmHg higher mean 24-hour SBP, 6.4 mmHg higher awake time SBP and 3.9 mmHg higher sleeping SBP when adjusted for age, sex and the use of accelerometry, compared with term controls (Table 8, Figure 11, model 1). Mean 24-hour DBP was 3.2 mmHg higher and awake DBP was 4.2 mmHg higher (Table 8, Figure 11, model 1) in the early preterm group and mean DBP during sleep was similar in the early preterm and control groups. Although the difference in ambulatory blood pressure was present during awake and sleeping hours, it seemed to be more pronounced while awake.

When model 1 was supplemented with perinatal factors (parental education, mother's BMI before pregnancy, gestational or chronic hypertension, pre-eclampsia, gestational diabetes mellitus, and birth weight SD-score (Article I, model 2) the results were attenuated and remained statistically significant as regards 24-hour and awake SBP but were no longer significant as regards 24-hour DPB, awake DBP and sleep SBP. When model 1 was supplemented further with current characteristics (parental education, height, BMI, physical activity, and smoking; Article I, model 3), the results remained similar. For adults born late preterm, the differences were smaller and not statistically significant (Table 8, Figure 11). When the length of gestation was analysed as a continuous variable, we found that lower gestational age was associated with higher mean 24-hour and awake ambulatory blood pressure, but not with mean sleeping ambulatory blood pressure. Our findings suggested a dose-response relationship between the degree of prematurity and elevated blood pressure in adulthood.

Although there were no statistically significant interactions between sex, early preterm birth and ambulatory blood pressure ($P \geq 0.08$ as presented in Supplementary Table 8 in Article I), we analysed the differences separately for women and men because the results of previous studies have suggested that the association between preterm birth and blood pressure may differ according to sex. The differences between adults born early preterm and controls were seen in awake SBP for both sexes ($P = 0.02$). The difference in 24-hour SBP was more prominent with men born early preterm compared with their controls than with women vs. their controls (men: 7.9 mmHg, $P = 0.02$; women: 3.9 mmHg, $P =$

0.07). The differences in 24-hour DBP and awake DBP were higher with women born early preterm than with control women, whereas in men the differences were non-significant. In the late preterm group, the differences were statistically significant only for men: men had 5.9 mmHg higher 24-hour SBP and 3.9 mmHg higher 24-hour DBP than control men.

5.3.2 Blood pressure variability

Blood pressure variability was evaluated by measuring the standard deviations (SDs) of individual values in 24-hour, awake and sleeping time systolic- and diastolic blood pressure, and the results were reported in Article I. As summarized in Table 8, we found that adults born early preterm had 1.7 mmHg higher SDs of 24-hour SBP and DBP, 1.3 mmHg higher SD of awake SBP and 1.0 mmHg higher SD of awake DBP when adjusted for age, sex and awake and sleep values with the use of accelerometry (Article I, model 1). When sleeping, the SD of DBP was 1.5 mmHg higher in the early preterm group, but the SD in SBP while asleep was similar in the early preterm and term control groups (Article I, model 1). We also found a 2.6 mmHg higher difference between awake and sleeping time SBP SD in the early preterm group when compared with term controls.

When adjusting further with current characteristics (Article I, model 3), the results remained similar. The differences were attenuated slightly, but remained mainly significant, when adjusted for perinatal characteristics (Article I, model 2). For adults born late preterm, the differences with the term group were smaller and not statistically significant, except for 24-hour DBP SD, which was 0.8 mmHg higher and for sleep SBP SD, which was 0.8 mmHg higher. When the length of gestation was analysed as a continuous variable, we found that shorter length of gestation was associated with larger SDs of ambulatory blood pressure, with the exception of sleep time SBP SD.

Table 8. Mean ambulatory blood pressures and ambulatory blood pressure standard deviations and differences compared with controls born at term in adults born early and late preterm, when adjusted for age, sex and awake and sleeping values with the use of accelerometry to detect sleep in the ESTER study (I).

Measurement	Early preterm (n = 42)		Late preterm (n = 72)		Controls (n = 103)
	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)
Mean ambulatory blood pressure (mmHg)					
24-hour systolic blood pressure	121.4 (12.7)	5.5 (1.9, 9.3)	119.1 (12.0)	2.7 (-0.5, 5.8)	116.3 (8.9)
24-hour diastolic blood pressure	71.2 (7.4)	3.2 (0.7, 5.7)	69.8 (6.2)	0.9 (-1.3, 3.1)	68.2 (6.6)
Awake systolic blood pressure	126.8 (13.1)	6.4 (2.8, 10.1)	122.9 (12.0)	2.0 (-1.2, 5.1)	120.8 (9.4)
Awake diastolic blood pressure	76.5 (8.4)	4.2 (1.6, 6.7)	73.9 (6.5)	1.9 (-0.2, 4.1)	72.7 (7.1)
Sleep systolic blood pressure	110.1 (11.8)	3.9 (0.3, 7.5)	108.5 (11.5)	1.3 (-1.8, 4.4)	106.4 (8.9)
Sleep diastolic blood pressure	59.2 (6.0)	1.2 (-1.3, 3.7)	58.7 (7.0)	0.6 (-1.5, 2.7)	58.2 (6.5)
Standard deviation of ambulatory blood pressure (mmHg)					
24-hour systolic blood pressure	12.6 (3.0)	1.7 (0.8, 2.7)	11.5 (2.7)	0.5 (-0.3, 1.4)	11.0 (2.6)
24-hour diastolic blood pressure	12.3 (2.3)	1.7 (0.9, 2.5)	11.4 (2.1)	0.8 (0.1, 1.4)	10.7 (2.1)
Awake systolic blood pressure	10.3 (2.5)	1.3 (-0.5, 2.1)	9.6 (2.5)	0.5 (-0.2, 1.2)	9.1 (2.1)
Awake diastolic blood pressure	9.6 (2.5)	1.0 (0.2, 1.7)	9.5 (2.4)	0.5 (-0.1, 1.2)	8.6 (1.9)
Sleep systolic blood pressure	7.9 (2.5)	0.7 (-0.2, 1.7)	8.2 (3.2)	0.8 (0.0, 1.6)	7.3 (2.4)
Sleep diastolic blood pressure	8.0 (2.5)	1.5 (0.6, 2.4)	7.2 (3.0)	0.6 (-0.2, 1.4)	6.4 (2.1)

5.4 Cardiac autonomic control (II, IV)

In sections 5.2 and 5.3 evidence is presented of a dose-response relationship between shorter gestational age and higher blood pressure and blood pressure variability in adulthood. Mean arterial blood pressure is a product of cardiac output and total peripheral resistance. Cardiac output is a product of heart rate and stroke volume. Cardiac output and vascular resistance are controlled by the autonomic nervous system; at rest HR is controlled mainly by the parasympathetic branch and vascular tone is mainly controlled via the sympathetic nervous system (Wehrwein *et al.* 2013). Therefore, assessment of HRV (indicating parasympathetic autonomic system activity) and PEP (indicating autonomic sympathetic activity) may in part help to explain the observed differences in BP. To expand the plausible mechanisms underlying the observed blood pressure differences, we addressed cardiac autonomic control, measured by heart rate variability in Articles II and IV. The correlations between office blood pressure and autonomic measures are presented in Article II, Table VI; rMSSD, LF and HF were inversely correlated with SBP and DBP (Ps < 0.002), though the correlation coefficients were small (r ranged from -0.13 to -0.25).

Table 9 and Figure 12 show mean differences in resting heart rate variability between the preterm or ELBW/VLBW-born groups compared with controls in the ESTER, HeSVA and McMaster cohorts. In the ESTER cohort, the point estimates of mean differences in rMSSD, LFP and HFP, describing the activity of cardiac vagal modulation of the heart, were negative and the differences were statistically significant only for rMSSD in the early preterm group and for LFP in the late preterm group. In McMaster cohorts, the mean LFP differences were negative but not statistically significant. The point estimate of mean HFP difference was negative in the McMaster young-adult cohort and positive in the adult assessment, though the differences were not statistically significant.

We also addressed sympathetic modulation of the heart in Article IV by evaluating the pre-ejection period (PEP) of the heart in the HeSVA cohort. We found that those born ELBW/VLBW had a 6.8 ms lower PEP compared with normal-birth-weight controls, when adjusted for age and sex, indicating increased cardiac sympathetic activity among those born with ELBW/VLBW.

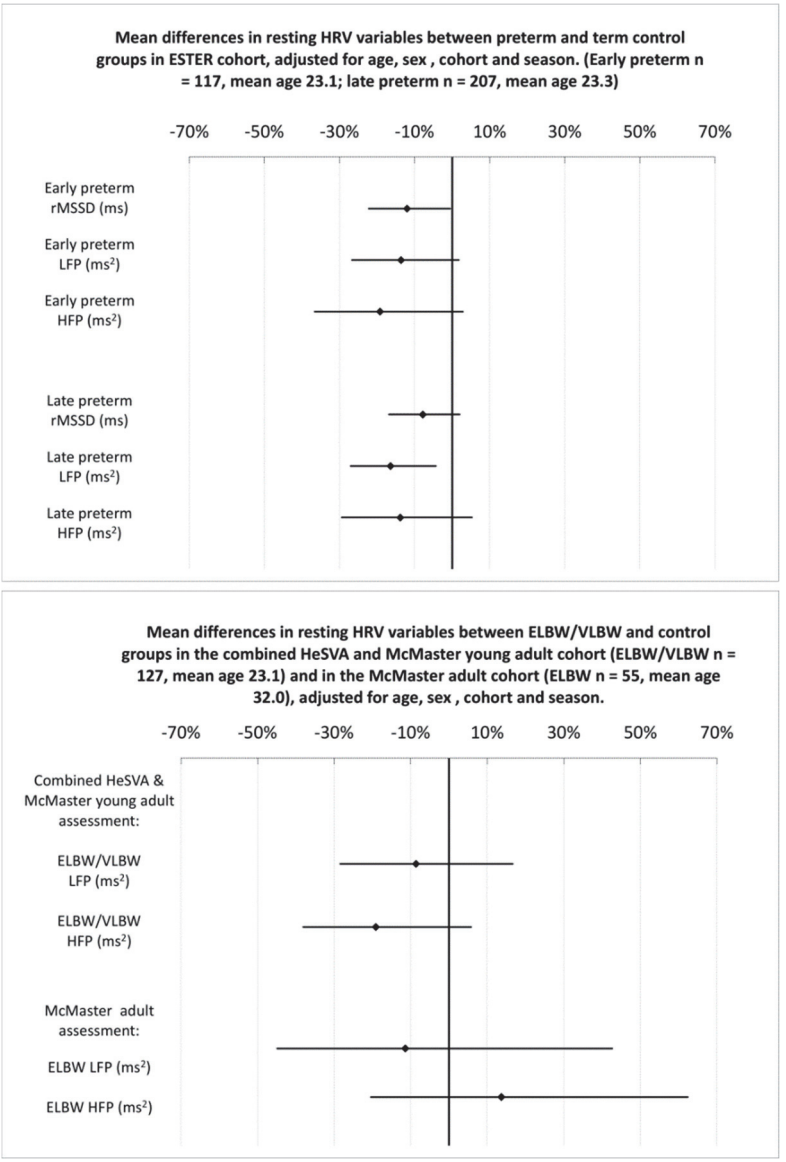


Fig. 12. Mean differences in resting heart rate variability with 95% confidence intervals in adults born preterm or at very- or extremely low birth weight compared with normal-birth-weight controls born at term (zero line), adjusted for age, sex and cohort. (HFP; high frequency power, LFP; low frequency power, rMSSD; root mean square of successive differences).

Table 9. Mean differences in resting heart rate variability and PEP between the preterm and ELBW/VLBW groups vs. controls.

Cohort	rMSSD (ms)		LFP (ms^2)		HFP (ms^2)		PEP (ms)	
	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)
ESTER								
Early preterm (n = 117)[a]	49.6 (1.8)	-12.0% (-22.2%, -0.5%)	1564 (2.1)	-13.6% (-26.7%, 1.8%)	881.2 (3.1)	-19.2% (-36.6%, 2.9%)	-	-
Late preterm (n = 207)[a]	51.1 (1.7)	-7.8% (-16.8%, 2.0%)	1508 (2.1)	-16.4% (-27.0%, -4.3%)	912.8 (2.8)	-13.8% (-29.4%, 5.3%)	-	-
Controls (n = 276)[a]	54.7 (1.8)	-	1788 (2.1)	-	1033 (3.1)	-	-	-
Combined HeSVA & McMaster young adult assessment								
ELBW/VLBW (n= 127)[b]	-	-	794.3 (2.7)	-8.6% (-28.4%, 16.7%)	403.6 (1.1)	-19.1% (-38.1%, 5.8%)	110.5 (10.9)[d]	-6.8 (-11.8, -1.8)[d]
Controls (n = 127)[b]	-	-	850.7 (2.5)	-	565.5 (3.4)	-	117.3 (12.3)[d]	
McMaster adult assessment								
ELBW (n = 55)[c]	-	-	620.4 (2.8)	13.7% (-20.4%, 62.4%)	369.7 (3.9)	-11.4% (-44.9%, 42.7%)	-	-
Controls (n = 56)[c]	-	-	556.3 (2.5)	-	409.3 (3.0)	-	-	-

Abbreviations: ELBW, extremely low birth weight (< 1000 g); VLBW, very low birth weight (< 1500 g); rMSSD, root mean square of successive differences; LFP, low frequency power; HFP, high frequency power; PEP, pre-ejection period. [a]Mean differences (95% CI) when adjusted for age, sex, recruitment cohort (NFBC or FMBR) and season of clinical examination. [b]Mean differences (95% CI) when adjusted for age, sex and cohort. [c]Mean differences (95% CI) when adjusted for age and sex. [d]Data from HeSVA cohort only. Group means are geometric means, except for PEP (arithmetic mean). Mean differences were calculated from log-transformed values, back-transformed, and expressed as percentage difference, except for PEP (difference in ms).

5.4.1 Resting heart rate variability in adults born preterm (II)

Differences in resting heart rate variability between adults born preterm and controls born at term were analysed in the ESTER study and reported in Article II. We found that compared with term-born controls, adults born preterm had lower cardiac vagal activity, indicated by 9.3% lower mean rMSSD and 15.5% lower LFP, when adjusted for age, sex, recruitment cohort, and season of clinical examination (Article II, model 1). When analysing separately with early or late preterm birth as the exposure, significantly lower cardiac vagal activity was observed in adults born early preterm (rMSSD -12.0%) and in adults born late preterm (LFP -16.4%) when compared with term-born controls (Table 9, Article II, model 1). Differences in mean HFP, a measurement of cardiac vagal modulation in respiratory frequency, did not differ significantly in any of the exposure groups (Table 9, Article II, model 1).

When adjusting further for birthweight SD score, gestational diabetes mellitus, gestational hypertension, maternal pre-eclampsia, parental educational level (as a measure of childhood socioeconomic status) and parental smoking, the results were similar (Article II, model 2). However, when the results were adjusted for daily smoking, BMI, height and physical activity, the results were attenuated (Article II, model 3). The results suggested that physical activity and BMI were the most important factors affecting group differences in autonomic control, though the differences were statistically significant only for physical activity: one metabolic equivalent hour of more physical activity per week was associated with 0.5% higher rMSSD, 0.6% higher LFP and 0.9% higher HFP. BMI predicted 1.0% lower rMSSD and 0.9% lower LFP.

5.5 Heart rate recovery in adults born preterm (III)

The association between preterm birth and postexercise heart rate recovery (HRR) in adulthood was analysed in the ESTER study (Article III). We found that those born early preterm had 3.2 bpm lower mean 30-second HRR (HRR_{30S}), 2.5 bpm lower mean 60-second HRR (HRR_{60S}) and 0.095 beats per second lower mean maximum slope in HRR (HRR_{SLOPE}) after exercise compared with controls born at term, when adjusted for age, sex and cohort (Table 10, Figure 13, model 1). Those born late preterm had 2.1 bpm lower HRR_{30s}, 2.8 bpm lower mean HRR_{60s} and 0.061 beats per second lower mean HRR_{SLOPE} after exercise.

When regression model 1 was then supplemented in model 2 with birth weight SD score, gestational diabetes mellitus, gestational hypertension, parental education and maternal smoking, the results were attenuated slightly but remained statistically significant (Article II). When regression model 2 was further supplemented with current smoking, BMI, height and physical activity (model 3), the differences became attenuated to non-significance except for HRR_{30S} in the early preterm group and HRR_{60S} in the late preterm group. Adding BMI and physical activity to the model covariates seemed to have the greatest effect on group differences in HRR variables. When analysing sex-specific differences, we found no statistically significant sex interactions in HRR differences between the groups.

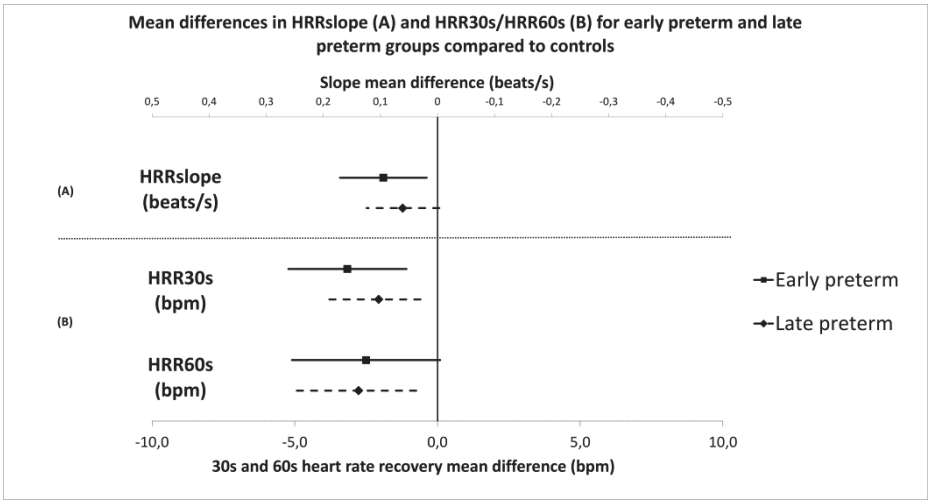


Fig. 13. Mean differences in mean maximum heart rate (HR) slope (HRRslope), HR 30 seconds (HRR30s) and 60 seconds (HRR60s) after cessation of submaximal step test exercise in adults born early and late preterm compared with term controls (zero line), adjusted for age, sex and cohort.

Table 10. Mean differences (with 95% CIs) in heart rate recovery (HRR) measures in adults born early and late preterm compared with controls born at term in the ESTER study (III).

Measurement	Early preterm (n = 103)		Late preterm (n = 178)		Controls (n = 264)
	Mean (SD)	Mean difference (95% CI)[a]	Mean (SD)	Mean difference (95% CI)[a]	Mean (SD)
HRR_{SLOPE} (bpm)	1.07 (0.30)	0.095 (0.019, 0.171)	1.10 (0.31)	0.061 (-0.003, 0.124)	1.16 (0.36)
HRR_{30S} (bpm)	27.3 (8.3)	-3.16 (-5.23, -1.08)	28.4 (8.5)	-2.06 (-3.79, -0.34)	30.6 (9.8)
HRR_{60S} (bpm)	45.0 (12.0)	-2.50 (-5.10, 0.09)	44.6 (9.7)	-2.77 (-4.93, -0.60)	47.3 (12.5)

[a]Mean differences (95% CI) when adjusted for age, sex, recruitment cohort (NFBC or FMBR) and season of clinical examination.

5.6 Sex differences and effects of body composition on cardiac and blood pressure regulation in adults born ELBW/VLBW (IV)

We evaluated sex-specific differences in cardiac autonomic and blood pressure regulation in adults born at extremely (< 1000 g) or very (< 1500 g) low birth weight in the Helsinki Study of VLBW Adults (HeSVA) and the McMaster ELBW cohort (Article IV). The outcomes were analysed in a combined group of young adult participants aged 19 – 27 years born at VLBW in the HeSVA cohort or at ELBW in the McMaster cohort. The analyses were repeated in the McMaster ELBW cohort 10 years later, when the subjects were 29 – 35 years old. At the later assessment (29 – 35 years) we also evaluated the effects of body composition on cardiac autonomic and blood pressure regulation. We found that young women (aged 19 – 27 years) born ELBW/VLBW had reduced parasympathetic control (lnHF -0.35) and higher sympathetic tone (PEP -8.64 ms) compared with control women born at term with normal birth weight when adjusted for age and cohort (Figure 14, Table 3 in Article IV). At the age of 29 – 35 years, women born ELBW had 6.05 mmHg higher systolic- and 4.26 mmHg higher diastolic blood pressure than controls born at term with normal birth weight when adjusted for age (Figure 15, Table 6 in Article IV). With men, none of the differences between ELBW/VLBW vs. control groups in autonomic control and blood pressure variables were statistically significant, except for RRI, which was 182 ms shorter in the ELBW group when adjusted for age, sex, parental educational level and maternal smoking.

When analysing the mediators of cardiac autonomic control and blood pressure in adults born ELBW (aged 29 – 35 years) in Article IV, we found that the birth-weight group (ELBW) explained substantial variance in SBP (3.1%) and DBP (2.7%), although the findings were significant among women only (SBP 8.5%, DBP 6.2%; $P \leq 0.04$). A higher amount of body fat explained a significant amount of variance in all of the measured autonomic outcomes: RRI +7.8%, lnHF +4.6%, lnHF +4.7%, SBP +8.7%, DBP +6.8%. The differences seemed to be driven by women: higher body fat was associated with 12.7% shorter RRI, 13.7% lower lnHF, 7.6% lower lnLF, 18.1% higher SBP and 10.2% higher DBP. Among men, none of the examined predictors of autonomic and blood pressure variables showed significant associations.

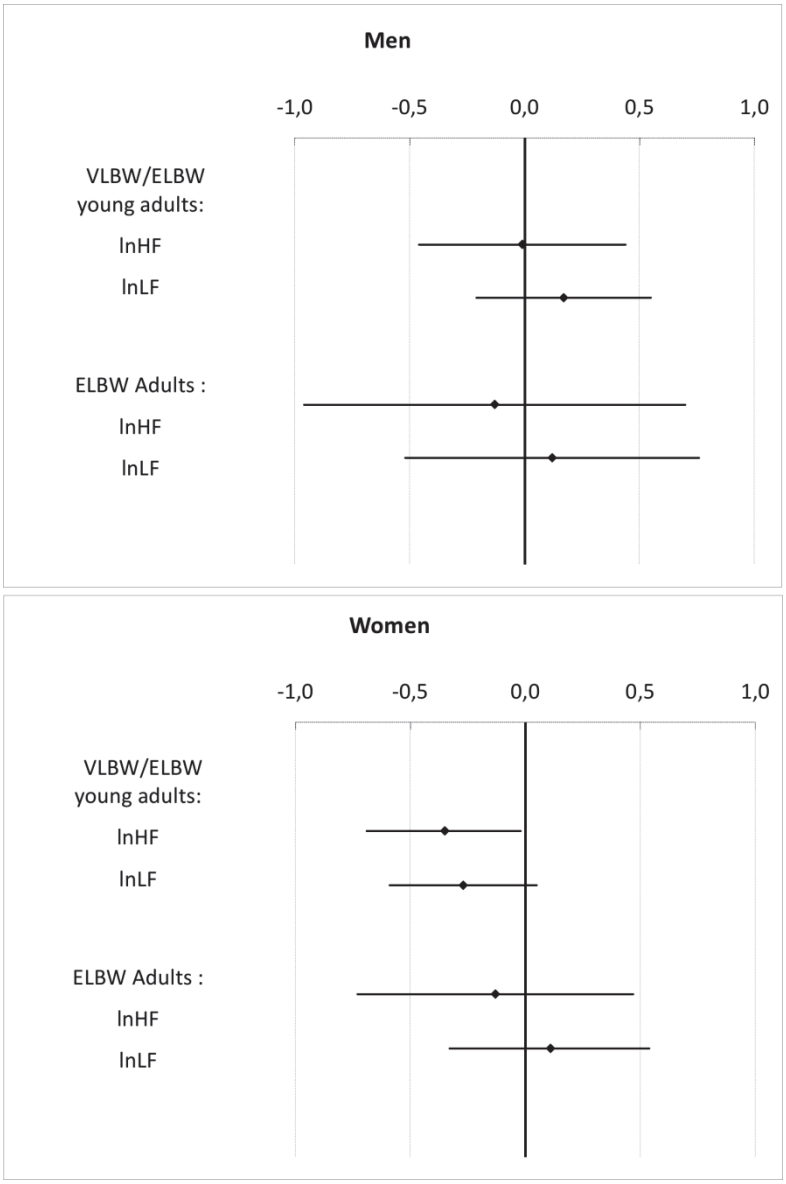


Fig. 14. Mean differences in autonomic control variables (with 95% confidence intervals) by sex in adults born very- or extremely low birth weight compared with normal birth weight controls (zero line), adjusted for age and cohort.

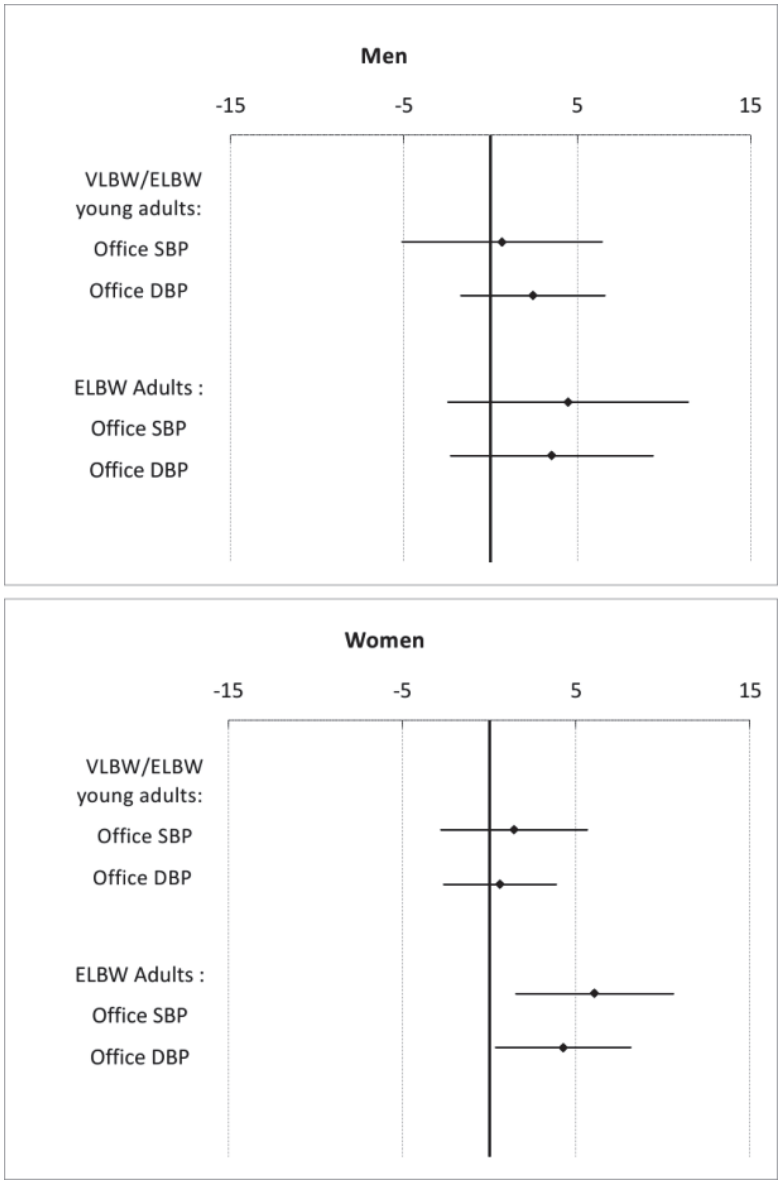


Fig. 15. Mean differences in blood pressure variables (with 95% confidence intervals) by sex in adults born very- or extremely low birth weight compared with normal birth weight controls (zero line), adjusted for age and cohort.

6 Discussion

As have others, we found that adults born preterm had elevated office and ambulatory blood pressure when compared with controls born at term. We also found higher blood pressure variability, reduced cardiac parasympathetic and elevated cardiac sympathetic regulation in adults born preterm. The association between preterm birth and higher blood pressure had already been established before, but the mechanisms were unclear. Our findings suggested that the interrupted maturation of the autonomic nervous system in the third trimester of pregnancy, due to preterm birth, may bear long-lasting consequences as regards later cardiac autonomic regulation. Our findings were consistent with the idea that impaired autonomic regulation may be one mechanism by which previous observations on elevated blood pressure and higher risks of cardiovascular disease in adults born preterm may in part be explained. Our results also suggested that less favourable body composition and reduced physical activity may mediate the association between preterm birth and reduced cardiac regulation in adulthood. Furthermore, our findings suggested that women born preterm may be particularly more vulnerable to the long-term effects of preterm birth on cardiac and blood pressure regulation. In the following sections I will discuss in more detail the individual findings in Articles I – IV.

6.1 Cohort differences

There were three separate cohorts analysed in this study: the ESTER cohort, the HeSVA cohort and the McMaster cohort. As these independent cohorts were not originally planned for combined analysis, there are some background and methodological differences between them (Table 6). On average, the preterm VLBW/ELBW exposure groups in the HeSVA and McMaster cohorts had shorter gestational age: the ELBW/VLBW groups' mean gestational age in the HeSVA cohort and the McMaster young adult cohort was 28.3 weeks; it was 27.2 weeks in the McMaster adult cohort ELBW group; in the ESTER early preterm group 31.8 weeks, and in the late preterm group, 35.8 weeks. The exposure groups' mean birth weights were also lower in the HeSVA and McMaster cohorts: the HeSVA cohort and the McMaster young adult cohort mean birth weight was 970 g, in the McMaster adult cohort 834 g, in the ESTER early preterm group 1780 g and in the late preterm group 2651 g. By design there were also more individuals born SGA in the HeSVA and McMaster young adult cohorts, and in the McMaster

adult cohort than in ESTER. While exposure (lower gestational age and lower birth weight) was stronger in the HeSVA and McMaster cohorts compared with the ESTER cohort, the ESTER study population was larger (N = 753), enabling more study power to detect differences between the study groups.

Although blood pressure was measured in a seated rest position in all cohorts, there were differences in the equipment used: an automatic oscillometric blood pressure monitor was used in ESTER (Omron Intellisense), in HeSVA, Omron HEM-773-E equipment, and in the McMaster adult cohort a BPTru device. In the McMaster young adult cohort a mercury sphygmomanometer was used to measure blood pressure. Surprisingly, mean office blood pressures were lower at the McMaster adult assessment than in the HeSVA, ESTER and McMaster young adult assessments (Table 7). This finding may be affected by the different equipment used in separate cohorts. Mean blood pressure recordings have been reported to show greater values when using a manual mercury manometer compared with an automated oscillometric device (Landgraf *et al.* 2010, Mirdamari & Etebari 2016, Pappaccogli *et al.* 2109).

There were also methodological differences in the measurement of autonomic control variables between the cohorts: while the R-R data was collected using a Polar heart-rate monitor in ESTER, in McMaster young adult assessment R-R intervals were extracted from seated ECG recordings acquired with electrodes applied to the forearms, and in McMaster adult assessment the ECG measurements were recorded with a Finometer. In ESTER, the R-R recordings used to calculate the autonomic measures were recorded while in a seated position during a study-nurse interview, whereas in HeSVA the measurements were done while the participants were standing quietly in a closed laboratory room. In the McMaster young adult study the participants sat quietly in a seated position during the ECG measurements, whereas in the McMaster adult study the measurements were done while the participants were resting in a supine position. Autonomic control measures have been reported to be affected by body position; HFP and LFP indices are relatively high in a supine position, reduced in a seated position and further reduced in a standing position (Young & Leicht 2011), which is in contrast with the cohort differences seen in autonomic variables (Table 9). The mean HFP and LFP values, indices of parasympathetic regulation, were higher in the ESTER cohort than in the HeSVA and McMaster cohorts (Table 9), which was surprising, since the ESTER HRV recordings were done during an seated interview and speaking has been reported to reduce autonomic parasympathetic activity (Mackersie & Calderon-Moultrie 2016).

The analysis software used to calculate the autonomic indices also varied between the cohorts: in ESTER, the HRV measures were calculated using Hearts 1.2 software, in HeSVA the results were calculated with WinCPRS and in McMaster, James Long software was used for analysis. However, similar HRV frequency ranges were selected in all cohorts: 0.04 – 0.15 Hz for LFP and 0.15 – 0.40 Hz for HFP. The R-R data used to calculate HRV measures was visually inspected for artifacts, noise sequences and ectopic beats, which were then replaced with local averages or deleted. As the HRV data used in this study was collected and analysed by different individuals in each cohort without any pre-set coordination of the methodology, it is likely that there were differences in manual processing and editing of the R-R data. These differences in clinical setups, equipment, data collection, processing and editing of the data may partially explain the differences in autonomic variables seen between the cohorts (Table 9). However, while these posture and methodological differences may affect results between the cohorts, the circumstances were similar for exposure and control groups within each cohort, and the source cohort was accounted for in all analyses where necessary.

6.2 Office blood pressure (I – IV)

The association between preterm birth and elevated blood pressure in later life has been extensively reported (Table 2). Most of the previous studies have been focused on adults born very preterm or at ELBW/VLBW. Our results align with earlier findings: we too found higher SBP and DBP in adults born early preterm. However, we were able to supplement earlier findings, as we also found higher SBP and DBP in adults born late preterm, at a mean age of 23 years. As the blood pressure differences were more prominent in adults born early preterm (ESTER cohort, Article I, Table 7), our results suggested a dose-response relationship between shorter gestational age and higher blood pressure in adulthood. This finding supports earlier reports on the inverse relationship between gestational age at birth and adulthood blood pressure (Siewert-Delle & Ljungman 1998, Leon *et al.* 2000, Järvelin *et al.* 2004, Dalziel *et al.* 2007, Sipola-Leppänen *et al.* 2014).

Studies on children and adolescents born preterm suggest that the changes in BP occur early in life (Bonamy *et al.* 2005, Martinez- Aguayo *et al.* 2012, Sipola-Leppänen *et al.* 2014) and that these alterations may become amplified with increasing age (Moore *et al.* 1999, Juonala *et al.* 2015). We found no statistically significant difference in office blood pressure in adults born ELBW/VLBW at a

mean age of 23 years compared with term controls (Article IV, Table 7). However, a decade later, at a mean age of 32 years, we found significantly higher SBP and DBP in adults with a history of ELBW, suggesting a more rapid increase in blood pressure with increasing age in young adulthood among those born preterm at ELBW (Article IV, Table 7). This finding supports the hypothesis that alterations in cardiac and blood pressure regulation may become amplified with increasing age.

6.3 Ambulatory blood pressure and blood pressure variability (I)

Evidence of a connection between preterm birth and elevated ambulatory blood pressure in adulthood has been reported in a few studies, as presented in Table 3. Recent literature has connected preterm birth with higher 24-hour, awake and sleep-time systolic and diastolic blood pressure (Doyle *et al.* 2003, Roberts *et al.* 2014, Lewandowski *et al.* 2015, Markopoulou *et al.* 2018, Paquette *et al.* 2018, Haikerwal *et al.* 2020). We also found a connection between early preterm birth and higher mean 24-hour, awake and sleep ambulatory blood pressure. The difference seemed to be more prominent in daytime measurements. In the late preterm group we found a tendency towards higher ambulatory blood pressure than in the control group, but the differences were smaller and the result did not reach statistical significance. This may again be suggestive of a dose-response relationship between the degree of prematurity at birth, and ambulatory blood pressure in adulthood.

Though blood pressure variability has been connected with higher overall mortality (Stevens *et al.* 2016), organ-damage progression (Frattola *et al.* 1993), vascular events (Clement et al. 2003) and left-ventricular hypertrophy (Parati *et al.* 2006), it has been less-well studied in adults born preterm or at low birth weight. Hovi *et al.* reported higher systolic blood pressure variability in men born preterm and Kerkhof *et al.* reported higher systolic and diastolic blood pressure variability in adults born preterm (Hovi *et al.* 2010, Kerkhof *et al.* 2012). We also found higher blood pressure variability in adults born early preterm, as indicated by higher individual standard deviations of systolic and diastolic blood pressure. In adults born late preterm, the differences in blood pressure variability were smaller and mainly non-significant, again suggesting a dose-response relationship between the degree of prematurity and blood pressure variability.

6.4 Cardiac autonomic control (II, IV)

We addressed resting cardiac autonomic function in adults born preterm in Articles II and IV. As presented in Figure 12 and Table 9, in the ESTER study we found lower mean rMSSD and lower mean LFP in adults born preterm compared with term-born controls. Mean HFP was also lower in the ESTER preterm-born groups, but the differences were not statistically significant. In the combined McMaster & HeSVA study (IV) we did not find significant group differences in autonomic parasympathetic control measures (LFP, HFP) in ELBW/VLBW vs. control groups. However, in sex-specific analyses we observed lower mean HFP in 23-year-old women born ELBW/VLBW. Interestingly, we also found shorter PEP in young adults born ELBW/VLBW, indicative of increased cardiac sympathetic activity in ELBW/VLBW adults compared with term-born controls. Although the confidence intervals, especially in the parasympathetic measures, leave some uncertainty as regards differences in cardiac autonomic control, overall, our results are consistent with altered autonomic regulation in adults born preterm. Our results suggest that both the sympathetic and the parasympathetic arms of the autonomic system are affected by preterm birth and that the alterations exceed in individuals born late preterm. Our findings suggest that the altered autonomic control seen in preterm-born children remains at least to young adulthood. We did not observe differences in autonomic regulation among ELBW/VLBW adults in their thirties, which may suggest that autonomic regulation does not decline more rapidly among those with a history of preterm birth at ELBW/VLBW. This finding is in contrast to findings in office blood pressure, which was significantly higher in ELBW/VLBW adults in their thirties, whereas there were no blood pressure differences in the sample studied at a mean age of 23.

6.5 Heart rate recovery (III)

Attenuated heart rate recovery after exercise, indicating reduced parasympathetic activity, is an independent and powerful predictor of overall mortality (Cole *et al.* 2000, Nishime *et al.* 2000). To our knowledge, only a few studies have addressed heart rate recovery in adults born preterm (Table 4). As presented in Table 4, lower HRR after maximal exercise has been reported in 13-year-old children born preterm and in adults born preterm at VLBW compared with controls born at term (Haraldsdottir *et al.* 2018, Haraldsdottir *et al.* 2019). Huckstep *et al.* found

decreased heart rate recovery after exercise in adults born preterm compared with term controls, suggestive of reduced parasympathetic function underlying reduced myocardial reserve (Huckstep *et al.* 2020).

Aligned with these reports, in the ESTER study (Article III) we also found significantly lower HRR after exercise in adults born early- or late preterm compared with term-born controls (Figure 13, Table 10). Though not all of the differences reached statistical significance, our results were suggestive of a dose-response relationship between the degree of prematurity and impaired HRR in adulthood. As HRR after exercise results primarily by way of reactivation of the parasympathetic arm of the autonomic nervous system (Imai *et al.* 1994), this finding further strengthens the suggested association (presented in section 6.4) between preterm birth and reduced cardiac vagal modulation in adulthood among those born preterm.

6.6 Sex differences in cardiac and blood pressure regulation (I - IV)

Earlier studies have shown that women born preterm, in particular, may have a more prominent increase in adulthood office blood pressure (Hovi *et al.* 2016 & Skudder-Hill *et al.* 2019) compared with women born at term. Our findings in the McMaster adult cohort (Article IV) were similar: women born ELBW had significantly higher office SBP and DBP compared with women born at term, whereas in men there was no difference between the ELBW and term control groups (Figure 15).

Previous studies have also suggested that the differences in ambulatory blood pressure in adults born preterm compared with peers born at term are also higher among women (Hovi *et al*. 2010, Parkinson *et al.* 2013, Haikerwal *et al.* 2020) than among men. In contrast to these results, we found higher systolic ambulatory blood pressure in early- and late-preterm-born men, whereas the difference in women was non-significant (Article I). However, as regards diastolic ambulatory blood pressure our findings were aligned with earlier literature and women born early preterm had higher 24-hour and awake diastolic blood pressure compared with term-born women, and the difference with men was non-significant.

Although we found no statistically significant interactions between the effects of sex and preterm birth on blood pressure, heart rate recovery or autonomic control variables (except for awake SBP, which was higher among late-preterm-born men in the ESTER study [I]), we ran analyses separated by sex for all key outcomes in Articles I-IV, because earlier literature on the association between

birth weight and autonomic control has shown sex differences (Kajantie & Räikkönen 2010). In contrast to earlier reports on higher blood pressure in preterm-born women (Hovi *et al.* 2016 & Skudder-Hill *et al.* 2019), in the ESTER study (Article II) we found that the group differences in autonomic control measurements (rMSSD, HFP, LFH) were nominally greater in men than women. However, in the ESTER study (Article III) we found that women born late preterm had lower mean HRR than men, in line with earlier findings on the association between preterm birth and pronounced adulthood office blood pressure in women (Kajantie & Hovi 2014), and with a stronger autonomic response to stress reported in women born VLBW (Kajantie & Räikkönen 2010). In the combined HeSVA & McMaster young-adult study (Article IV) women born ELBW/VLBW seemed to drive the observed differences between the groups in autonomic regulation: women born ELBW/VLBW had significantly lower HFP and shorter PEP, indicating lower parasympathetic activity and higher sympathetic tone, whereas with men there were no differences between ELBW/VLBW and NBW groups as regards any of the autonomic or blood pressure outcomes.

Although the sex-specific differences were not replicated in all studies in this thesis, our combined results suggest that women born preterm may be more vulnerable to the long-term effects of preterm birth at ELBW/VLBE on blood pressure and autonomic regulation. Though the pathogenesis behind this finding is unknown, it has been proposed that women born preterm are more sensitive to raised blood pressure during stress (Kistner *et al.* 2010), and low birth weight has been connected to stronger autonomic and blood pressure responses to stress in women (Kajantie & Räikkönen 2010), which may in part explain this finding.

6.7 The effects of body composition on cardiac and blood pressure regulation (II-IV)

Previous literature has connected reduced cardiac autonomic function with lower physical activity and a more unfavourable body composition (Rossi *et al.* 1989, Karason *et al.* 1999, Felber *et al.* 2006, Kajantie *et al.* 2010). Higher BMI, an increased amount of body fat and increased visceral fat tissue have been connected to higher blood pressure, higher sympathetic activity and reduced parasympathetic activity in healthy adults (Molfino *et al.* 2009, Hillebrand *et al.* 2014, Smoljo *et al.* 2020). As body composition and physical activity may influence autonomic regulation, and adults born very preterm are reported to have

a less favourable body composition (Breukhoven *et al.* 2012, Mathai *et al.* 2013, Crane *et al.* 2016), lower fitness levels (Svedenkrans *et al.* 2013, Tikanmäki *et al.* 2016) and they take less exercise (Kajantie *et al.* 2010b), it may be likely that they are at a higher risk of altered autonomic regulation, and the differences may be mediated via these factors. We evaluated the impact of physical activity on cardiac and blood pressure regulation in Articles II – IV. We found that lower rates of physical activity and increased adiposity may partly mediate the altered parasympathetic regulation (Articles II-IV). In Article IV we also found that a higher body fat explained amount of variance in SBP and DPB in addition to autonomic variables, and the differences were more pronounced in women than in men. This suggests that women born preterm may be more vulnerable to the adverse effects of low-level physical activity and unfavourable body composition than men. We found impaired autonomic regulation in those born preterm at ELBW/VLBW even when body composition was accounted for in the analysis, though the connection is also likely to be mediated in other ways.

In the general population physical activity and exercise are known key lifestyle measures in the prevention and management of hypertension (Chobanian *et al.* 2003, Guidelines Committee 2003, Pescatello *et al*. 2004, Cornelissen *et al.* 2005). Aerobic endurance training promotes a more favourable body composition via reducing vascular resistance, via sympathetic nervous system activity and via the renin-angiotensin system (Pescatello *et al.* 2004). Although we are unaware of any lifestyle intervention studies focusing specifically on adults born preterm or at ELBW/VLBW, it may be expected that beneficial lifestyle and dietary changes in this group would be at least similar to those seen in the general population. In fact, as we know that adults with a history of preterm birth engage in less physical activity (Kajantie *et al.* 2004), have an increased preference for fatty foods (Lussana *et al*. 2008), and have a lower intake of vegetables, fruit and milk products (Kaseva *et al.* 2013, Matinolli *et al.* 2018), adults born preterm may actually have a greater potential to benefit from specific lifestyle interventions enhancing physical activity and a healthier diet. This may apply especially to young women born very preterm, who are reported to have poorer adherence to healthy eating guidelines than peers born at term (Matinolli *et al.* 2018).

6.8 Strengths and limitations

This study is based on data from three different cohorts (ESTER, HeSVA and McMaster) with a wide range of outcome measurements. The main strength in the

ESTER cohort is the relatively large study population, which was selected to cover the whole range of preterm births in a specific geographical region (reducing the chance of referral bias). The relatively large sample size in the ESTER study enabled us to evaluate the effects of late preterm birth and the dose-response relationships between the degree of prematurity and the outcomes. The wide range of measurements in ESTER allowed us to examine autonomic function by several methods; via heart rate variability and via heart rate recovery after exercise stimulus. A strength of the HeSVA study population is the prospective cohort with controls matched for age, sex and birth hospital. Strengths in the McMaster study included a geographically determined cohort with reasonably high follow-up rates, first at young adulthood and second at more mature adulthood, which enabled comparisons at different stages of adulthood.

A key strength of this study is that there were three separate cohorts, which enabled us to test our hypotheses as regards autonomic and blood pressure regulation in separate cohort populations from different geographic regions. Replicating the results allowed us to evaluate better how well the observed findings can be generalized to the whole population of adults born preterm. There was a wide range of background variables and clinical measurements in all three source cohorts, which enabled us to adjust the results for several key confounding and mediating factors in all cohorts. However, it cannot be excluded that in addition to the prenatal, maternal and parental background variables which we adjusted for, additional factors such as sepsis, post-natal growth, bronchopulmonary dysplasia or nutrition during the neonatal period might affect the long-term cardiovascular health of those born preterm. As we were not able to account for all the potential early-life insults in our analyses, as a result of the selected study protocols, the possibility of residual confounding still remains.

A limitation of this study is that because these cohorts were not originally planned together, there were differences in study recruitment between cohorts, and methodological differences between the study procedures and clinical measurements. As the data in all three cohorts was already collected when this study was initiated, we were unable to retrospectively harmonize data-collection procedures and methods. Thus, any comparisons of differences between the cohorts should be made with caution. However, when the data from two different cohorts (HeSVA and McMaster) was combined in Article IV, the two study cohorts exhibited no overall differences in age, height, weight, general health, or SES, and the source cohort was accounted for in all analyses where necessary. A significant limitation as regards this thesis is that I did not participate in the

clinical data-collection phase in any of the cohorts. Although the study protocols and methods were carefully recorded during data collection, a chance of misinterpretation, unknown bias or unawareness of significant information during data collection may confound the results.

In Article I we assessed short-term (24-hour) blood pressure variability (SD) using ambulatory measurements with 20- or 30-min blood pressure measurement intervals. A shortcoming in Article I was that we did not have data on beat-to-beat very short-term variability analysis. Beat-to-beat blood pressure data would have enabled a more detailed spectral analysis of very short-term blood pressure variability (Parati *et al.* 2018), but as it would have required continuous laboratory-setting blood-pressure measurement, it was out of the scope of this study. Similarly, mid-term (day-to-day) and long-term (visit-to-visit) blood pressure variability would have provided a good deal of important information on cardiac regulation, but such analyses were out of the scope of the study as a result of the selected study protocol, with one clinical visit for each participant. As short-term, mid-term and long-term blood pressure variabilities seem to correlate poorly (Abellàn-Huerta *et al.* 2018), and as long-term blood systolic blood pressure variability has been shown to predict cardiovascular disease events, cardiovascular disease mortality, coronary artery disease and stroke, in addition to overall mortality (Stevens *et al.* 2016), such analyses would have given valuable additional information in the context of this study. Other limitations in Article I include the availability of ABP measurement devices, which was limited, and some of the participants declined to wear the equipment, which might have led to selection bias. However, this would have affected the results only if there were differences in selection between the exposure and control groups, which is unlikely, but cannot be excluded. Additionally, as presented in Article I, Table S2, the background characteristics were similar among those who participated in clinical examination and were included in ABP measurement, compared with those who participated but did not have sufficient ABP data recorded. Furthermore, as some of the participants did not wear an accelometer, we were not able to objectively measure sleep and awake times for all participants, which may have affected the accuracy of the outcomes.

In Article II a significant limitation was that due to suboptimal data quality, we were unable to calculate HRV outcomes for a number of participants, which could have led to increased inaccuracy and more conservative outcome estimates. Furthermore, as the R-R recordings were done during an interview, talking may have affected the analysis of respiratory frequency (HFP). However, as the study

protocol was similar for all study groups, it is unlikely that this would have affected the observed group differences.

A limitation in Article III was that we did not evaluate maximal exercise stimulus, and the exercise stimulus was not individually personalized to match each individual's maximum exercise capacity. However, as sub-maximal exercise is reported to provide comparable prognostic information as maximal exercise (Cole *et al.* 2000), and as the test protocol was similar for all study groups, it is unlikely, but cannot be excluded, that this would have had an effect on the observed differences. Additionally, as the relative exercise load and physical fitness of each individual participant may affect HRR, it cannot be excluded that group differences in physical fitness may have confounded the results. Therefore, it is possible that the results could be partially explained by differences in the participants' physical fitness. However, this is unlikely, as there were no differences in self-reported physical activity between the study groups and the differences remained after adjusting the models for physical activity.

The main limitation in Article IV was that the number of participants having HRV and BP measurements available in connection with both clinical visits was limited. However, the study power was still sufficient to reveal differences in autonomic and blood pressure regulation between the study groups. Increased participation rates might have increased precision. Other limitations in Article IV were differences in recruitment, measurements and study protocols between the HeSVA and McMaster cohorts. However, there were no differences in key background variables between the cohorts and we adjusted for source cohort in all analyses where necessary.

6.9 Significance and future perspectives

Previous research has shown that preterm birth is associated with increased risks of cardiovascular diseases including elevated blood pressure and ischaemic heart disease, but the mechanisms, though already widely studied, are not yet fully understood (Lewandowski *et al.* 2020). Although there is yet much to learn about the detailed mechanisms by which cardiovascular disease risks are connected with preterm birth, our findings support the DOHaD theory suggesting that early-life experiences may have consequences as regards cardiometabolic health throughout an individual's life. Our findings on altered cardiac and blood pressure regulation in adults born preterm suggest one significant mechanism by which cardiovascular risks in adults born preterm are increased. As the recognition of

preterm birth as a significant risk factor of cardiovascular disease may be important for future clinicians and best-practice guidelines (Lewandowski *et al.* 2020), the evidence provided in this study may further help to highlight the significance of preterm birth as a risk factor of cardiovascular disease. The observations on elevated cardiovascular risks in adults born preterm reported in Article I of this study have already affected best-practice guidelines and have been referenced in a national position paper on cardiovascular prevention in high-risk patients (Campanini *et al.* 2015).

Only a few earlier studies have concerned ABP in adults born preterm, and those that have were focused on subjects born at very- or extremely low birth weight. Even fewer studies have been carried out on ABP variability. Previous studies reporting cardiac autonomic function and heart rate recovery in adults born preterm are also scarce and the ones that exist report on adults born at ELBW. Our findings on ABP, ABP variability and alterations in autonomic control concerned not only adults born early preterm, but also adults born late preterm – a group representing the great majority of all individuals born preterm. Our finding of increased sympathetic activity in adults born preterm at VLBW has not been reported earlier to our knowledge.

Our findings on the associations between body composition and physical activity versus reduced autonomic control further highlight the importance of healthy lifestyles and physical activity for individuals with a history of preterm birth. As regulatory disturbances in individuals born preterm may be revealed only with increasing age (Morrison *et al.* 2016), long-term follow-up of these cohorts of preterm individuals will be very important in future.

This study was conducted on adults born ELBW, VLBW, and early or late preterm or at term, when the participants were in their twenties or early thirties. Clinical manifestations of common cardiovascular risk factors rarely occur at this young age. The participants in the earliest cohorts of this study are now reaching middle age. As it has been suggested that the alterations in autonomic regulatory control among those born ELBW may become more pronounced with increasing age and declining cardiovascular health (Mathewson *et al.* 2014 and Mathewson *et al.* 2015), it may be that the observations we made in this study would be even more pronounced if the analyses were to be repeated at a later age. Also, it will be very interesting in future research to evaluate the extent to which the increased risks will become manifest as cardiovascular disease outcomes. Additionally, future investigators will have the opportunity establish more clearly the prognostic value of preterm birth as a risk factor of cardiovascular disease. A

clearer picture of the mechanisms and the magnitude of risks of cardiovascular disease associated with preterm birth will allow a better possibility to create appropriate screening policies and raise awareness among preterm-born individuals themselves. Finally, the effectiveness of dietary and/or lifestyle interventions in the aging and growing population of adults with a history of preterm birth remains as an intriguing opportunity for future research.

7 Conclusions

1. Adults born preterm show elevated levels of several risk factors of cardiovascular disease compared with peers born at term: higher office blood pressure; higher 24-hour, awake- and sleep ambulatory blood pressure; higher blood pressure variability; lower resting parasympathetic activity; and higher sympathetic activity and reduced heart rate recovery after exercise.
2. These risks were also present, though to a lesser extent, in a larger group of young adults born late preterm, suggesting a dose-response relationship between gestational age at birth and elevated levels of risk factors of cardiovascular disease.
3. Impaired autonomic regulation may be one mechanism by which elevated blood pressure in adults born preterm can be explained.
4. Reduced physical activity and increased adiposity may explain the observed differences in cardiac autonomic and blood pressure regulation.
5. Many of the relative risks seemed more prominent with women born preterm, suggesting a sex-specific difference in early programming of cardiac regulation.
6. Combined, our findings suggest that adults born preterm, especially women, may be at a greater risk of developing manifest cardiovascular disease and thus may specifically benefit from a healthy lifestyle.

List of references

Abellán-Huerta J, Prieto-Valiente L, Montoro-García S, Abellán-Alemán J, Soria-Arcos F. (2018). Correlation of Blood Pressure Variability as Measured By Clinic, Self-measurement at Home, and Ambulatory Blood Pressure Monitoring. *Am J Hypertens,* 31(3):305-312. https://doi.org/10.1093/ajh/hpx183

Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PF, Blanco CE. (2005). Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. *J Physiol,* 568(Pt 1):333-341. https://doi.org/10.1113/jphysiol.2005.093641

Arai Y, Saul JP, Albrecht P, et al. (1989). Modulation of cardiac autonomic activity during and immediately after exercise. *Am J Physiol,* 256(1):H141. https://doi.org/ 10.1152/ ajpheart.1989.256.1.h132

Åstrand PO, Ryhming I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol,* 7(2):218-221. https://doi.org/10.1152/jappl.1954.7.2.218

Barker DJP. (1998). Mothers, babies and health in later life. *Edinburgh: Churchill Livingstone.*

Barker DJP & Osmond C. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *The Lancet,* 327(8489): 1077—1081. https://doi.org/10.1016/s0140-6736(86)91340-1

Barker DJP, Winter PD, Osmond C, Margetts B & Simmonds SJ. (1989). Weight in infancy and death from ischaemic heart disease. *Lancet,* 2(8663): 577—80. https://doi.org/10.1016/s0140-6736(89)90710-1

Barker DJP, Godfrey KM, Gluckman PD, Harding JE, Owens JA & Robinson JS. (1993). Fetal nutrition and cardiovascular disease in adult life. *The Lancet,* 341(8850): 938—941. https://doi.org/10.1016/0140-6736(93)91224-a

Barker DJ, Osmond C, Forsen TJ, Kajantie E & Eriksson JG (2005). Trajectories of growth among children who have coronary events as adults. *N Engl J Med,* 353(17): 1802—9. https://doi.org/10.1056/nejmoa044160

Barker DJP (2007) The origins of the developmental origins theory. *Journal of Internal Medicine,* 261(5): 412—417. https://doi.org/10.1111/j.1365-2796.2007.01809.x

Bates ML, Levy PT, Nuyt AM, Goss KN, Lewandowski AJ, McNamara PJ. (2020). Adult Cardiovascular Health Risk and Cardiovascular Phenotypes of Prematurity. *The Journal of Pediatrics,* Volume 227: 17-30. https://doi.org/10.1016/j.jpeds.2020.09.019

Benarroch EE. (2008). The arterial baroreflex Functional organization and involvement in neurologic disease. *Neurology,* 71(21):1733-8. https://doi.org/10.1212/01. wnl.0000335246.93495.92

Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med,* 338:1650–1656. https://doi.org/10.1056/nejm199806043382302

Bigger JT, Steinman RC., Rolnitzky LM., Fleiss JL., Albrecht P., & Cohen RJ. (1996). Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation,* 93(12), 2142-2151. https://doi.org/10.1161/01.cir.93.12.2142

Billman GE. (2013). The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Frontiers in Physiology,* 4, 26. https://dx.doi.org/10.3389%2Ffphys.2013.00026

Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. (2006). Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. *International Heart Journal,* 47 (3):431–440. https://doi.org/10.1536/ihj.47.431

Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, et al. (2012). 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,* 379:2162–2172. https://doi.org/10.1016/s0140-6736(12)60820-4

Boivin A, Luo ZC, Audibert F, et al. (2012). Pregnancy complications among women born preterm. *CMAJ,* 184(16):1777-1784. https://dx.doi.org/10.1503%2Fcmaj.120143

Bonamy AK, Bendito A, Martin H, Andolf E, Sedin G, Norman M. (2005). Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. *Pediatr Res,* 58(5):845-9. https://doi.org/10.1203/01.pdr.0000181373.29290.80

Breukhoven PE, Kerkhof GF, Willemsen RH, Hokken-Koelega AC. (2012). Fat mass and lipid profile in young adults born preterm. *J Clin Endocrinol Metab,* 97(4):1294-302. https://doi.org/10.1210/jc.2011-2621

Campanini M, Pinna G, Nardi R. (2015). on behalf of the FADOI Cardiovascular Prevention Position Statements Group Nardi. The FADOI (Federation of Associations of Hospital Doctors on Internal Medicine) position paper on cardiovascular prevention in the higher risk complex patients. *Ital J Med,* 9: 387-404. http://dx.doi.org/10.4081/itjm.2015.669

Carey RM, Padia SH. (2018). Physiology and Regulation of the Renin–Angiotensin–Aldosterone System. *Textbook of Nephro-Endocrinology (Second Edition),*1-25. https://doi.org/10.1016/B978-0-12-803247-3.00001-5

Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI, Chambless LE. (2003). Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol,* 158, 1058-1067. https://doi.org/10.1093/aje/kwg260

Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. (2017). Preterm birth and risk of heart failure up to early adulthood. *J Am Coll Cardiol,* 69:2634–2642. https://doi.org/10.1016/j.jacc.2017.03.572

Chawanpaiboon S, Vogel JP, Moller AB, et al. (2019). Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Global Health,* 7:e37-46. https://doi.org/10.1016/S2214-109X(18)30451-0

Chess GF, Tam RMK, Calaresu FR. (1975). Influence of cardiac neural inputs on rhythmic variations of heart period in the cat. *Am J Physiol,* 228:775-780. https://doi.org/10.1152/ajplegacy.1975.228.3.775

Christensen JH, Toft E, Christensen MS, Schmidt EB. (1999). Heart rate variability and plasma lipids in men with and without ischaemic heart disease. *Atherosclerosis,* 145, 181-186. https://doi.org/10.1016/s0021-9150(99)00052-0

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. (2003). National high blood pressure education program coordination committee. Seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension,* 42: 1206–125. https://doi.org/10.1161/01.HYP.0000107251.49515.c2

Clairambault J, Curzi-Dascalova L, Kauffmann F, Medigue C, Leffler C. (1992). Heart rate variability in normal sleeping full-term and preterm neonates. *Early Hum Dev,* 28:169–83. https://doi.org/10.1016/0378-3782(92)90111-s

Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. (2003). Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med,* 348:2407–2415. https://doi.org/10.1056/nejmoa022273

Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med,* 341(18):1351-7. https://doi.org/10.1056/nejm199910283411804

Cole CR, Foody JM, Blackstone EH, Lauer MS. (2000). Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med,* 132(7):552-5. https://doi.org/10.7326/0003-4819-132-7-200004040-00007

Cornelissen VA, Fagard RH. (2005). Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension,* 46(4): 667-675. https://doi.org/10.1161/01.hyp.0000184225.05629.51

Crane JD, Yellin SA, Ong FJ, Singh NP, Konyer N, Noseworthy MD, et al. (2016). ELBW survivors in early adulthood have higher hepatic, pancreatic and subcutaneous fat. *Sci Rep,* 6: 31560. http://dx.doi.org/10.1038/srep31560

Crump C, Sundquist K, Sundquist J, Winkleby MA. (2011). Gestational age at birth and mortality in young adulthood. *JAMA,* 306:1233–1240. https://doi.org/10.1001/jama.2011.1331

Crump C, Winkleby MA, Sundquist K, Sundquist J. (2011). Risk of hypertension among young adults who were born preterm: a Swedish national study of 636,000 births. *Am J Epidemiol,* 173:797–803. https://doi.org/10.1093/aje/kwq440

Crump C, Howell EA, Stroustrup A, McLaughlin MA, Sundquist J, Sundquist K. (2019). Association of preterm birth with risk of ischemic heart disease in adulthood. *JAMA Pediatr,* 173(8):736–743. https://doi.org/10.1001/jamapediatrics.2019.1327

Crump C, Sundquist J, Sundquist K. (2020). Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. *Diabetologia,* 63:508–518. https://doi.org/10.1007/s00125-019-05044-z

Cooper R, Atherton K & Power C. (2009). Gestational age and risk factors for cardiovascular disease: evidence from the 1958 British birth cohort followed to midlife. *Int J Epidemiol,* 38(1): 235—44. https://doi.org/10.1093/ije/dyn154

Dalziel SR, Parag V, Rodgers A & Harding JE. (2007). Cardiovascular risk factors at age 30 following pre-term birth. *International Journal of Epidemiology,* 36(4): 907—915. https://doi.org/10.1093/ije/dym067

de Boer RW, Karemaker JM, Strackee J. (1987). Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol,* 253:H680–H689. https://doi.org/10.1152/ajpheart.1987.253.3.h680

de Jong F, Monuteaux MC, van Elburg RM, Gillman MW & Belfort MB. (2012). Systematic Review and Meta-Analysis of Preterm Birth and Later Systolic Blood Pressure. *Hypertension,* 59(2): 226—234. https://doi.org/10.1161/hypertensionaha.111.181784

Dekker, J. M., Crow, R. S., Folsom, A. R., Hannan, P. J., Liao, D., Swenne, C. A., & Schouten EG. (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: The ARIC study.atherosclerosis risk in communities. *Circulation 102(11),* 1239-1244. https://doi.org/10.1161/01.cir.102.11.1239

De Rogalski Landrod I, Roche F, Pichot V, et al. (2007). Autonomic nervous system functioning in premature and full-term infants from theoretical term to 7 years. *Auton Neurosci,* 136:105-109. https://doi.org/10.1016/j.autneu.2007.04.008

Doyle LW, Faber B, Callanan C, Morley R. (2003). Blood pressure in late adolescence and very low birth weight. *Pediatrics,* 111:252-257. https://doi.org/10.1542/peds.111.2.252

Engle WA, Tomashek KM, Wallman C. (2007). and the Committee on F & Newborn "Late-Preterm" Infants: A Population at Risk. *Pediatrics,* 120(6): 1390—1401.

Eiselt M, Curzi-Dascalova L, Clairambault J, Kauffmann F, Medigue C, Peirano P. (1993). Heart-rate variability in low-risk prematurely born infants reaching normal term: a comparison with full-term newborns. *Early Hum Dev,* 32:183–95. https://doi.org/10.1016/0378-3782(93)90011-i

Felber Dietrich D, Schindler C, Schwartz J, Barthélémy JC, Tschopp JM, Roche F, et al. (2006). Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: Results of the SAPALDIA study. *Europace,* 8(7):521-529. https://doi.org/10.1093/europace/eul063

Flahault A, Oliveira FR, De Meulemeester J, Ravizzoni DD, Cloutier A, Gyger G, et al. (2020). Arterial Structure and Stiffness Are Altered in Young Adults Born Preterm. *Arterioscler Thromb Vasc Biol,* 40(10):2548-2556. https://doi.org/10.1161/atvbaha.120.315099

Fountain JH, Lappin SL. Physiology, Renin Angiotensin System. [Updated 2020 Jul 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Accessed 27.1.2021.

Frattola A, Parati G, Cuspidi C, Albini F, Mancia G. (1993). Prognostic value of 24-hour blood pressure variability. *J Hypertens,* 11:1133–1137. https://doi.org/10.1097/00004872-199310000-00019

Fritsch JM, Rea RF, Eckberg DL. (1989). Carotid baroreflex resetting during drug-induced arterial pressure changes in humans. *Am J Physiol,* 256:R549–R553. https://doi.org/10.1152/ajpregu.1989.256.2.r549

Fyfe KL, Yiallourou SR, Wong FY, Horne RSC. (2014). The development of cardiovascular and cerebral vascular control in preterm infants. *Sleep Med Rev,* 18:299-310. https://doi.org/10.1016/j.smrv.2013.06.002

Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RSC. (2015). The effect of gestational age at birth on post-term maturation of heart rate variability. *Sleep,* 38 pp. 1635-1644. https://doi.org/10.5665/sleep.5064

Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM et al. (2001). Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care,* 24, 1793-1798. https://doi.org/10.2337/diacare.24.10.1793

Gluckman PD, Hanson MA, Cooper C, Thornburg KL. (2008). Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med,* 359:61e73. https://doi.org/10.1056/nejmra0708473

Guidelines Committee (2003) European society of hypertension-European society of cardiology guidelines for the management of arterial hypertension. *J Hypertens,* 21: 1011–1053.50. https://doi.org/10.1097/00004872-200306000-00001

Goldenberg RL, Culhane JF, Iams JD & Romero R. (2008). Epidemiology and causes of preterm birth. *The Lancet,* 371(9606): 75—84. https://doi.org/10.1016/s0140-6736(08)60074-4

Gournay V, Drouin E, Rozé JC. (2002). Development of baroreflex control of heart rate in preterm and full term infants. *Arch Dis Child Fetal Neonatal,* 86(3):F151-F154. http://dx.doi.org/10.1136/fn.86.3.F151

Hack M, Schluchter M, Cartar L, Rahman M. (2005). Blood pressure among very low birth weight (<1.5 kg) young adults. *Pediatric Research,* 58:677-684. https://doi.org/10.1203/01.pdr.0000180551.93470.56

Haikerwal A, Doyle LW, Cheung MM, Wark JD, Opie G, Roberts G, Patton G, Cheong JLY. (2020). High Blood Pressure in Young Adult Survivors Born Extremely Preterm or Extremely Low Birthweight in the Post Surfactant Era. *Hypertension,* 75:211–217. https://doi.org/10.1161/HYPERTENSIONAHA.119.13780

Haraldsdottir K, Watson AM, Goss KN, Beshish AG, Pegelow DF, Palta M, Tetri LH, Barton GP, Brix MD, Centanni RM, Eldridge MW. (2018). Impaired autonomic function in adolescents born preterm. *Physiol Rep,* 6(6):e13620. https://dx.doi.org/10.14814%2Fphy2.13620

Haraldsdottir K, Watson AM, Beshish AG, et al. (2019). Heart rate recovery after maximal exercise is impaired in healthy young adults born preterm. *Eur J Appl Physiol,* 119(4):857-866. https://doi.org/10.1007/s00421-019-04075-z

Hayano J, Yamada M, Sakakibara Y, et al. (1990). Short- and long-term effects of cigarettesmoking on heart rate variability. *Am J Cardiol,* 65:84–8. https://doi.org/10.1016/0002-9149(90)90030-5

Head GA, Lukoshkova EV, Burke SL, Malpas SC, Lambert EA, Janssen BJ. (2001). Comparing spectral and invasive estimates of baroreflex gain. *IEEE Eng Med Biol Mag,* 20:43–52. https://doi.org/10.1109/51.917723

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. (1996). *Circulation,* 93:1043-65. https://doi.org/10.1161/01.CIR.93.5.1043

Hillebrand S, de Mutsert R, Christen T, Maan AC, Jukema JW, Lamb HJ, de Roos A, Rosendaal FR, den Heijer M, Swenne CA; NEO Study Group. (2014). Body fat, especially visceral fat, is associated with electrocardiographic measures of sympathetic activation. *Obesity (Silver Spring),* 22(6):1553-9. https://doi.org/10.1002/oby.20709

Hintsanen M, Elovainio M, Puttonen S, et al. (2007). Effort-reward imbalance, heart rate,and heart rate variability: the Cardiovascular Risk in Young Finns Study. *Int JBehav Med,* 14:202–12. https://doi.org/10.1007/bf03002994

Honzíková N, Fišer B, Honzík J. (1992). Noninvasive determination of baroreflex sensitivity in man by means of spectral analysis. *Physiol Res,* 41:31–37.

Hovi P, Andersson S, Eriksson JG, Järvenpää AL, Strang-Karlsson S, Mäkitie O, et al. (2007). Glucose regulation in young adults with very low birth weight. *N Engl J Med,* 356(20):2053–2063. https://doi.org/10.1056/NEJMoa067187

Hovi P, Andersson S, Jarvenpaa AL, Eriksson JG, Strang-Karlsson S, Kajantie E, et al. (. 2009). Decreased bone mineral density in adults born with very low birth weight: a cohort study. *PLoS Med,* 6(8):e1000135. https://dx.doi.org/10.1371%2Fjournal.pmed.1000135

Hovi P, Andersson S, Räikkönen K, Strang-Karlsson S, Järvenpää AL, Eriksson JG, Pesonen AK, Heinonen K, Pyhälä R & Kajantie E. (2010). Ambulatory blood pressure in young adults with very low birth weight. *J Pediatr,* 156(1): 54—59 e1. https://doi.org/10.1016/j.jpeds.2009.07.022

Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, Evensen KA, van der Pal S, Grunau RE, Brubakk AM, et al. (2016). APIC Adults Born Preterm International Collaboration. Blood pressure in young adults born at very low birth weight: adults born preterm international collaboration. *Hypertension,* 68:880–887. https://doi.org/10.1161/hypertensionaha.116.08167

Howson CP, Kinney MV, Lawn JE. (2012). March of Dimes, PMNCH, Save the children, Who. Born Too Soon: The Global action report on preterm Birth. World health organization. Geneva.

Huckstep OJ, Burchert H, Williamson W, Telles F, Tan CMJ, Bertagnolli B, Arnold L, Mohamed A, McCormick K, Hanssen H, et al. (2020). Impaired myocardial reserve underlies reduced exercise capacity and heart rate recovery in preterm-born young adults. *Eur Heart J Cardiovasc Imaging,* jeaa060. https://doi.org/10.1093/ehjci/jeaa060

Huikuri, H. V., Mäkikallio, T. H., Peng, C. K., Goldberger, A. L., Hintze, U., & Moller, M. (2000). Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation,* 101(1), 47-53. https://doi.org/10.1161/01.cir.101.1.47

Imai K, Sato H, Hori M, et al. (1994). Vagally mediated heart-rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart-failure. *J Am Coll Cardiol,* 24(6):1529-1535. https://doi.org/10.1016/0735-1097(94)90150-3

Indredavik Evensen KA, Steinshamn S, Tjønna AE, Stølen T, Høydal MA, Wisløff U, Brubakk A-M & Vik T. (2009). Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Hum Dev,* 85(4): 239—245. https://doi.org/10.1016/j.earlhumdev.2008.10.008

Irving RJ, Belton NR, Elton RA & Walker BR. (2000). Adult cardiovascular risk factors in premature babies. *Lancet,* 355(9221): 2135—6. https://doi.org/10.1016/s0140-6736(00)02384-9

James N, Batin PD, Richard A, Lindsay SJ, Paul B, Michael M, Fox KA. (1998). Prospective study of heart rate variability and mortality in chronic heart failure. *Circulation,* 98(15), 1510-1516. https://doi.org/10.1161/01.CIR.98.15.1510

Järvelin MR, Hartikainen-Sorri AL & Rantakallio P. (1993). Labour induction policy in hospitals of different levels of specialisation. *Br J Obstet Gynaecol,* 100(4): 310-315. https://doi.org/10.1111/j.1471-0528.1993.tb12971.x

Järvelin MR, Sovio U, King V, Lauren L, Xu B, McCarthy M.I, et al. (2004). Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. *Hypertension,* 44, pp. 838-846. https://doi.org/10.1161/01.hyp.0000148304.33869.ee

Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M & Cnattingius S. (2005). Risk of high blood pressure among young men increases with the degree of immaturity at birth. *Circulation,* 112(22): 3430—6. https://doi.org/10.1161/circulationaha.105.540906

Juonala M, Cheung MM, Sabin MA, Burgner D, Skilton MR, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Jula A, Laitinen T, Jokinen E, Taittonen L, Tossavainen P, Viikari JS, Magnussen CG, Raitakari OT. (2015). Effect of birth weight on life-course blood pressure levels among children born premature: the Cardiovascular Risk in Young Finns Study. *J Hypertens,.* 33(8):1542-8. https://doi.org/10.1097/hjh.0000000000000612

Kajantie E., Räikkönen K. (2010a). Early life predictors of the physiological stress response later in life. *Neurosci. Biobehav. Rev,* 35(1):23–32. https://doi.org/10.1016/j.neubiorev.2009.11.013

Kajantie E, Strang-Karlsson S, Hovi P, Räikkönen K, Pesonen AK, Heinonen K, Järvenpää AL, Eriksson JG, Andersson S (2010b) Adults born at very low birth weight exercise less than their peers born at term. *J Pediatr,* 157(4):610-616. https://doi.org/10.1016/j.jpeds.2010.04.002

Kajantie E, Hovi P. (2014). Is very preterm birth a risk factor for adult cardiometabolic disease? *Semin Fetal Neonatal Med,* 19(2):112-117. https://doi.org/10.1016/j.siny.2013.11.006

Kang MG, Koh SB, Cha BS, Park JK, Woo JM, Chang SJ. (2004). Association between job stress on heart rate variability and metabolic syndrome in shipyard male workers. *Yonsei Med J,* 45:838–46. https://doi.org/10.3349/ymj.2004.45.5.838

Karason K, Molgaard H, Wikstrand J, Sjostrom L. (1999). Heart rate variability in obesityand the effect of weight loss. *Am J Cardiol,* 83:1242–7. https://doi.org/10.1016/s0002-9149(99)00066-1

Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, et al. (2019a). Cardiac Autonomic Function in Adults Born Preterm. *The Journal of Pediatrics,* 208:103. https://doi.org/10.1016/j.jpeds.2018.12.061

Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, et al. (2019b). Post-exercise heart rate recovery in adults born preterm. *The Journal of Pediatrics,* 214:89-95. https://doi.org/10.1016/j.jpeds.2019.06.056

Kaseva N, Wehkalampi K, Hemiö K, Hovi P, Järvenpää AL, Andersson S, et al. (2013). Diet and nutrient intake in young adults born preterm at very low birth weight. *J Pediatr,.* 163(1):43-8. https://doi.org/10.1016/j.jpeds.2012.12.076

Keijzer-Veen MG, Dulger A, Dekker FW, Nauta J & van der Heijden. (2010). Very preterm birth is a risk factor for increased systolic blood pressure at a young adult age. *Pediatr Nephrol,* 25(3): 509—16. https://doi.org/10.1007/s00467-009-1373-9

Kerkhof GF, Breukhoven PE, Leunissen RW, Willemsen RH, Hokken-Koelega AC. (2012). Does preterm birth influence cardiovascular risk in early adulthood? *The Journal of Pediatrics,* 161(3):390-396. https://doi.org/10.1016/j.jpeds.2012.03.048

Kistner A, Celsi G, Vanpee M & Jacobson SH. (2000). Increased blood pressure but normal renal function in adult women born preterm. *Pediatric Nephrology,* 15(3): 215-220. https://doi.org/10.1007/s004670000473

Kiviniemi AM, Tulppo MP, Hautala AJ, Perkiömäki JS, Ylitalo A, Kesäniemi YA, Huikuri HV. (2014). Prognostic significance of impaired baroreflex sensitivity assessed from phase IV of the valsalva maneuver in a population-based sample of middle-aged subjects. *American Journal of Cardiology,* 114(4), 571-576. https://doi.org/10.1016/j.amjcard.2014.05.032

Kleiger RE, Miller JP, Bigger JT Jr & Moss AJ. (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *American Journal of Cardiology,* 59(4), 256-262. https://doi.org/10.1016/0002-9149(87)90795-8

Kluess HA, Wood RH, Welsch MA. (2000). Vagal modulation of the heart and central hemodynamics during handgrip exercise. *Am J Physiol Heart Circ Physiol,* 278: H1648–H1652. https://doi.org/10.1152/ajpheart.2000.278.5.h1648

Korner PI, West MJ, Shaw J, Uther JB. (1974). 'Steady state' properties of the baroreceptor heart rate reflex in essential hypertension in man. *Clin Exp Pharmacol Physiol,* 1:65–76. https://doi.org/10.1111/j.1440-1681.1974.tb00528.x

Krohova J, Czippelova B, Turianikova Z, Lazarova I, Tonhajzerova I, Javorka M. (2017). Preejection Period as a Sympathetic Activity Index: a Role of Confounding Factors. *Physiol. Res,* 66 (Suppl. 2): S265-S275. https://doi.org/10.33549/physiolres.933682

Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. (1993). Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. *Am J Cardiol,* 72, 897-903. https://doi.org/10.1016/0002-9149(93)91103-o

Landgraf J, Wishner SH, Kloner RA. (2010). Comparison of automated oscillometric versus auscultatory blood pressure measurement. *Am J Cardiol,* 106(3):386-8. https://doi.org/10.1016/j.amjcard.2010.03.040

Lanfranchi PA, Somers VK. (2002). Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am J Physiol Regul Integr Comp Physiol,* 283(4):R815-26. https://doi.org/10.1152/ajpregu.00051.2002

La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, & Schwartz PJ. (1998). 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,* 351(9101), 478-484. https://doi.org/10.1016/s0140-6736(97)11144-8

Larkin KT, Kasprowicz AL. (1986). Validation of a Simple Method of Assessing Cardiac Preejection Period: A Potential Index of Sympathetic Nervous System Activity. *Perceptual and Motor Skills,* 63(1):295-302. https://doi.org/10.2466/pms.1986.63.1.295

Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, Kylintireas I, Contractor H, Singhal A, Lucas A, Neubauer S, Kharbanda R, Alp N, Kelly B, Leeson P. (2010). Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? *Hypertension,* 56(1):159-65. https://doi.org/10.1161/hypertensionaha.110.150235

Leeson P. (2010). Elevated Blood Pressure in Offspring Born Premature to Hypertensive Pregnancy: Is Endothelial Dysfunction the Underlying Vascular Mechanism? *Hypertension,* 56(1): 159—165. https://doi.org/10.1161/hypertensionaha.110.150235

Leon DA, Johansson M & Rasmussen F. (200l). Gestational age and growth rate of fetal mass are inversely associated with systolic blood pressure in young adults: an epidemiologic study of 165,136 Swedish men aged 18 years. *Am J Epidemiol,* 152(7): 597—604. https://doi.org/10.1093/aje/152.7.597

Levy MN. (1971). Sympathetic-parasympathetic interactions in the heart. *Circ Res,* 29:437-445. https://doi.org/10.1161/01.res.29.5.437

Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, McCormick K, Wilkinson AR, Singhal A, Lucas A, Smith NP, Neubauer S & Leeson P. (2013a). Preterm Heart in Adult Life: Cardiovascular Magnetic Resonance Reveals Distinct Differences in Left Ventricular Mass, Geometry, and Function. *Circulation,* 127(2): 197—206. https://doi.org/10.1161/circulationaha.112.126920

Lewandowski AJ, Bradlow WM, Augustine D, Davis EF, Francis J, Singhal A, Lucas A, Neubauer S, McCormick K, Leeson P. (2013b). Right ventricular systolic dysfunction in young adults born preterm. *Circulation,* 128(7):713-20. https://doi.org/10.1161/circulationaha.113.002583

Lewandowski AJ, Davis EF, Yu G, Digby JE, Boardman H, Whitworth P, et al. (2015). Elevated blood pressure in preterm-born offspring associates with a distinct antiangiogenic state and microvascular abnormalities in adult life. *Hypertension,* 65 pp: 607-614. https://doi.org/10.1161/hypertensionaha.114.04662

Lewandowski AJ, Levy PT, Bates ML, McNamara PJ, Nuyt AM, Goss KN. (2020). Impact of the vulnerable preterm heart and circulation on adult cardiovascular disease risk. *Hypertension,* 76(4):1028-1037. https://doi.org/10.1161/HYPERTENSIONAHA.120.15574

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. (2002). Prospective studies collaboration. Age-specific relevance ofusual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospectivestudies. *Lancet,* 360:1903–1913. https://doi.org/10.1016/s0140-6736(02)11911-8

Liao D, Cai J, Brancati FL, Folsom A, Barnes RW, Tyroler HA, & Heiss G. (1995). Association of vagal tone with serum insulin, glucose, and diabetes mellitus-the ARIC study. *Diabetes Research and Clinical Practice,* 30(3), 211-221. https://doi.org/10.1016/0168-8227(95)01190-0

Liao D, Cai J, Barnes RW, Tyroler HA, Rautaharju P, Holme I et al. (1996). Association of Cardiac Automatic Function and the Development of Hypertension: The ARIC Study, *American Journal of Hypertension,* Volume 9, Issue 12, 1147–1156. https://doi.org/10.1016/S0895-7061(96)00249-X

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. (2012). A comparative risk assessment ofburden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380:2224–2260. https://doi.org/10.1016/s0140-6736(12)61766-8

Longin, E., Gerstner, T., Schaible, T., Lenz, T., König, S. (2006). Maturation of the autonomic nervous system: Differences in heart rate variability in premature vs. term infants. *Journal of Perinatal Medicine,* 34: 303-308. https://doi.org/10.1515/jpm.2006.058

Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ. (2008). Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. *Am J Clin Nutr,* 88:1648–52. https://doi.org/10.3945/ajcn.2008.26140

Luu TM, Katz SL, Leeson P, Thébaud B, Nuyt A. (2016). Preterm birth: Risk factor for early-onset chronic diseases. *CMAJ,* 188(10):736-746. https://doi.org/10.1503/cmaj.150450

Mackersie CL, Calderon-Moultrie N. (2016). Autonomic Nervous System Reactivity During Speech Repetition Tasks: Heart Rate Variability and Skin Conductance. *Ear Hear,* 37 Suppl 1:118S-25S. https://doi.org/10.1097/aud.0000000000000305

Mancia G, Parati G, Hennig M, Flatau B, Omboni S, Glavina F, Costa B, Scherz R, Bond G, Zanchetti A; ELSA Investigators. (2001). Relation between blood pressure variability and carotid artery damage in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis (ELSA). *J Hypertens,* 19:1981–19. https://doi.org/10.1097/00004872-200111000-00008

Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. (2019). Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: A systematic review and meta-analysis. *J Pediatr,* 210:69-80. https://doi.org/10.1016/j.jpeds.2019.02.041

Mathai S, Derraik JG, Cutfield WS, Dalziel SR, Harding JE, Biggs J, et al. (2013). Increased adiposity in adults born preterm and their children. *PLoS One,* 8(11). https://doi.org/10.1371/journal.pone.0081840

Mathewson KJ, Van Lieshout RJ, Saigal S, Boyle MH, Schmidt LA. (2014). Reduced respiratory sinus arrhythmia in adults born at extremely low birth weight: evidence of premature parasympathetic decline? *Int J Psychophysiol,* 93(2):198–203. https://doi.org/10.1016/j.ijpsycho.2014.04.005

Mathewson, KJ, Van Lieshout RJ, Saigal S, et al. (2015). Autonomic Functioning in Young Adults Born at Extremely Low Birth Weight. *Global pediatric health,* 2, 2333794X15589560. https://doi.org/10.1177%2F2333794X15589560

Mathewson KJ, Pyhälä R, Hovi P, Räikkönen K, Van Lieshout RJ, Boyle MH, Saigal S, Morrison KM, Kajantie E, Schmidt LA. (2015). Cardiovascular Responses to Psychosocial Stress Reflect Motivation State in Adults Born at Extremely Low Birth Weight. *Glob Pediatr Health,* 2:2333794X15574092. https://doi.org/10.1177/2333794x15574092

Matinolli HM, Männistö S, Sipola-Leppänen M, Tikanmäki M, Heinonen K, Eriksson JG, et al. (2018). Food and nutrient intakes in young adults born preterm. *Pediatr Res,* 83(3):589-596. https://doi.org/10.1038/pr.2017.301

Malliani A, Pagani M, Lombardi, F, & Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation,* 84(2), 482-492. https://doi.org/10.1161/01.cir.84.2.482

Martinez-Aguayo A, Aglony M, Bancalari R, Avalos C, Bolte L, Garcia H, Loureiro C, Carvajal C, Campino C, Inostroza A, Fardella C. (2012). Birth weight is inversely associated with blood pressure and serum aldosterone and cortisol levels in children. *Clin Endocrinol (Oxf),* 76(5):713-8. https://doi.org/10.1111/j.1365-2265.2011.04308.x

Mendis S, Puska P & editors NB. (2011). Global Atlas on cardiovascular disease prevention and control. World Health Organization, Geneva.

Mills KT, et al. (2016). Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation,* 134, 441–450. https://doi.org/10.1161/circulationaha.115.018912

Minami J, Ishimitsu T, Matsuoka H. (1999). Effects of smoking cessation on blood pressureand heart rate variability in habitual smokers. *Hypertension,* 33:586–90. https://doi.org/10.1161/01.hyp.33.1.586

Mirdamadi A, Etebari M. (2017). Comparison of manual versus automated blood pressure measurement in intensive care unit, coronary care unit, and emergency room. *ARYA Atheroscler*, 13(1):29-34.

Molfino A, Fiorentini A, Tubani L, Martuscelli M, Rossi Fanelli F, Laviano A. (2009). Body mass index is related to autonomic nervous system activity as measured by heart rate variability. *Eur J Clin Nutr,* 63(10):1263-5. https://doi.org/10.1038/ejcn.2009.35

Morrison KM, Ramsingh L, Gunn E, Streiner D, Van Lieshout R, Boyle M, et al. (2016). Cardiometabolic health in adults born premature with extremely low birth weight. *Pediatrics,* 138(4). https://doi.org/10.1542/peds.2016-0515

Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. (2000). Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA-J Am Med Assoc,* 284(11):1392-1398. https://doi.org/10.1001/jama.284.11.1392

Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. (2002). Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens,*. 20(11):2183-9. https://doi.org/10.1097/00004872-200211000-00017

Pagani M Lombardi F Guzzetti S et al. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res,* 59(2): 178–193. https://doi.org/10.1161/01.res.59.2.178

Pappano AJ & Wier WG. (2013). Cardiovascular physiology (10th ed.). Philadelphia, PA: Elsevier/Mosby. Retrieved from https://oula.finna.fi/Record/oula.1219694

Paquette K, Fernandes RO, Xie LF, Cloutier A, Fallaha C, Girard-Bock C, Mian MOR, Lukaszewski MA, Mâsse B, El-Jalbout R, Lapeyraque AL, Santos RA, Luu TM, Nuyt AM. (2018). Kidney Size, Renal Function, Ang (Angiotensin) Peptides, and Blood Pressure in Young Adults Born Preterm. *Hypertension,* 72(4):918-928. https://doi.org/10.1161/hypertensionaha.118.11397

Patural H, Barthelemy JC, Pichot V, et al. (2004). Birth prematurity determines prolonged autonomic nervous system immaturity. *Clin Auton Res,* 14:391-395. https://doi.org/10.1007/s10286-004-0216-9

Pappaccogli M, Di Monaco S, Perlo E, Burrello J, D'Ascenzo F, Veglio F, Monticone S, Rabbia F. (2019). Comparison of Automated Office Blood Pressure With Office and Out-Off-Office Measurement Techniques. *Hypertension,* 73(2):481-490. https://doi.org/10.1161/hypertensionaha.118.12079

Parati G, Valentini M. (2006). Prognostic relevance of blood pressure variability. *Hypertension,* 137–138. https://doi.org/10.1161/HYPERTENSIONAHA.113.01801

Parati, G, Stergiou, GS, Dolan, E, Bilo, G. (2018). Blood pressure variability: clinical relevance and application. *J Clin Hypertens,* 20: 1133– 1137. https://doi.org/10.1111/jch.13304

Parkinson JRC, Hyde MJ, Gale C, Santhakumaran S & Modi N. (2013). Preterm Birth and the Metabolic Syndrome in Adult Life: A Systematic Review and Meta-analysis. *Pediatrics,* 131(4): e1240—63. https://doi.org/10.1542/peds.2012-2177

Patural H, Pichot V, Jaziri F, Teyssier G, Gaspoz JM, Roche F, Barthelemy JC. (2008). Autonomic cardiac control of very preterm newborns: a prolonged dysfunction. *Early Hum Dev,* 84(10):681-7. https://doi.org/10.1016/j.earlhumdev.2008.04.010

Pescatello LS, Franklin BA, Fagard R, Farqijar WB, Kelley GA, Ray CA. (2004). Exercise and hypertension: American College of Sports Medicine, Position Stand. *Med Sci Sports Exerc,* 36: 533–552. https://doi.org/10.1249/01.mss.0000115224.88514.3a

Pierpont GL, Adabag S, Yannopoulos D. (2013). Pathophysiology of Exercise Heart Rate Recovery: A Comprehensive Analysis. *Annals of Noninvasive Electrocardiology,* 18 (2):107–117. https://doi.org/10.1111/anec.12061

Perini R, Orizio C, Comandè A, Castellano M, Beschi M, Veicsteinas A. (1989). Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man. *Eur J Appl Physiol Occup Physiol,* 58(8):879-83.

Petretta M, Bonaduce D, de Filippo E, et al. (1995). Assessment of cardiac autonomic control by heart period variability in patients with early-onset familial obesity. *EurJ Clin Invest*, 25:826–32. https://doi.org/10.1111/j.1365-2362.1995.tb01691.x

Philip AG. (2005). The evolution of neonatology. *Pediatr Res,* 58(4): 799—815. https://doi.org/10.1203/01.pdr.0000151693.46655.66

Pihkala, J., Hakala, T., Voutilainen, P., & Raivio, K. (1989). [Characteristic of recent fetal growth curves in Finland]. *Duodecim,* 105(18), 1540-1546.

Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol,* 248: H151-H153. https://doi.org/10.1152/ajpheart.1985.248.1.h151

Pyhala R, Raikkonen K, Feldt K, et al. (2009). Blood pressure responses to psychosocial stress in young adults with very low birth weight: Helsinki study of very low birth weight adults. *Pediatrics,* 123(2):731—734. https://doi.org/10.1542/peds.2008-0277

Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S. (2017). Adults born preterm: A review of general health and system-specific outcomes. *Acta Paediatr,* 106(9):1409-1437. https://doi.org/10.1111/apa.13880

Rakow A, Katz-Salamon M, Ericson M, Edner A, Vanpeé M. (2013). Decreased heart rate variability in children born with low birth weight. *Pediatric Research,* 74:339–343. https://doi.org/10.1038/pr.2013.97

Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. (2003). Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am J Epidemiol,* 158:135–43. https://doi.org/10.1093/aje/kwg120

Robbe HW, Mulder LJM, Rüddel H, Langewitz WA, Veldman JBP, Mulder G. (1987). Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension,* 10:538–543. https://doi.org/10.1161/01.hyp.10.5.538

Roberts G, Lee KJ, Cheong JLY & Doyle LW. (2014). Higher ambulatory blood pressure at 18 years in adolescents born less than 28 weeks' gestation in the 1990s compared with term controls. *Journal of Hypertension,* 32(3): 620—626. https://doi.org/ 10.1097/hjh.0000000000000055

Romero R, Dey SK & Fisher SJ. (2014). Preterm labor: One syndrome, many causes. *Science,* 345(6198): 760—765. https://doi.org/10.1126/science.1251816

Rossi M, Marti G, Ricordi L, Fornasari G, Finardi G, Fratino P, et al. (1989). Cardiac autonomic dysfunction in obese subjects. *Clin Sci (Lond),* 76(6):567-72. https://doi.org/10.1042/cs0760567

Rossy LA, Thayer JF. (1998). Fitness and gender-related differences in heart period variability. *Psychosom Med,* 60:773–81. https://doi.org/10.1097/00006842-199811000-00022

Rotteveel J, van Weissenbruch MM, Twisk JWR & Delemarre-Van de Waal HA. (2008). Infant and Childhood Growth Patterns, Insulin Sensitivity, and Blood Pressure in Prematurely Born Young Adults. *Pediatrics,* 122(2): 313—321. https://doi.org/10.1542/peds.2007-2012

Sachis PN, Armstrong DL, Becker LE, Bryan AC. (1982). Myelination of the human vagus nerve from 24 weeks postconceptional age to adolescence. *J Neuropathol Exp Neurol,* 41:466-472. https://doi.org/10.1097/00005072-198207000-00009

Sadeh A, Sharkey KM & Carskadon MA. (1994). Activity-based sleep-wake identification: an empirical test of methodological issues. *Sleep,* 17(3): 201—7. https://doi.org/10.1093/sleep/17.3.201

Savin WM, Davidson DM, Haskell WL. (1982). Autonomic contribution to heart rate recovery from exercise in humans. *J Appl Physiol,* 53:1572–5. https://doi.org/10.1152/jappl.1982.53.6.1572

Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, de la Sierra A, Hermida RC, Dolan E, O'Brien E, Roush GC; ABC-H Investigators (2016) Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension. (ABC-H) Meta-Analysis. *Hypertension,* 67(4):693-700. https://doi.org/10.1161/hypertensionaha.115.06981

Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. (2003). Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. *Hypertension,* 42, 1106-1111. https://doi.org/10.1161/01.hyp.0000100444.71069.73

Schächinger H, Weinbacher M, Kiss A, Ritz R, Langewitz W. (2001). Cardiovascular indices of peripheral and central sympathetic activation. *Psychosom Med,* 63: 788-796. https://doi.org/10.1097/00006842-200109000-00012

Shaffer F, McCraty R, Zerr CL. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol,* 5:1040. https://dx.doi.org/10.3389%2Ffpsyg.2014.01040

Stanaway, J. D. et al. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet,* 392, 1923–1994. https://doi.org/10.1016/s0140-6736(18)32225-6

Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ et al. (2016). Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ,* 354 :i4098. https://doi.org/10.1136/bmj.i4098

Siewert-Delle A & Ljungman S. (1998). The Impact of Birth Weight and Gestational Age on Blood Pressure in Adult Life: A Population-Based Study of 49-Year-Old Men. *American Journal of Hypertension,* 11(8): 946—953. https://doi.org/10.1016/s0895-7061(98)00090-9

Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. (1998). Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension,* 32, 293-297. https://doi.org/10.1161/01.hyp.32.2.293

Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM. (2000). Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). *Am J Cardiol,* 86, 309-312. https://doi.org/10.1016/s0002-9149(00)00920-6

Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Hovi P, Miettola S, Ruokonen A, et al. (2014). Cardiovascular risk factors in adolescents born preterm. *Pediatrics,* 134(4):1072. https://doi.org/10.1542/peds.2013-4186

Sipola-Leppänen M. (2015). Preterm birth and cardiometabolic risk factors in adolescence and early adulthood. Doctoral Dissertation. University of Oulu, Finland.

Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli HM, Miettola S, Hovi P, et al. (2015). Cardiometabolic risk factors in young adults who were born preterm. *Am J Epidemiol,* 181(11):861-873. https://doi.org/10.1093/aje/kwu443

Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli HM, Martikainen S, Pesonen AK, et al. (2015). Ambulatory blood pressure and its variability in adults born preterm. *Hypertension,* 65(3):615-621. https://doi.org/10.1161/HYPERTENSIONAHA.114.04717

Skudder-Hill L, Ahlsson F, Lundgren M, Cutfield WS, Derraik JGB. (2019). Preterm Birth is Associated With Increased Blood Pressure in Young Adult Women. *J Am Heart Assoc*, 8(12):e012274. https://doi.org/10.1161/jaha.119.012274

Sloan RP, Shapiro PA, DeMeersman RE, et al. (2009). The effect of aerobic training and cardiac autonomic regulation in young adults. *Am J Public Health,* 99:921–8. https://doi.org/10.2105/ajph.2007.133165

Smoljo T, Stanić I, Sila S, et al. (2020). The Relationship between Autonomic Regulation of Cardiovascular Function and Body Composition. *J Obes Metab Syndr,* 29(3):188-197. https://dx.doi.org/10.7570%2Fjomes20041

Smyth HS, Sleight P, Pickering GW. (1969). Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. *Circ Res,* 24:109–121. https://doi.org/10.1161/01.res.24.1.109

Tatasciore A, Renda G, Zimarino M, Soccio M, Bilo G, Parati G, Schillaci G, De Caterina R. (2007). Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension,* 50:325–332. https://doi.org/10.1161/hypertensionaha.107.090084

Tauzin L, Rossi P, Grosse C, Boussuges A, Frances Y, Tsimaratos M & Simeoni U. (2014). Increased systemic blood pressure and arterial stiffness in young adults born prematurely. *Journal of Developmental Origins of Health and Disease,* First View (Supplement -1): 1—5. https://doi.org/10.1017/s2040174414000385

Thayer JF, Lane RD. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol,* 74(2):224-42. https://doi.org/10.1016/j.biopsycho.2005.11.013

Thayer JF, Yamamoto SS, Brosschot JF. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol,* 141(2):122-131. https://doi.org/10.1016/j.ijcard.2009.09.543

Thomas EL, Parkinson JR, Hyde MJ, Yap IKS, Holmes E, Dore CJ, Bell JD & Modi N. (2011). Aberrant Adiposity and Ectopic Lipid Deposition Characterize the Adult Phenotype of the Preterm Infant. *Pediatric Research,* 70(5): 507—512. https://doi.org/10.1203/pdr.0b013e31822d7860

Tikanmäki M, Tammelin T, Sipola-Leppänen M, Kaseva N, Matinolli HM, Miettola S, et al. (2016). Physical fitness in young adults born preterm. *Pediatrics,* 137(1). https://doi.org/10.1542/peds.2015-1289

Tikanmäki M. (2018). Preterm birth and parental and pregnancy related factors in association with physical activity and fitness in adolescence and young adulthood. Doctoral Dissertation. University of Oulu, Finland.

Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL & Levy D. (1994). Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation,* 90 pp. 878-883. https://doi.org/10.1161/01.cir.90.2.878

Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham heart study. *Circulation,* 94(11):2850-2855. https://doi.org/10.1161/01.cir.94.11.2850

Qiu SH, Cai X, Sun ZL, Li L, Zuegel M, Steinacker JM, Schumann U. (2017). Heart Rate Recovery and Risk of Cardiovascular Events and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association,* 6 (5). https://doi.org/10.1161/jaha.117.005505

Vääräsmäki M, Pouta A, Elliot P, Tapanainen P, Sovio U, Ruokonen A, Hartikainen AL, McCarthy M & Järvelin MR. (2009). Adolescent manifestations of metabolic syndrome among children born to women with gestational diabetes in a general-population birth cohort. *Am J Epidemiol,* 169(10): 1209-1215. https://doi.org/10.1093/aje/kwp020

Van Leeuwen P, Lange S, Betterman H, Grönemeyer D, Hatzman W. (1999). Fetal heart rate variability and complexity in the course of pregnancy. *Early Hum Dev,* 54:259-269. https://doi.org/10.1016/s0378-3782(98)00102-9

Van Lith JM, Visser GH, Mantingh A, Beekhuis JR. (1992). Fetal heart rate in early pregnancy and chromosomal disorders. *Br J Obstet Gynaecol,* 99(9):741-4. https://doi.org/10.1111/j.1471-0528.1992.tb13876.x

Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G, et al. (1994). Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension,* 24(6):793-801. https://doi.org/10.1161/01.hyp.24.6.793

Verdecchia P, Angeli F, Gattobigio R, Rapicetta C, Reboldi G. (2007). Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens,* 20(2):154-61. https://doi.org/10.1016/j.amjhyper.2006.07.017

Wehrwein A, Joyner MJ. (2013). Regulation of blood pressure by the arterial baroreflex and autonomic nervous system. *Handbook of Clinical Neurology,* 117C:89-102. https://doi.org/10.1016/b978-0-444-53491-0.00008-0

Wakai RT. (2004). Assessment of fetal neurodevelopment via fetal magnetocardiography. *Exp Neurol,* 190(Suppl 1):65. https://doi.org/10.1016/j.expneurol.2004.04.019

Wikimedia Commons. 2021. Available at: https://commons.wikimedia.org/wiki/File:FFT-Time-Frequency-View.png. (Accessed 22.2.2021)

Witcombe NB, Yiallourou SR, Sands SA, Walker AM, Horne RSC. (2012). Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. *Pediatrics,* 129:e89-e96. https://doi.org/10.1542/peds.2011-1504

World health organization. (1977). Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand,* 56(3):247—53.

World health organization. (2007). Cardiovascular diseases (CVDs). Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). (Accessed 25.1.2021)

Yiallourou SR, Witcombe NB, Sands SA, Walker AM, Horne RS. (2013). The development of autonomic cardiovascular control is altered by preterm birth. *Early Hum Dev,* 89:145–52. https://doi.org/10.1016/j.earlhumdev.2012.09.009

Yiallourou SR, Wallace EM, Whatley C, Odoi A, Hollis S, Weichard AJ, et al. (2017). Sleep: a window into autonomic control in children born preterm and growth restricted. *Sleep,* 40(5). https://doi.org/10.1093/sleep/zsx048

Yotsukura M, Koide Y, Fujii K, et al. (1998). Heart rate variability during the first month of smoking cessation. *Am Heart J,* 135:1004–9. https://doi.org/10.1016/s0002-8703(98)70065-1

Young FLS, Leicht AS. (2011). Short-term stability of resting heart rate variability: influence of position and gender. *Applied Physiology, Nutrition, and Metabolism,* 36(2): 210-218. https://doi.org/10.1139/h10-103

Zawadzki MJ, Small AK, Gerin W. (2017). Ambulatory blood pressure variability: a conceptual review. *Blood Pressure Monitoring,* 22: 53-58. https://doi.org/10.1097/mbp.0000000000000230

Original publications

I Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli HM, Martikainen S, Pesonen A, Räikkönen K, Järvelin M, Hovi P, Eriksson JG, Vääräsmäki M, Kajantie E. (2015). Ambulatory blood pressure and its variability in adults born preterm. *Hypertension*, 65(3), 615-621.

II Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, Tulppo M, Vääräsmäki M, Kajantie E. (2019). Cardiac autonomic function in adults born preterm. *The Journal of Pediatrics,* 208, 96-103.

III Karvonen R, Sipola M, Kiviniemi A, Tikanmäki M, Järvelin M, Eriksson JG, Tulppo M, Vääräsmäki M, Kajantie E. (2019). Post-exercise heart rate recovery in adults born preterm. *The Journal of Pediatrics,* 214, 89-95.

IV Karvonen R, Mathewson KJ, Pyhälä R, Gunn E, Tikanmäki M, Kiviniemi A, Hovi P, Andersson S, Räikkönen K, Van Lieshout R, Schmidt L, Saigal S, Morrison K, Kajantie E. Sex-specific differences in cardiac and blood pressure regulation in very and extremely low birth weight survivors: A 10-year multi-center study. (Manuscript submitted).

Original publications are not included in the electronic version of the dissertation.

Book orders:
Virtual book store
http://verkkokauppa.juvenesprint.fi

UNIVERSITY OF OULU P.O. Box 8000 FI-90014 UNIVERSITY OF OULU FINLAND

ACTA UNIVERSITATIS OULUENSIS

ISBN 978-952-62-2951-5 (Paperback)
ISBN 978-952-62-2952-2 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)

UNIVERSITY OF OULU