CARDIOVASCULAR PHENOTYPE AND RESPONSE TO EXERCISE TRAINING IN PRETERM-BORN ADULTS

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Afifah

DEDICATIONS

To mom, dad, Mahmud, Yusuf and my twin babies

You're my world

With all my love

ABBREVIATIONS

ACT	Antenatal glucocorticoids
AHA	American Heart Association
Ang II	Angiotensin II
AT1	Ang II type 1
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BSA	Body surface area
CCRF	Oxford Cardiovascular Clinical Research Facility
CI	Cardiac index
cm	Centimetre
CMR	Cardiac magnetic resonance
CO	Cardiac output
CRP	C-reactive protein
CVD	Cardiovascular disease
cvi42	Circle cardiovascular imaging
ECM	Essential extracellular matrix
EDD	End-diastolic dimension

EDV	End-diastolic volume
EDVI	End-diastolic volume index
EF	Ejection fraction
ESC	European Society of Cardiology
ESV	End-systolic volume
ESVI	End-systolic volume index
ET	Ejection time
EVS	Early Vascular Study
FAC	Fractional area of change
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GFR	Glomerular filtration rate
HFpEF	Heart failure and preserved LV ejection fraction
ICC	Intraclass correlation
IJN	National Heart Institute
LBW	Low birth weight
LDL:HDL	Low-density lipoprotein: high-density lipoprotein
LGE	Late gadolinium enhancement
LV	Left ventricular
LVH	LV hypertrophy
LVM	LV mass
LVMI	LV mass index

MRI	Magnetic resonance imaging
OCMR	Oxford Centre for Clinical Magnetic Resonance
PAAT	Pulmonary artery acceleration time
PCA	Principal component analysis
PVR	Pulmonary vascular resistance
RA	Right atrium
RDS	Respiratory distress syndrome
RV	Right ventricular
RVEDA	RV end-diastolic area
RVESA	RV end-systolic area
RVH	RV hypertrophy
RVM	RV mass
RV-PA	RV to pulmonary arterial vascular
SD	Standard deviation
SSFP	Steady state free precession
SV	Stroke volume
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TEPHRA	Trial of Exercise to Prevent Hypertension in young Adults
VLBW	Very low birth weight
VO_2 max	Maximal oxygen consumption
YACHT	Young Adult Cardiovascular Health Study

ABSTRACT

CARDIOVASCULAR PHENOTYPE AND RESPONSE TO EXERCISE TRAINING IN PRETERM-BORN ADULTS

THESIS PRESENTED FOR THE DEGREE DOCTOR OF PHILOSOPHY IN MEDICAL SCIENCES

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Preterm birth affects more than 10% of live births worldwide and associates with significant increases in cardiovascular risk in later life. It occurs during a critical window for organogenesis, disrupting normal organ development, with an early, physiologically demanding transition to the extrauterine environment. This thesis aimed to further investigate the cardiac phenotype of adults born preterm and whether a prescribed aerobic exercise training intervention can beneficially modify prematurity-related cardiac changes. The first results chapter focused on normotensive adults born preterm and term (n=101) and used multimodality cardiac imaging (echocardiography and cardiac magnetic resonance, CMR) to

determine whether previously observed changes in right ventricular (RV) function in preterm-born adults were out of proportion to changes seen in the pulmonary system. It was demonstrated that those born preterm had reductions in RV function, independent of any alterations to lung physiology, but that the RV remained hemodynamically coupled to the pulmonary circulation. In the second results chapter, adults born preterm and term (n=468) were studied to explore the relationship between systolic blood pressure elevation and cardiac remodelling. Using CMR, it was found that left ventricular (LV) mass index and LV mass to end-diastolic volume ratio increased more per 1mmHg rise in systolic blood pressure in preterm-born adults than in term-born adults, with the greatest change in those born very and extremely preterm. In the third results chapter, cardiac remodelling was explored by CMR following a 16-week prescribed aerobic exercise training intervention in adults born preterm and term (n=100) with elevated blood pressure. Preterm-born adults showed significant increases in systolic myocardial deformation parameters for both the RV and LV following the intervention. Overall, these findings have contributed to the growing body of research into the long term cardiovascular risk of being born preterm and the potential benefit of lifestyle interventions in this at-risk population.

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Mohamed A, Lamata P, Williamson W, Alsharqi M, Tan CMJ, Burchert H, Huckstep OJ, Suriano K, Francis JM, Pelado JL, Monteiro C, Neubauer S, Levy PT, Leeson P and Lewandowski AJ. Multimodality imaging demonstrates reduced right-ventricular function independent of pulmonary physiology in moderately preterm-born adults. JACC: Cardiovascular Imaging. 2020. 13(9): p. 2046-2048.

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CHAPTER 1

INTRODUCTION

1.1 Preterm birth

1.1.1 Definition and prevalence of preterm birth

Preterm birth is defined as birth before 37 weeks of completed gestation. It is estimated that approximately 15 million preterm newborn babies were born in 2014 with a liveborn prevalence of 10.6% worldwide, 9.6% in the United States, and 5 to 9% in most European countries [1]. Estimated preterm birth rates in 103 selected countries in 2014 are demonstrated in **Figure 1.1** [1] . Despite being the leading cause of under five child mortality [2, 3], the advances in perinatal care have allowed preterm survivors to survive to adulthood [4]. However, survival comes at the expense of future health consequences [5]. Subsequently, research to understand the global epidemiology following preterm birth is essential to help clinicians understand the possible short term and long term health risks, eventually allowing for better management and care in the future.

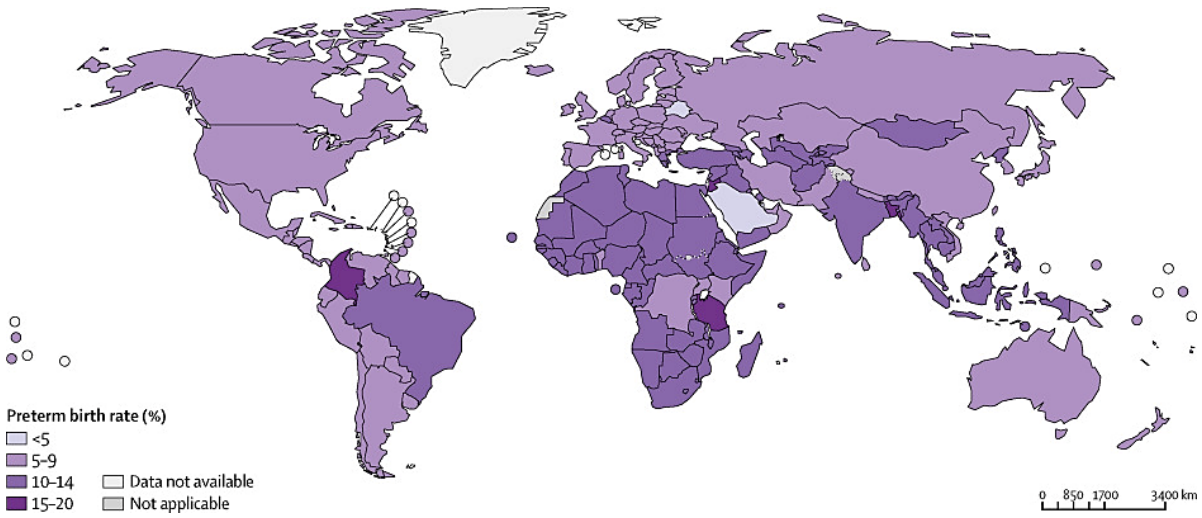


Figure 1.1: Estimated preterm birth rates of 103 selected countries in 2014. Bangladesh had the highest estimated national rate of 19.1%. Image taken from Chawanpaiboon et al*, The Lancet, 2018.*

Table 1.1 summarises preterm birth categories according to gestational age range, population percentage and birth weight categories. Moderate or late preterm birth accounts for nearly 85% of the preterm population, which is partly why the survival rates of preterm-born individuals are so high [6]. Very preterm-born and extremely preterm-born individuals make up 10.4% and 5.2% of the preterm population, respectively. Birth weight is an important indicator of infant health that can be used as a predictor of prenatal health status, risk of postnatal complication, and survival [7]. Based on the World Health Organization (WHO), low birth weight (LBW) is defined as a birth weight of an infant below 2500 grams, regardless of gestational age [8]. Currently, neonatal death due to LBW infants exceeds 80%, of which nearly two-thirds are caused by preterm birth [7].

Table 1.1 Preterm birth categories in relation to gestational age and birth weight categories.

<table>
<tr><th>Preterm birth categories</th><th>Gestational age range (weeks)</th><th>Percentage of preterm population</th><th colspan="3">Birth weight categories</th></tr>
<tr><td>Extremely preterm</td><td><28</td><td>5.2%</td><td rowspan="4">LBW <2500 g</td><td rowspan="2">VLBW <1500 g</td><td>ELBW <1000 g</td></tr>
<tr><td>Very preterm</td><td>28 - 31</td><td>10.4%</td><td rowspan="3"></td></tr>
<tr><td>Moderate or late</td><td>32 - 36</td><td>84.3%</td></tr>
<tr><td>Early term</td><td>37 – 38</td><td rowspan="2"></td><td></td></tr>
<tr><td>Full-term</td><td>>38</td><td></td><td></td></tr>
</table>

According to WHO 2012, preterm birth is grouped based on extremely preterm, very preterm and moderate or late preterm. Population percentages were obtained from Blencowe et al, *The Lancet, 2013.* LBW indicates low birth weight; VLBW, very low birth weight; ELBW, extremely low birth weight.

It is therefore important to establish accurate birth weight for gestational age centile charts to identify newborns that are at high risk of any postnatal complications. The recently updated chart below was published by Norris et al. in 2018 using a large contemporary sample of 1.3 million singleton births in England and Wales as shown in **Figure 1.2** [9]. These charts can help clinicians perform better death case identification at infancy and improve decision making to ensure appropriate care is given to the high risk babies. Another commonly referred to fetal growth standard chart is The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) [10]. This program will help gather all available data worldwide and construct more accurate and precise international fetal and preterm postnatal growth standards, which will be beneficial to clinicians and researchers in the field [11].

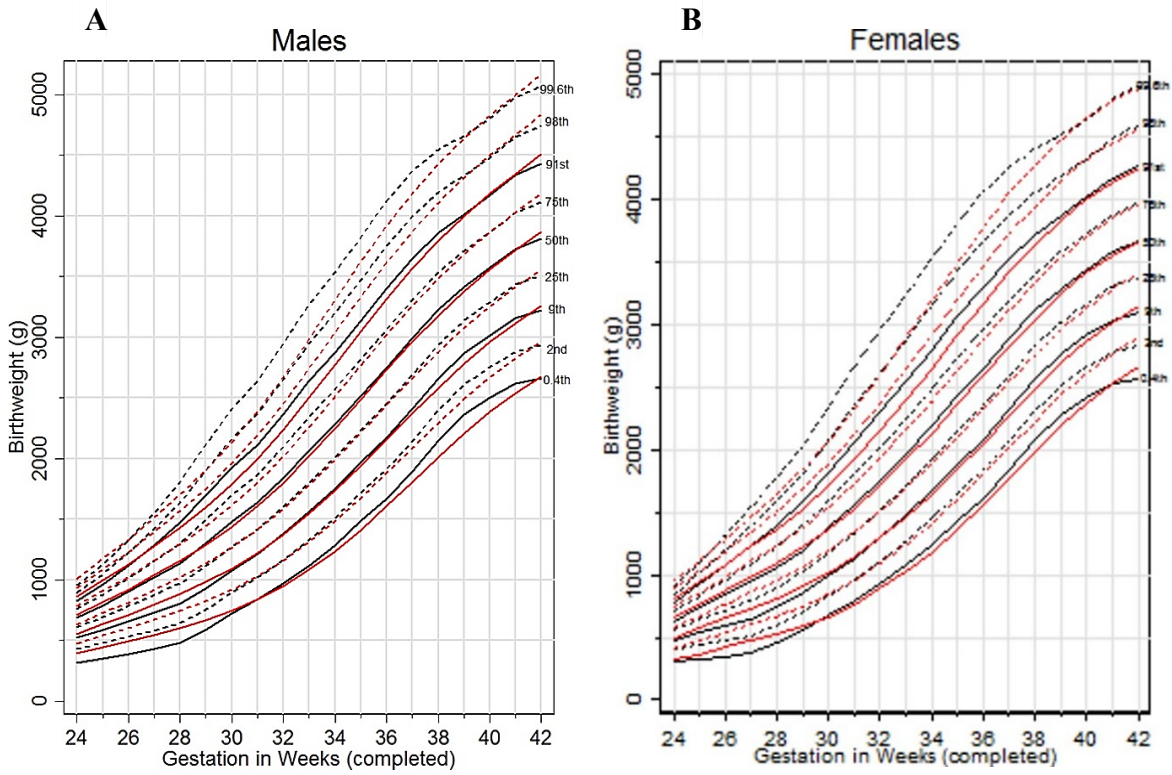


Figure 1.2: Updated birth weight centiles for England and Wales. Birth weight centile charts for males **(A)** and females **(B)** born in 2013-2014 in England and Wales. Black line and red line derived from MBRRACE-UK and UK-WHO, respectively. Image taken from Norris et al, *Arch Dis Child Fetal Neonatal Ed*, *2018*.

1.1.2 Epidemiology and cardiovascular risk following preterm birth

Within the last decade, a growing number of studies have reported the association between preterm birth and all-cause mortality. This association has been reported in young adulthood [5], with risk including early heart failure [12], hypertension [13, 14], pulmonary vascular disease [15-17], type 1 and 2 diabetes [18, 19], and ischemic heart failure [20]. Much of this research comes from large epidemiological studies based on national populations in Sweden. A recent Swedish cohort study including over 2.1 million individuals who were born as

singleton live births between 1973 and 1994 found an increased risk of ischemic heart disease among those born preterm and early term, from birth through to adulthood [20]. Another large Swedish national cohort registry study of over 2.6 million individuals born between 1987 and 2012 identified preterm birth as a novel risk factor for incidental heart failure in childhood and adolescence [12]. Similarly, a birth cohort study of over 4.1 million individuals born in Sweden between 1973 and 2014 identified an increased risk of hypertension into early adulthood among those born preterm [13]. The increased risk may be related to the interruption to organogenesis as a result of preterm birth, where most of the organs are not functionally or structurally prepared for the transition from fetal to neonatal circulation [21]. Furthermore, the extrauterine conditions following preterm birth can further exacerbate the postnatal growth and continued organ development in those born preterm. This supports the notion that the developmental origins of cardiovascular disease (CVD) susceptibility can be triggered by events very early in life [22].

1.1.2.1 Preterm birth and risk of hypertension

Hypertension is an established modifiable risk factor for several adverse events including premature death [23] and correlates well with coronary artery disease and stroke [24]. In 2012, a meta-analysis of 1342 preterm- and 1738 term-born individuals from early childhood to young adulthood (age range: 6-23 years) demonstrated a higher resting systolic blood pressure in the preterm-born individuals of 5 mmHg compared to the term-born individuals [25]. Even though data on ambulatory blood pressure was limited, a higher awake 24-hour ambulatory

blood pressure was still observed in the preterm-born or very low birth weight (VLBW) participants, compared to those born at term [25]. A year later, a comparable meta-analysis of 17,030 preterm and 295,261 term-born adults including only young adults ≥ 18 years of age was published. These findings showed significantly higher resting systolic, resting diastolic and 24-hour ambulatory systolic blood pressures in preterm-born adults compared to term-born adults, with an average mean difference of 4.2 mmHg, 2.6 mmHg and 3.1 mmHg, respectively [26].

The high blood pressures seen in preterm-born individuals are in line with the findings from a large Swedish national cohort registry of 636,552 people born between 1973 and 1979, followed up at ages 25-37 years. In this study, it was found that antihypertensive medication prescription rates were significantly higher in the preterm cohort, increasing with greater prematurity and independent of fetal growth restriction [14]. Interestingly, those born near term at 35-36 weeks were also seen to be at higher risk of hypertension. Recently, another meta-analysis reported a 4.2 mmHg and 2.3 mmHg increase in systolic and diastolic blood pressure in the preterm-born participants compared to those born at term [27]. In contrast, a meta-analysis reported that higher blood pressure was found to be unrelated to gestational age or severe neonatal morbidity, and women were more affected than men [28]. In this study, when smaller body size of VLBW adults was taken into account, significantly higher blood pressures were noticeable in the preterm-born individuals compared to controls (3.4 mmHg higher systolic and 2.1 mmHg higher diastolic), which is in line with previous findings [29]. This suggests that despite being born very premature, birth weight may be an important factor that contributes to the dissimilar findings in the literature.

1.1.2.2 Mechanisms underlying hypertension in preterm

High blood pressure is a complex disease that involves several risk factors and pathophysiological pathways. However, mechanisms underlying hypertension in the preterm population are not entirely clear. To date, several possible causative pathophysiological mechanisms have been proposed to underlie this increased blood pressure. For instance, previous studies have identified a slower rate of baroreflex sensitivity in preterm infants that increases with gestational age [30, 31]. The baroreflex is the body's rapid homeostatic mechanism that functions to regulate acute changes in blood pressure and maintain blood pressure at a nearly constant level. Impaired baroreflex maturation minimises the ability to counterbalance the prohypertensive systems, ultimately increasing the risk of hypertension in preterm individuals later in life. Experimental and clinical studies have shown that baroreflex maturation develops throughout gestation and significantly in the third trimester of pregnancy [32, 33]; a critical period in which 84% of preterm births occur [6].

Similarly, preterm birth interrupts the development and maturation of kidneys in infants [34]. About 60% of nephrons, the vital measure of renal functional capacity, are formed during the last trimester of pregnancy [35], with average completion of nephrogenesis by around 36 weeks' gestation [36, 37]. Preterm birth occurs when nephrogenesis is incomplete, leading to nephron reduction and lower glomerular filtration rate (GFR) [38]. A review by Morton et al. suggested that reduced nephron number following preterm birth consequently induced glomerular hyperfiltration, glomerular enlargement, and ultimately, inhibited normal handling of salt and water [39]. Furthermore, these renal developmental alterations may persist throughout life, likely promoting the development of high blood pressure and kidney disease

[40]. This is supported by a recent national cohort study of over four million individuals in Sweden showing that preterm birth is strongly associated with chronic kidney disease from childhood to adulthood [40].

Lack of early nutritional interventions in the postnatal period via breastfeeding are believed to increase the burden of CVD in the preterm population [41]. One of the earliest randomised controlled trials highlighting the favourable effects of breastfeeding was done in 926 preterm neonates followed up at ages 13-16 years [42]. The findings showed adolescents randomised to banked breast milk in infancy had a 2.7 mmHg reduction in blood pressure compared to those given preterm formula [42]. In addition, assessment of lipid profile in this cohort showed that those fed with breast milk in infancy had a 14% lower mean low-density lipoprotein: high-density lipoprotein (LDL:HDL) ratio, and significantly lower C-reactive protein (CRP), a marker of inflammation in atherosclerosis [43]. Using the same cohort of 102 participants, Lewandowski et al. went on to show a beneficial association between breast milk and cardiac morphology and function in adult life in those born preterm [44]. In contrast, a previous study in adults born at term showed that prolonged breastfeeding could be detrimental, with evidence of increased arterial stiffness [45]. Nevertheless, the benefits in neonatal born preterm, particularly in the early postnatal stage, appear to be sustained long term (**Figure 1.3**). More research is needed to uncover the potential contributory mechanisms underlying the protective effects of human milk feeding [41].

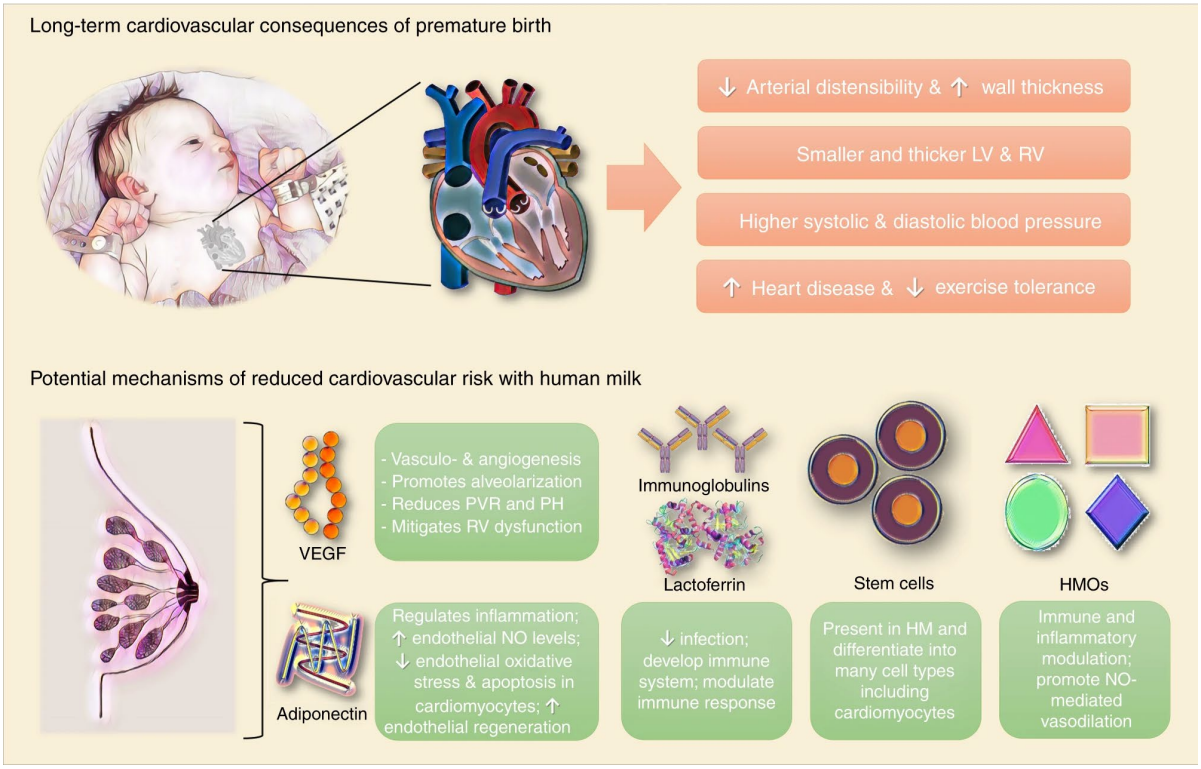


Figure 1.3: Impact of preterm birth on long-term cardiovascular health and potential benefits of human milk on cardiovascular prevention. Image taken from Afif, E.-K., et al, *Pediatric Research, 2019.* VEGF indicates vascular endothelial growth factor; PVR, pulmonary vascular resistance; PH, pulmonary hypertension; NO, nitric oxide; HMOs, human milk oligosaccharides.

Early postnatal weight gain in preterm-born individuals is also one of the underlying factors proposed to explain the increase in blood pressure in preterm-born individuals. Catch-up growth occurs more rapidly in the first months of life in preterm-born individuals [46, 47]. In cohort populations, higher weight gain trajectories in childhood have been linked to later obesity in adulthood as well as other health-related events [48-52]. Those with early rapid weight gain are at greater risk of alterations in metabolic profiles [47, 52], higher insulin resistance in infancy [53], as well as higher blood pressure [54, 55] and endothelial dysfunction [55] in adolescence and adulthood. Human milk as part of early nutritional

management is considered a vital intervention during infancy [41] that promotes slower weight gain [42] and lower fat mass deposition than nutrient-enriched preterm formula [56].

Altered angiogenesis in preterm-born individuals has also been linked to the development of hypertension. Capillary rarefaction, also known as reduction in capillary density, is understood to drive a compensatory response, which may partly explain the blood pressure increases commonly seen in those born preterm [57]. Our research group has demonstrated an increased peripheral vascular resistance resulting from reduced capillary density in preterm-born individuals in adulthood [57]. Similarly, Bonamy et al. demonstrated, using similar methods, that very preterm-born children have reduced functional capillary density, independent of systolic blood pressure [58]. Capillary rarefaction has been found to precede the development of high blood pressure and causes an increase in peripheral vascular resistance, eventually linked to the onset of hypertension [59].

Preterm birth occurs during a critical period of elastin synthesis and may disrupt the proper development of the vascular tree in infants. Elastin is an essential extracellular matrix (ECM) protein responsible for the elastic properties of tissues and organs. It has been hypothesised that arterial stiffening occurs as a result of elastin deficiency following retarded growth in pregnancy [60]. Importantly, arterial stiffening following preterm birth is currently related to several complications including higher blood pressure [61]. Additionally, offspring born prematurely from a pregnant mother who developed hypertension or preeclampsia are predisposed to hypertension risk earlier in life [62].

1.2 The preterm heart

1.2.1 Adaptation for life: Transitioning into neonatal circulation

Before birth, the lungs of a fetus are filled with fluid and are not yet functioning. Thus, most of the vital functions including the exchange of oxygen occur through the placenta [63]. In addition, the fetal heart is right side dominant with a thick-walled chamber where the RV accommodates for approximately 65% of total cardiac output (CO) through the ductus arteriosus and into the systemic circulation [64]. The remaining 35% of the total CO is provided by the LV. The first breath at birth marks a significant transition of life from fetal to neonatal circulation, leading to a major reorganization of the fetal cardiovascular system including the initiation of physiological respiratory and hemodynamic changes [65].

Ventilation of the lungs after birth stimulates a dramatic decrease in pulmonary vascular resistance (PVR) and forces the RV cardiac output (RVCO) to begin to flow predominantly through the pulmonary artery into the lungs [66]. The workload of the RV now becomes proportionally lower than that of the LV. These events further lead to an increase in pulmonary blood flow and pulmonary venous return to the left atrium, leading to the closure of the major vascular shunts [65, 67]. The elimination of the low resistance placental circulation through umbilical cord clamping also contributes to these pressure and hemodynamic changes, marked by an increase in systemic vascular resistance (SVR) [67]. The sudden increase in SVR places the immature heart under stress. To maintain CO, compensatory short term cardiac and blood vessel remodelling may occur.

During fetal life, the cardiomyocytes proliferate until late gestation by hyperplasia (increased cell reproduction) and switch to a predominantly adult hypertrophic growth pattern (increase in cell size) after birth [68]. The mechanism of cardiac growth at preterm birth is derived predominantly by the drastic physiological changes to compensate for the extrauterine conditions to ensure preterm survival. As such, in the first few months of postnatal life, myocardial cell volume increases approximately 30-fold in humans [63]. Similarly, improvement in cardiac function takes place alongside the maturation of contractile and relaxation properties of cardiomyocytes [69]. These events thereby cause the preterm heart to remodel differently compared with their term-born counterparts.

1.2.1.1 Perinatal interventions

Premature babies, especially those born very preterm, are highly predisposed to develop respiratory distress syndrome (RDS) and other health complications at birth and later in life [70]. Consequently, advancements in perinatal medicine to improve preterm outcomes are of importance. One of the most widely used standard maternal treatments in the 1980s and 1990s is antenatal glucocorticoids (ACT) that are also known as corticosteroid therapy [71]. ACT is given to pregnant women with the possibility of having premature labour (particularly less than 35 weeks) to reduce preterm morbidities and mortality. In addition, the exogenous surfactant is commonly given to extremely preterm infants with a higher risk of developing RDS [72, 73].

1.2.2 Cardiac remodelling in infants and children

Babies born preterm are at risk for future health problems. Therefore, emerging research has now focused on the early developmental stages to provide more prematurity-related knowledge and eventually seek to develop interventions in this population. Importantly, cardiac differences between preterm-born and term-born infants can be seen even in very early life, which may be the driver for higher risk of CVD in the preterm-born individuals [74]. In 1986, two studies first highlighted cardiac differences in preterm and term neonates. Using echocardiography, the studies showed that preterm neonates had smaller LV stroke volume (LVSV) [75] as well as smaller LV diastolic and systolic dimensions [76] in proportion to decreasing birth weight and gestational age. In the following years, more studies investigating cardiac differences using echocardiography between preterm-born and term-born infants have been published. Some studies have reported that preterm infants have altered diastolic function [77-80], decreased systolic myocardial function [81-84], while others have shown no differences in diastolic ventricular filling patterns [85] or LV contractile function [86].

One of the most significant findings highlighting the adverse effect of being born prematurely is the increase in LV mass (LVM). An early study investigating cardiac differences between preterm-born and term-born infants (mean gestation 33.8±1.0 vs 39.3±1.3 weeks) during the first month of life demonstrated that preterm infants have lower LV mass index (LVMI) with systolic and diastolic alterations at birth [87]. Interestingly, after one month follow up, there were no significant differences in LVMI between the preterm-born and term-born infants due to significant increases in LVMI in the preterm infants [87]. Similarly, echocardiography findings have been reported in an independent cohort of 392 infants, of

which 129 were born preterm (mean gestation 34±2 weeks). At birth, the study reported reduced heart mass (relative to body weight) with a smaller, globular heart seen in the preterm infants [88]. Over the first three months of life, preterm neonates had a disproportionate increase in both LVM and RV mass (RVM), with a reduction in cardiac size and function [88].

Another study utilising CMR imaging was conducted on preterm infants in the early postnatal period [89]. To better explore the cardiac differences between preterm infants and controls, LV and RV CMR scans were done, as well as the creation of a computational atlas of the heart. Preterm infants had significantly elevated weight indexed LVM and LV end-diastolic volume (LVEDV) at term-corrected age. This remodelling was worse in those born extremely preterm, marked with 64% greater weight-indexed LVM in the preterm infants compared to controls at term-corrected age [89]. LV and RV computational atlases revealed that, at term corrected age, preterm infants had a more globular LV shape, with a more spherical blood pool [89]. The increase in LVM seen in the first few months of life was likely due to disproportionate cardiac hypertrophy that occurred as part of catch-up growth after preterm birth [87-90].

Previous studies have reported the differences in the structure and function of the RV. An early, small study of 35 neonates, of which 17 were born preterm, demonstrated that preterm neonates had a smaller RV stroke volume (RVSV), but maintained the same RVCO, compared with the term neonates. This was likely due to the higher heart rate recorded in the preterm group [91]. Another study attempting to establish reference values of tricuspid annular plane systolic excursion (TAPSE) was performed in 258 neonates of which 174 were born preterm. The findings demonstrated that TAPSE, a marker of RV contractile function,

decreased linearly with greater prematurity. Interestingly, TAPSE, gestational age and birth weight were strongly correlated [92]. In an independent cohort study published by the same authors [93], reduced RV systolic function measured by echocardiography, represented by RV S', was associated with a greater degree of prematurity. One possible explanation for the RV systolic alterations observed in the preterm group is that the RV consists of a thin-walled chamber that is more likely to remodel as a result of stressors and alterations in flow and is not as strong as the LV in overcoming increased pressure and hemodynamic fluctuations [94].

Similarly, a marker of diastolic dysfunction, elevated E/E' ratio, has been reported in both the LV and RV with a relationship with the degree of prematurity [95]. In this study, 43 neonates were categorised into three groups: very preterm (n=15), moderately preterm (n=12) and term (n=16). RV myocardial peak systolic velocities were higher than the LV in all three groups and decreased with decreasing gestational age. The preterm neonates were also found to have more interventions during the perinatal period, which the authors concluded may have contributed to the lower RV myocardial velocities seen in the preterm group [95]. Similarly, Erickson et al. recently published a study investigating RV development at one year of age in 80 preterm infants which confirmed these findings [96]. Echocardiography assessments at 32 weeks post-menstrual age and one year of age demonstrated evidence of RV structural and functional remodelling in the preterm infants compared to term infants [96].

Other research has attempted to distinguish the independent effects of early life factors on cardiac dysfunction in those born premature. A study of 503 preterm infants with a birth weight of ≤2,000 grams demonstrated that the cardiac alterations may reflect the effect of ACT and being born small for gestational age [97]. Research has demonstrated that the effects of

ACT are apparent in adult life whereby young adults with a history of in utero glucocorticoid exposure display a localized increase in aortic arch stiffness [98], though cardiac alterations have not been observed. Evidence suggests that preterm neonates with RDS have significantly reduced cardiac function at birth compared to preterm and term controls, although most of the cardiac differences between the groups disappear by one month [99]. A more recent study addressing the patterns of myocardial function in VLBW infants with or without bronchopulmonary dysplasia (BPD) showed delayed myocardial function maturation in those who developed BPD [100].

Overall, these findings suggest that the impairment in cardiac function that occurs during early postnatal life may increase the risk of hemodynamic instability in the postnatal circulatory transition period [101]. To date, only one cardiac autopsy study has been performed to identify the effects of preterm birth on structure and cardiomyocyte development in preterm infants were compared with age-matched control fetuses [102]. The findings demonstrated a reduction in cardiomyocyte proliferation in preterm infants, which may occur due to an increase in heart rate and arterial pressure following preterm birth [102]. These important findings highlight the challenges experienced by these immature cardiomyocytes in the ex-utero environment, which likely leads to inhibited myocardial maturation and promotes cardiac hypertrophy and fibrosis. This may eventually increase the susceptibility of abnormal cardiac remodelling and cardiac dysfunction in later life [102-104]. Most of the research findings discussed above are consistent with each other, and thus warrant a longitudinal study that can provide better insight into cardiac remodelling patterns over time, from birth through childhood and into adulthood. Furthermore, findings also suggest that targeted neonatal

interventions could potentially improve long term cardiac function in this unique population [88, 105].

1.2.3 Cardiac remodelling in adulthood

The association between preterm birth and later cardiac remodelling is now well established. A recent meta-analysis of 32 observational studies based on cardiac imaging revealed that preterm individuals appear to have an altered cardiac structure and function from birth to adulthood [94]. The findings have shown that the marker for diastolic function, LV diastolic velocity (e') measured by echocardiography, was persistently lower throughout the developmental stages. Preterm-born individuals appeared to have smaller LV end-diastolic dimensions (LVEDD), which were consistently observed across all developmental stages, with a reduction in LVEDV index (LVEDVI) and shorter LV length in young adulthood. Similarly, a marker of myocardial contractility, RV s', was reduced across all ages and the magnitude of difference relative to term-born controls increased from birth to adulthood. Data in adolescents and older adults is currently limited [94]. Overall, some cardiac impairments seen in preterm-born individuals appear to worsen with greater prematurity, which may partly explain why those born very and extremely preterm are the most susceptible to early heart failure [12].

One of the earliest CMR studies investigating cardiac differences between preterm- and term-born young adults was conducted in 102 preterm-born (30.3±2.5 weeks) and 132 term-born (39.6±0.9 weeks) individuals aged 20-39 years [106]. This study demonstrated that

LV structure and function were altered in preterm-born adults. The average LVM was 19 grams higher in the preterm group independent of the higher blood pressure readings. Importantly, this finding is equivalent to that associated with a 9 kg/m^2 increase in body mass index (BMI) [107] and in longitudinal studies, would equate to a 50% increased risk of cardiovascular clinical events in later adult life [106]. Functional parameters including LVSV and longitudinal systolic myocardial contractile function were reduced despite preserved resting LV ejection fraction (LVEF) in the preterm-born individuals. CMR data used to create the first preterm LV computational atlas revealed that the preterm-born group had significantly shorter and smaller LV dimensions, increased LV wall thickness and a displaced apex away from the RV. The same authors subsequently published on the RV using the same cohort, and revealed a greater impact of being born preterm, marked by increased mass, as well as shorter and smaller RV internal dimensions [108]. In contrast to the LV findings, the RV systolic function was significantly lower with six out of 102 of the preterm group exhibiting lowered resting RV ejection fraction (RVEF), between 42% to 45%, indicating mild RV dysfunction. Interestingly, the strongest independent predictor of the reported RV findings (higher mass, reduced EF and reduced EDV) was the degree of prematurity.

Another recent study of 47 normotensive young adults born preterm (32.8±3.2 weeks) versus 54 term-born controls utilising echocardiography demonstrated that the preterm group had a greater LVMI, lower indexed LV volumes, as well as shorter and smaller LV internal dimensions, resulting in disproportionately increased indexed LVM to LVEDV [109]. Resting LVEF was preserved, but when subjected to increased exercise intensity using stress echocardiography, the preterm group exhibited lower LVEF than the controls at 60% and 80%

of peak exercise intensity. The findings of this research are consistent with the later study published by Goss et al [110]. In their small study of extremely preterm-born young adults using invasive right heart catheterization, they found that the preterm-born young adults had an impaired ability to increase RV cardiac index (RVCI) and RVSV from rest to 70% of maximum exercise capacity [110]. These observed subclinical cardiac impairments following stress echocardiography [109] and right heart catheterization [110] in preterm-born individuals, combined with the underlying cardiac differences from experimental and clinical studies, may represent a unique form of cardiomyopathy [111].

1.2.4 Insights from animal studies

Experimental studies with different animal models have helped provide early insights into the effect of preterm birth from a cellular level. Previous studies have demonstrated the evidence of increased interstitial myocardial fibrosis and alterations in cardiomyocyte maturation and size within the myocardium, as early as neonatal life [112, 113]. A landmark study on the preterm-born ovine model has shown structural remodelling of the myocardium marked by an increase in interstitial collagen deposition accompanied with five- to seven-fold greater cardiomyocyte hypertrophy (**Figure 1.4**) [113]. Interestingly, these alterations were seen in the ovine model even without the presence of the normal physiological and inflammatory state that commonly occurs during preterm birth in humans [114]. The findings also reported greater mononucleated (immature) cells in the preterm RV and LV. There were no differences in the number of cardiomyocytes, however cardiomyocyte volume was significantly increased in the

preterm group, which indirectly demonstrates that catch-up growth predominantly occurs by cardiomyocyte hypertrophy [113].

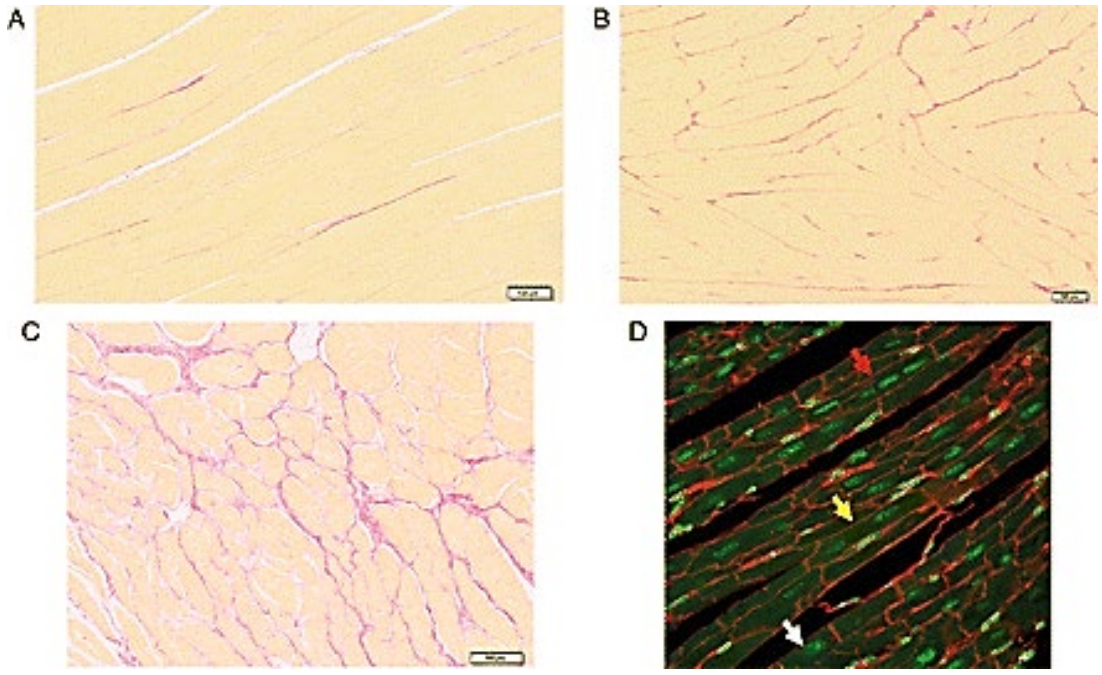


Figure 1.4: Remodelling of the myocardium in 9-week-old lambs post-term-equivalent age. Representative photomicrographs showed LV and septum with **(A)**, Minimal collagen deposition in a term lamb. **(B)**, Greater collagen deposition in a preterm lamb. **(C)**, Severe fibrosis in a preterm lamb. **(D)**, Mononucleated (white arrow), binucleated (yellow arrow) and trinucleated (red arrow) cardiomyocytes in a preterm lamb. Image taken from Bensley, J.G., et al, *Eur Heart J, 2010.*

Similarly, an animal study using a rat model of an extrauterine environment mimicking preterm-birth related conditions has reported cardiac changes such as cardiomyocyte hypertrophy and greater collagen deposition (**Figure 1.5**) [104]. Interestingly, the increase in cardiomyocyte volume and altered collagen content occurred before blood pressure elevation. Furthermore, the rats receiving angiotensin II (Ang II) infusion were found to have a greater

risk of developing heart failure later in life. In an independent study, the same authors reported the beneficial effects of short-term Ang II type 1 (AT1) receptor antagonist Losartan usage, which halted the progression of myocardial fibrosis and hypertrophy [115]. Another study in rats using a similar model has also explicitly focused on the RV. In 2014, Goss et al. investigated the long-term effect on RV and pulmonary function in hyperoxia exposed rats. At one year of age, hyperoxia-exposed rats had reduced RVEF, increased RV hypertrophy (RVH), and RV-pulmonary vascular decoupling [116]. The authors subsequently published another study investigating the impact of postnatal hyperoxia exposure throughout life. The findings reported bimodal RV dysfunction, possibly caused by the accumulation of mitochondrial DNA mutations in hyperoxia-exposed rats [117].

A study by Mrocki et al. found thinner RV walls with reduced cardiomyocytes and a reduction in pulmonary artery peak systolic blood flow velocity in moderate preterm-born adult sheep [118]. Using ultrasound imaging and perfusion-fixed heart imaging analysis, the authors studied 14 male sheep delivered moderately preterm (132±1 days; n=7) or at term (14±1 days; n=7) and followed them up to 14.5 months of age, which is equivalent to 20 years of age in humans. The authors concluded that although being born moderately preterm leads to less neonatal complications after birth, it can still contribute to abnormal postnatal development in major organs later in life. This is likely due to the abundance of mononucleated cardiomyocytes (immature cells) found in child animals born preterm that are still capable of proliferation.

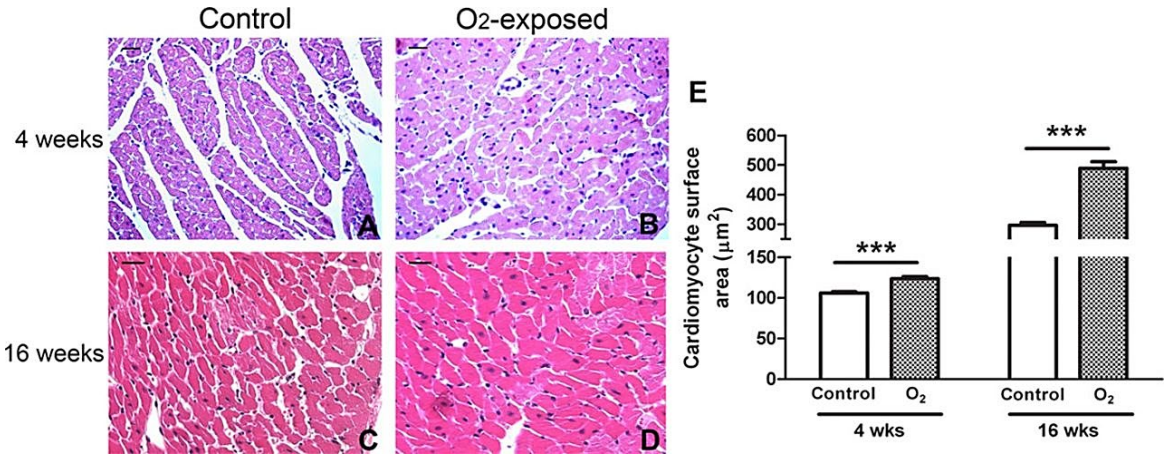


Figure 1.5: Remodelling of the myocardium in 4- and 16-week-old rats. Photomicrographs of LV cardiac sections showed the differences of myocardial hypertrophy in rats exposed to high oxygen (O_2), which is a model representing preterm birth conditions, as newborns vs room air controls at 4- **(A** and **B)** and 16-weeks **(C** and **D)** with no difference in cardiomyocyte cell numbers between groups. However, increased cardiomyocyte surface area was observed in rats exposed to O_2 **(E)**. Image taken from Bertagnolli, M., et al, *Hypertension, 2014.* Wks indicates weeks; O_2, high oxygen.

1.3 High blood pressure in young adults

Hypertension is a major risk factor for CVD and mortality [119]. Beyond its impact on mortality, raised systolic blood pressure is the leading contributor to global disability, accounting for 211.8 million (95% uncertainty interval 192.7–231.1 million) global disability-adjusted life years for both sexes [120]. It is estimated that the prevalence of hypertension will increase by about 60% by 2025, with approximately one-quarter of the world's adult population living with hypertension [121]. In the United Kingdom, one in four adults is now hypertensive [122], with even higher rates in those predisposed to hypertensive disease due to familial history, or a history of pregnancy complications such as preterm birth, hypertensive pregnancy, and fetal growth restriction [123]. Hypertension in young adults is associated with

target organ damage including LV hypertrophy (LVH) that precedes other organ damage [124] as well as increased risk of cerebrovascular alterations [125, 126]. Meta-analysis of 61 prospective cohort studies investigating age-specific relevance of blood pressure to mortality has revealed a linear association between increased blood pressure and vascular events. Patients with systolic blood pressure equal to or more than 115 mmHg and diastolic blood pressure at 75 mmHg or more have an increased risk of adverse cerebrovascular events [24]. This is further supported by research that found that systolic blood pressure exceeding 120 to 125 mmHg starts to lead to a significant deviation towards developing hypertension, making earlier blood pressure management of great importance [127]. Similarly, due to low levels of interaction in the young adults cohort with health services, early diagnosis and management of high blood pressure has been a challenge [128, 129].

Realising the serious multisystem impact of hypertension, international bodies have prompted substantial ongoing efforts to define the optimal range of blood pressure. Current blood pressure guidelines from the American Heart Association (AHA) and the European Society of Cardiology (ESC) have classified lower levels of blood pressure of ≥130 systolic and/or >80 mmHg diastolic and ≥140 systolic and/or >90 mmHg diastolic to define hypertension [130, 131]. With predisposing factors like prematurity, the progressive increase of blood pressure might occur sooner, and worsen in those with a previous history of perinatal insults. However, research to reduce blood pressure in this population and thereby reduce CVD risk is still lacking, with no effective strategy for clinical practice yet reported.

1.3.1 The general effect of high blood pressure on the heart and potential vulnerability of the preterm heart

The effect of systemic hypertension on the heart is now clearly established in older populations. LVH is known as a primary pathophysiological adaptive response of the heart to high blood pressure and is frequently seen in hypertensive individuals. It occurs as a result of several complex interactions of hemodynamic and non-hemodynamic factors including pressure overload, sex, and body size [132]. Typically, the pattern of LVH in hypertension involves global thickening of the LV walls and an overall increase in LVM. This LV remodelling happens as a compensatory mechanism to minimise the wall stress arising from the elevated blood pressure [133]. Based on Laplace's Law, an increase in intraventricular pressure must be accompanied by a decrease in the radius and/or increase in relative wall thickness [wall stress = (pressure x radius)/(2 x wall thickness)] [134]. This morpho-functional remodelling leads to alterations not only in cardiomyocytes, but also to the interstitial space and coronary microvasculature of the heart [135]. As the remodelling progresses, diastolic dysfunction becomes apparent, characterised by abnormal LV relaxation [136-138]. Left atrial enlargement is evident in hypertensive individuals as a result of abnormal LV filling pressure, which is associated with increased RV anterior wall thickness, including RVH [139].

Emerging research has now started reporting the effect of systemic hypertension on the right heart. The RV and LV are interdependent structures that work together to overcome the pressure and/or volume overload [140]. A meta-analysis of echocardiography has shown that nearly 30% of the participants with systemic hypertension presented with RVH as a

common feature of the hypertensive heart [141]. Chronic pressure overload can result in pathological ventricular remodelling and functional impairment, and ultimately, increase risk of clinical heart failure [142]. Furthermore, research has now focused on the impact of progressing suboptimal blood pressure on the heart, in line with the new blood pressure classification by the AHA [130]. In a meta-analysis of echocardiographic studies of 60,949 individuals, Cuspidi et al. demonstrated a strong correlation between the prevalence of LVH and increased LVMI with increasing blood pressure [143]. Prehypertensive individuals appeared to have intermediate cardiac alterations, with greater changes than in normotensive adults but less remodelling than in hypertensive individuals [143]. The same authors subsequently published a study reporting a strong association between those with high normal blood pressure and subsequent development of LVH [144].

In a young adult study of 1154 individuals followed up from childhood to adulthood, individuals with LVH were those who had prolonged, higher systolic blood pressure readings since childhood [145]. In another study investigating cardiovascular differences between males and females with increased blood pressure, it was demonstrated that an increase in CO was considered the main cardiac adaptation in early stages of blood pressure elevation in young individuals. These cardiac changes were predominantly found in males. In women, changes were seen most often in the vasculature, including elevations in peripheral vascular resistance, aortic pulse wave velocity, and augmentation index [146]. LVMI, an independent predictor of CVD, was highest in hypertensive individuals and lowest in normotensive individuals. The percentages of individuals with LVH were 2.5%, 6.1% and 14.9% in normotensive, pre-hypertensive and hypertensive individuals, respectively [143]. The same

authors also published a study reporting a strong association between those with high normal blood pressure and subsequent development of LVH [144]. These results suggest that earlier blood pressure management could slow down the negative impact on cardiac remodelling.

In the 2013 CMR study by Lewandowski et al. in 234 individuals, including 102 born preterm, a strong association between both blood pressure and LVMI with brachial pulse pressure was demonstrated across all groups [106]. In this study, individuals with higher blood pressure had higher LVMI. Furthermore, when dividing preterm- and term-born adults by the cohort median pulse pressure, it was shown that those born preterm had increased LVMI compared to the term-born adults with similar pulse pressures [106].

These findings emphasize the clinical importance of research in individuals with hypertension and elevated blood pressure. It is also important to note that several factors, including pressure and volume load, demographics, medical conditions, alterations of the extracellular matrix, genetic factors and neurohormonal milieu may also impact on how elevations in blood pressure modify cardiac structure and function in hypertensive individuals [147]. Thus, specific, targeted interventions that take into account these different factors are needed to potentially revert the progression of pathological cardiac remodelling.

1.4 Cardiovascular benefits of aerobic exercise training on the heart and potential benefits in the preterm and hypertensive young adult population

1.4.1 Insight from clinical studies

The benefits of exercise training interventions as safe, low-cost strategies to prevent cardiovascular and metabolic diseases, are widely established. The AHA has defined cardiorespiratory fitness and physical activity levels as important and standard physiological function assessments in clinical settings [148]. Regular exercise training is associated with reduced risk from CVD (e.g. coronary artery diseases and heart failure), reduced blood pressure, decreased inflammatory processes, improved metabolic health, as well as increased rates of survival [149-153]. Beneficial cardiovascular improvements following exercise occur via adaptations to the cardiac and vascular systems, which include decreased activation of the sympathetic nervous system and dilation in blood vessels, which leads to decreased SVR. With training, the arteries and capillaries carrying oxygenated blood to the working muscles also expand [154]. This adaptation increases capillary density within muscle tissue and improves aerobic metabolism, ultimately increasing the availability of oxygen for the working muscles [155]. Through exercise, not only can the adverse effects of increased arterial stiffness be halted [156, 157], but regular exercise can also promote angiogenesis and enhance nitric oxide release, increasing blood flow and inducing vascularisation, which minimises the chances of adverse cardiac events [134, 154]. Several reviews have shown that regular aerobic exercise

correlates well with a reduction in arterial stiffness [158-160] and post-exercise hypotension [161] in both healthy and diseased individuals.

When somebody starts to exercise, the heart, muscles and other body systems need to work harder to effectively supply blood to the rest of the body. Endurance training commonly leads to a volume overload and increased diastolic wall stress, ultimately inducing physiological, eccentric remodelling of the LV with some hypertrophy. The increase in LVM and LV ventricular cavity dimensions are physiological adaptations that lead to improvements in cardiac function [162, 163]. The LV and RV are interconnected chambers and work closely together to ensure optimum function throughout exercise. LV cardiac output (LVCO) increases five to eight-fold during exercise and the enhanced venous return to the RV indirectly places more pressure on the RV, suggesting increased RV wall stress. However, RV adaptations following sustained periods of exercise training are not widely reported.

Several clinical studies have demonstrated the potential cardiac adaptations in response to regular endurance exercise in young adults. In 2014, Arbab-Zadeh et al. conducted a study to investigate cardiac adaptations following a one-year endurance exercise training programme in young, healthy individuals [164]. Their findings showed that long term cardiovascular adaptations to endurance exercise training led to significant improvements in cardiac remodelling and cardiorespiratory fitness [164]. Improvement in maximal oxygen consumption (VO_2 max) as a result of increased CO and arteriovenous oxygen uptake was reported in the exercise group. Those in the exercise group had increased LVCO, LVEDV, and ventricular wall thickness on CMR. In contrast with the concentric remodelling pattern in

the LV, changes were also seen in RVM and RV volumes, with an eccentric remodelling pattern following exercise intervention [164].

Another study was conducted in adult males aged 48±7 years who underwent an 18-week structured marathon training program [165]. This study demonstrated smaller but significant exercise-induced cardiac remodelling including improvements in LV diastolic function, biventricular dilatation, and increased VO_2 max. However, no significant changes in RV parameters were seen following training. Other clinical studies have previously reported improvements in systolic and diastolic function in exercise-trained individuals [166, 167]. D'Silva et al. had conducted another study where 68 young, novice marathon runners underwent a 17-week unsupervised marathon training programme, which showed minimal exercise-induced cardiac remodelling [168]. The study reported evidence of eccentric remodelling and minimal increases in ventricular sizes as well as VO_2 max. Only three RV cardiac parameters were reported including RVEF, RV end-diastolic volume index (RVEDVI) and RV end-systolic volume index (RVESVI). The results showed no change in most of the cardiac parameters, including no change in LVEF or RVEF, diastolic function, and myocardial strain following exercise training. However, there was evidence of eccentric remodelling with 3–5% increases in LV and RV cavity sizes, respectively [168]. It is worth noting that the concept of unsupervised training in itself might contribute to the modest changes seen following exercise intervention.

Despite the proven benefits of exercise on the cardiovascular system, most lifestyle interventions in the literature have been evaluated in older adults and it is unclear if these measures for managing cardiovascular risk are effective in a younger population. A recent

systematic review reported that the benefits associated with prescribed exercise programs in young adults (mean age=42 years) are limited with training intervention programmes of only three to six months, with blood pressures returning to baseline by 12 months post-intervention. This reveals significant investigative deficiencies on the effect of exercise on blood pressure and related cardiovascular risk in young adults [169]. It is also unclear whether all individuals will respond the same to exercise and why some people continue to exercise while others stop. As such, we still lack the evidence to support personalised exercise recommendations in combatting hypertension. A key factor that may be important in the inter-individual variation or lack of response to exercise is how the cardiovascular system of an individual responds to exercise [170]. This further emphasises the importance of exploring specific exercise training recommendations to improve cardiovascular physiological capacity in young people, and whether exercise regimes need to be tailored to individual requirements.

Cardiac adaptations following exercise training may be beneficial in people with hypertension [171, 172]. In general, hypertension can induce pathological cardiac hypertrophy or alterations in LV systolic and diastolic volumes [173, 174], which may attenuate cardiac function, cause ventricular stiffening and contractile dysfunction, thereby leading to prominent decreased CO [175, 176]. This process ultimately increases the risk of heart failure [177, 178]. With the mounting evidence of the benefits of exercise in the general population, exercise may specifically benefit hypertensive individuals. Previous studies have demonstrated that regular physical activity reduced LVMI [179, 180] and slowed down the development of LVH in active hypertensive individuals [181]. In young hypertensive individuals, improvements in endothelial function have been observed in response to exercise

training [182], which could reduce cardiac afterload. A review investigating the cardiovascular effects of exercise training in young hypertensives demonstrated positive effects following exercise, including a reduction in blood pressure and attenuation of blood pressure response to the cold stress pressor test [134].

In a randomised controlled trial, Yakasai et al. reported a reduction in systolic and diastolic blood pressure following a six-week moderate exercise intensity programme in the experimental hypertensive group, but no cardiac response was reported [183]. Improved LVSV, LVEDV and LVEF as well as a reduction in blood pressure has been demonstrated in older hypertensive individuals following 12 weeks of aerobic interval training [184]. These results, which primarily focus on an older population, suggest that cardiac remodelling in response to exercise may be part of the protective effect of exercise in those with hypertension [171]. However, this has yet to be explored in young adults with elevated and high blood pressure. The underlying cardiac remodelling patterns in preterm-born individuals may mean that they respond differently to exercise interventions, though this has not previously been explored. Furthermore, preterm-born individuals demonstrate a reduced myocardial functional reserve [109] that leads to a reduction in exercise capacity and heart rate recovery [185, 186], which may affect how they are able to train [185] and how their heart will remodel. **Figure 1.6** demonstrates how risk of developing heart failure in preterm-born individuals may be due to their reduced myocardial functional reserve emerging from birth [74].

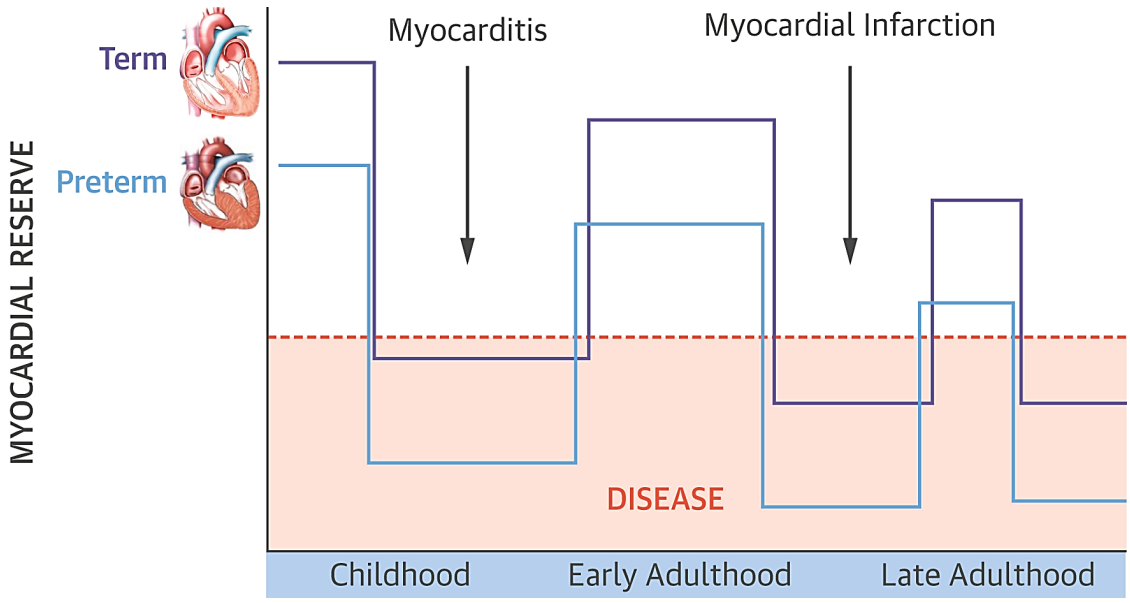


Figure 1.6: Impact of reduced myocardial reserve in preterm-born versus term-born individuals across ages based on the human and animal experimental studies. Premature infants have increased LV and RV mass, decreased LV and RV volumes, and reduced LV and RV systolic and diastolic function. As these changes track throughout life, people born preterm have a reduced myocardial reserve that may make them more susceptible to early heart failure. Image taken from Leeson, P., and Lewandowski, A.J. *J Am Coll Cardiol, 2017.*

1.4.2 Insight from animal studies

Emerging animal studies in hypertensive models have been performed to investigate the possible protective cardiac effects of exercise. Most research has suggested that the protective cardiac impact following exercise relates to signalling pathways involved in hypertrophy and fibrosis [187]. Recent work using spontaneously hypertensive rats has demonstrated that low exercise intensity (55% of maximal oxygen uptake) reduced myocardial Ang II levels, which delayed the progression of hypertension via attenuation of cardiac hypertrophy. In contrast, Ang II levels were significantly increased in the rats, with evidence of cardiac hypertrophy [188]. In the diseased heart, cardiac fibrosis is known as an excess

deposition of ECM in the interstitium [189]. Experimental animal exercise models have identified that both moderate- and high-intensity interval training can reduce interstitial collagen content in cardiac muscle, while only high-intensity interval training improves capillary density [190]. In an independent study using the same rat model, apoptosis, an essential component of pathological adaptation, has been found to be reduced in the myocardium [191, 192] and improvement of systolic function was reported following exercise training [191]. Slower increases in LV collagen deposition and early modulation of the renin-angiotensin system pathways have been suggested as adaptive responses to protect the heart in the exercise rat group [193].

1.5 Thesis hypotheses and objectives

Given the current evidence and gaps in our understanding of the preterm heart, this thesis aims to further characterise the cardiac phenotype of people born preterm and whether aerobic exercise training can modify prematurity-related cardiac changes. My specific hypotheses are:

1. Preterm-born adults will have reduced RV systolic function independent to changes in pulmonary physiology (Chapter 4).
2. Preterm-born adults will exhibit greater cardiac remodelling changes in relation to blood pressure elevation compared to term-born adults due to their known abnormal cardiac remodelling patterns even in the normotensive range (Chapter 5).
3. The pattern of changes of LV and RV remodelling and function in response to a 16-week aerobic exercise training program will vary with birth history, with preterm-born

adults exhibiting less LV and RV structural and functional remodelling compared to term-born adults (Chapter 6).

CHAPTER 2

STUDY POPULATION

2.1 Overview

This chapter explains the study population, recruitment and study procedures for each specific protocol. The work in this thesis is based on three completed studies: the Early Vascular Study (EVS), the Young Adult Cardiovascular Health sTudy (YACHT) and the Trial of Exercise to Prevent Hypertension in young Adults (TEPHRA). These protocols were conducted at the Oxford Cardiovascular Clinical Research Facility (CCRF) for full study assessments and Oxford Centre for Clinical Magnetic Resonance (OCMR) for magnetic resonance imaging (MRI). CCRF is a core clinical research facility that provides research expertise in the fields of echocardiography, vascular assessment and clinical physiology. The principal investigators for these studies are my supervisors: Dr Adam Lewandowski and Professor Paul Leeson.

The design of these three studies was based on a standardised study structure and methodology. EVS and YACHT are observational, cross sectional studies of participants in young adulthood that collected detailed birth history information, while TEPHRA is a

randomised controlled trial of an aerobic exercise training programme in young adults with elevated blood pressure. Cardiovascular deep phenotyping measures were used in the three studies, allowing for baseline study integration and future longitudinal study linkage. The overall focus of this thesis is to characterize the baseline cardiovascular phenotype and cardiac morphology of preterm-born young adults, building on previous research, as well as to investigate how an exercise intervention can modify prematurity-related cardiovascular changes. The integrated study protocol structure for EVS, YACHT & TEPHRA is shown in **Figure 2.1**.

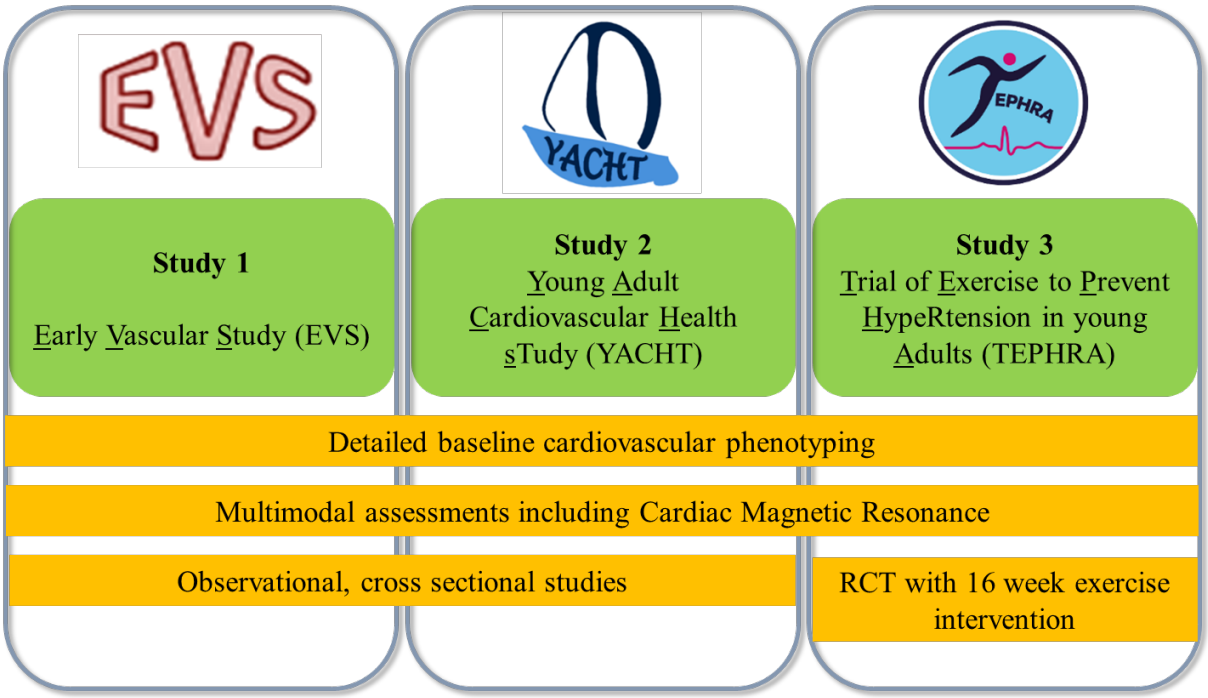


Figure 2.1: Integrated study protocol structure used in this thesis

2.2 Study cohorts

2.2.1 Cohort 1: EVS

EVS is a longitudinal study conducted in young adults, with a preterm-born subgroup. The aim of EVS was to more accurately quantify cardiovascular changes in adults born preterm, as well as gain a more comprehensive understanding of the factors driving these changes. The study population in this cohort incorporates 234 participants, of which 102 were born preterm, and recruited from 2009 to 2013 by Dr Adam Lewandowski and Professor Paul Leeson. The summary of the EVS cohort is shown in **Figure 2.2**.

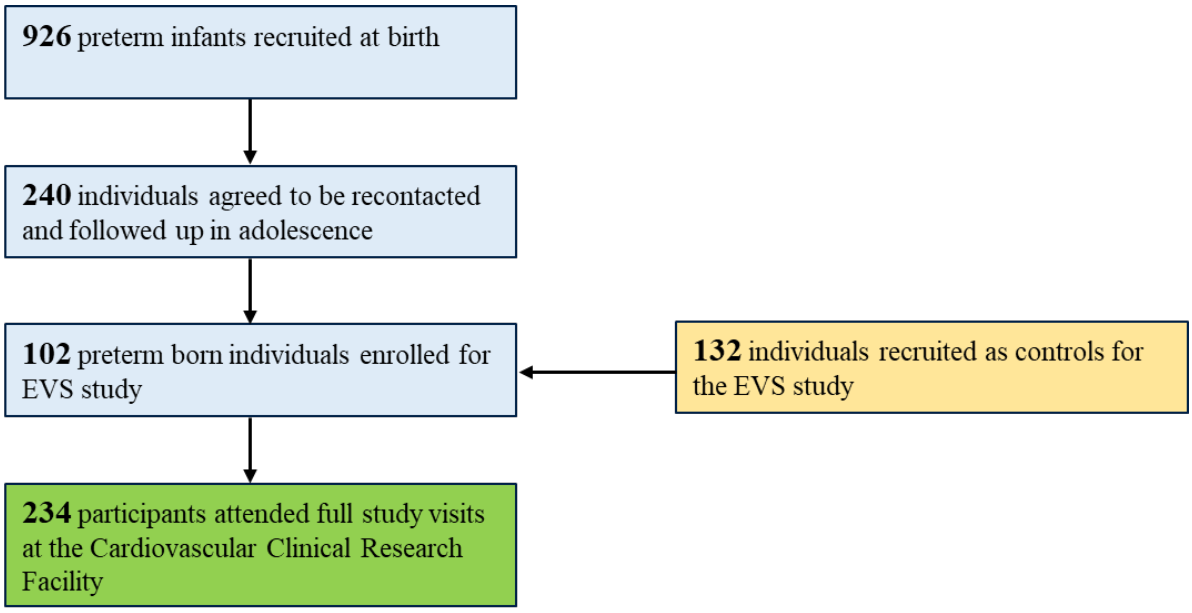


Figure 2.2: The EVS cohort.

2.2.2 Cohort 2: YACHT

YACHT is an observational, case-controlled study designed to understand how preterm birth and the development of high blood pressure in early adult life influences cardiovascular structure and function. The study population was 149 healthy young participants who were recruited from August 2014 to May 2016 by Dr Adam Lewandowski and former DPhil candidates, Dr Wilby Williamson and Dr Odaro Huckstep. The final study visit completed on January 2020. The study PI was Professor Paul Leeson.

2.2.3 Cohort 3: TEPHRA

TEPHRA is a prospective, single blinded, two-arm, parallel, randomised controlled trial of a 16-week physical activity intervention, involving behaviour change and a structured exercise programme in young adults with elevated blood pressure. The aim of TEPHRA was to study the effects of an aerobic exercise intervention on the cardiovascular health of young adults at risk of early hypertension and CVD, including individuals born preterm. The study population in this cohort includes 540 participants who were recruited for screening from June 2016 to June 2018 by the dedicated TEPHRA study team. In total, 203 participants were eligible and randomised to the trial. Of these, half (n=102) were randomised to the 16-week aerobic exercise programme, and the other half (n=101) into the control group. The original sample size calculation for randomisation was 200 participants, allowing for 18% attrition. We slightly over recruited to ensure adequate data collection to achieve study power and ended up

with 203 randomised participants. The summary of TEPHRA recruitment is shown in **Figure 2.3**.

2.3 General study recruitment

Recruitment of participants for EVS, YACHT and TEPHRA was accomplished through multilayered recruitment approaches. For EVS, we prospectively followed up individuals born preterm between 1982 and 1985 who were recruited at birth into a randomised study investigating different milk feeding regimens. Those who agreed to be contacted for further studies were invited to attend an appointment in Oxford for detailed cardiovascular phenotyping. Control participants, born full term to uncomplicated pregnancies, with a similar age and sex distribution to the preterm-born young adults were recruited via advertisement to undergo identical investigations.

As for the YACHT and TEPHRA studies, participants were recruited through open recruitment in the local Oxford community using posters, mailed invitations from the John Radcliffe Hospital birth registries, word of mouth, and invitations following participation in previous studies. Active recruitment was also carried out by inviting young adults who had visited the John Radcliffe Hospital Hypertension Service Clinic. Additional recruitment strategies for TEPHRA included: 1) on-line recruitment using TrialSpark to engage the targeted study population and optimize recruitment and 2) preterm birth cohorts from studies conducted by the Institute of Child Health, University College London were approached for cardiovascular follow up in Oxford.

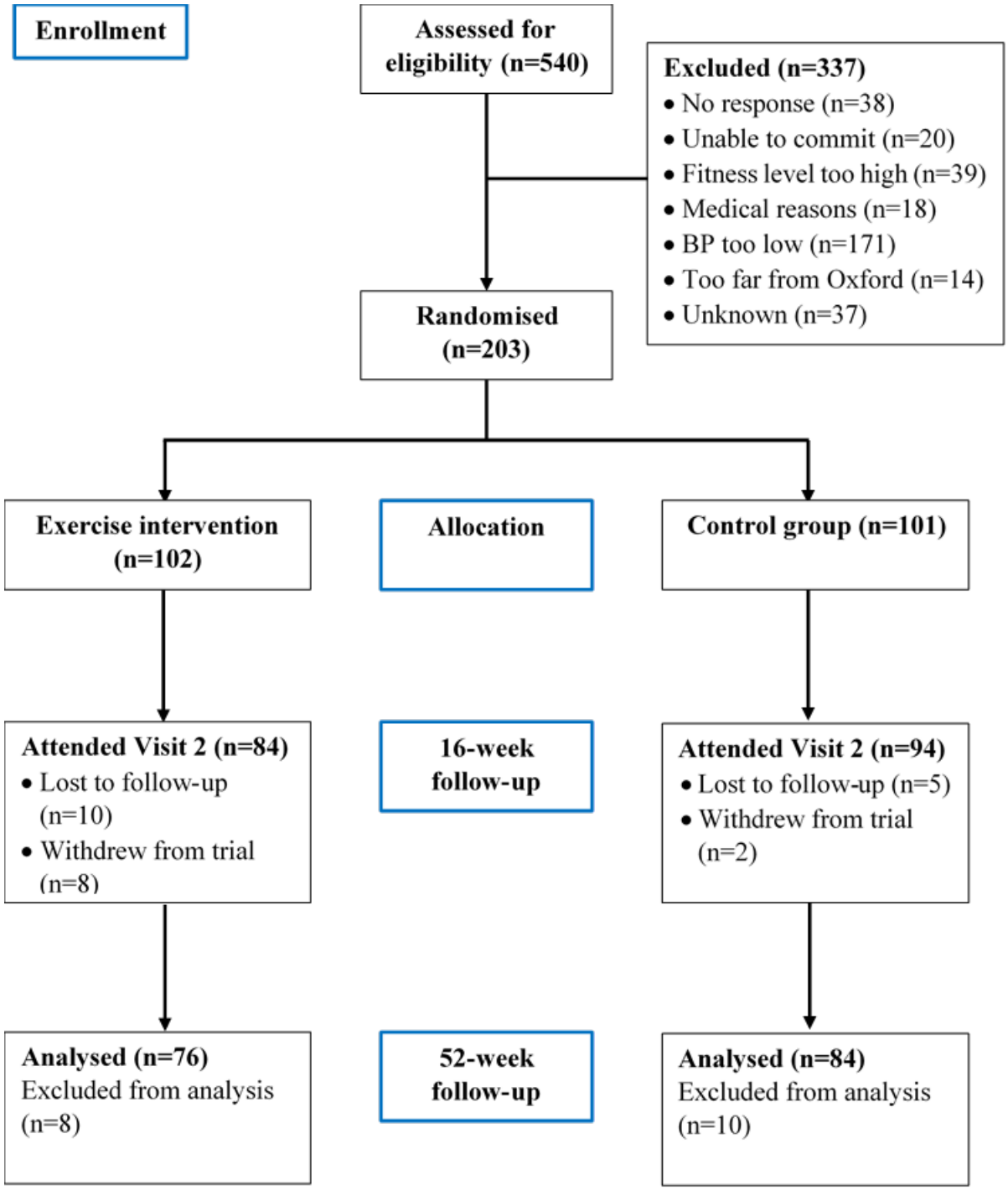


Figure 2.3: The TEPHRA cohort.

2.4 General study visit overview

Potential participants were asked to attend a study visit at CCRF and OCMR in the John Radcliffe Hospital, Oxford. All participants fasted for 6-12 hours before the study visit, consuming only water. Before coming to the study visit, all participants received the study participant information leaflet. On the day, the overview of the study visit was explained by a trained clinical research investigator. All participants had the opportunity to ask questions about the study and, for all studies, written consent was obtained before study enrollment. A copy of the consent form was given to the participants before the study visit started, while the original consent form was kept with the study investigators in CCRF. All measurements were recorded in a case report form and kept in a separate folder and cupboard from the original consent form. Data were coded with a subject-specific identification code to ensure participant anonymity, which allowed for blinded analysis. Investigators were also blinded to birth history and other relevant clinical information. Additional study blinding was used in TEPHRA, where the study investigators were blinded to the trial intervention allocation. The general study visit outline for EVS, YACHT and TEPHRA is provided in **Figure 2.4**.

2.4.1 EVS & YACHT study visit

In EVS and YACHT, the study assessments began with the measurement of resting blood pressure, and other non-invasive vascular assessments followed by the multi-modal cardiovascular imaging assessments using MRI of the heart, brain, liver and/or

echocardiography. Blood samples were taken to allow for biomarker assessments. Diet, lifestyle and medical history questionnaires were given to the participants in between the study

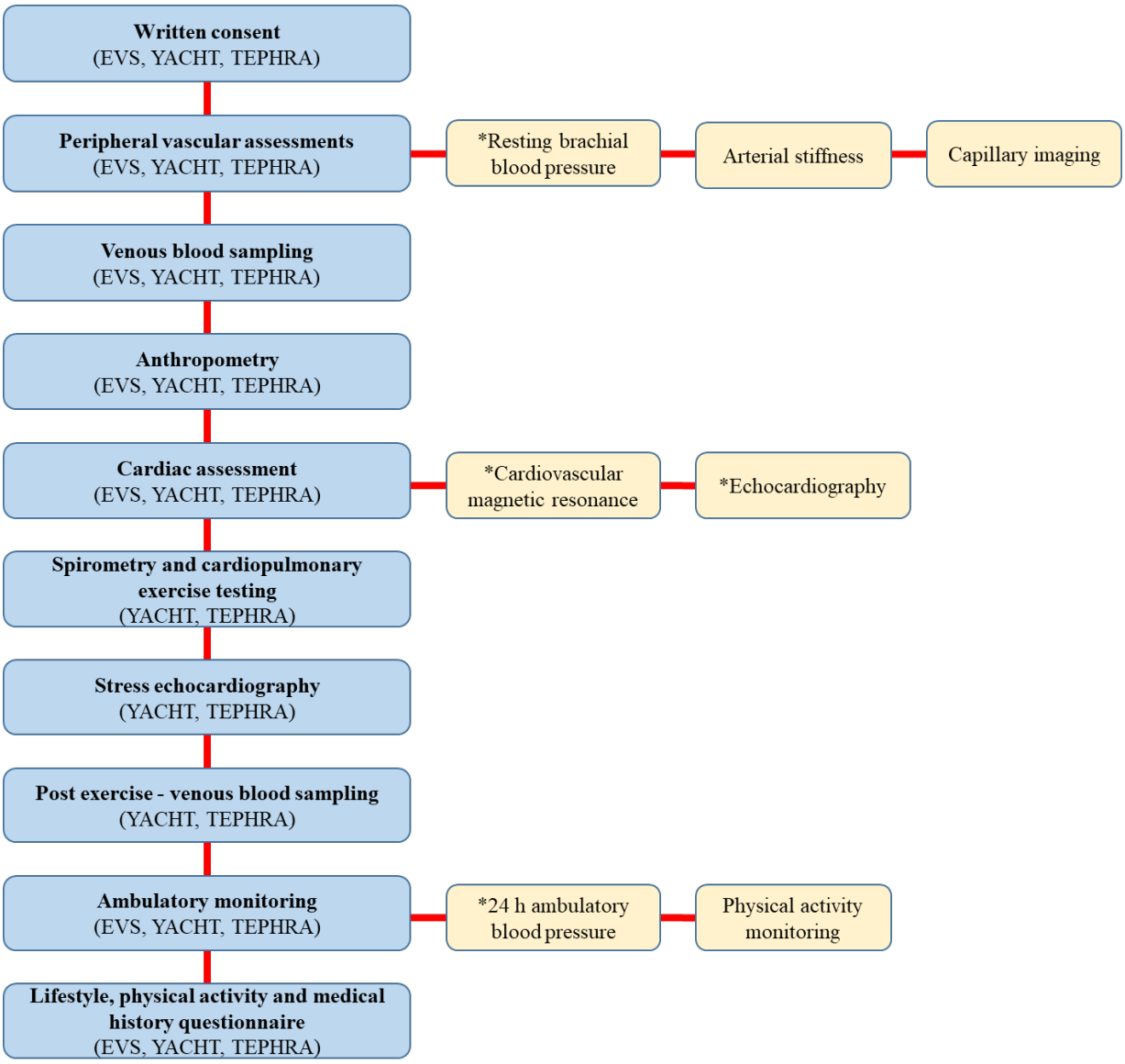


Figure 2.4: General study visit outline for EVS, YACHT and TEPHRA. The mark * indicates assessments that were included in this thesis.

visits. Specifically, in YACHT, spirometry, cardiopulmonary exercise testing and stress echocardiography were conducted on all participants. The last measures for all participants included the fitting of a 24-hour ambulatory blood pressure monitor and wrist worn seven-day accelerometer.

Within this thesis, I reported resting and awake blood pressure data derived from 24-hour awake ambulatory blood pressure monitoring. I also reported the CMR and echocardiography data from these two studies to develop the core findings. The spirometry data from YACHT provided information regarding the lung function of the young adult participants. The blood sample data provided biochemistry information. Information from the questionnaire provided information related to participants' family history and confirmed their gestational age category.

2.4.2 TEPHRA study visit

TEPHRA included three main study visits across one year: a baseline visit and two follow up visits post-randomisation at 16 weeks and 52 weeks, as shown in **Figure 2.5**. The study assessments began with the same assessments carried out in the EVS and YACHT studies. MRI was performed at baseline and during the 16-week follow up visit while echocardiography was performed at all three visits. After blood samples were taken, all participants were given two cereal bars as a standard light snack. All participants underwent a cardiopulmonary exercise test and spirometry test that was run by two experienced research investigators. An exercise stress echocardiogram was performed during the maximal exercise

testing. A set of lifestyle, physical activity and medical history questionnaires were sent to the participants via email after the study visit.

Due to the nature of the intervention, the study investigators were divided into two teams to protect the trial integrity. The first team, the research study team, was responsible for performing the assessments for screening, baseline and follow up study visits throughout the trial. This also included management work that did not relate to specific group intervention queries. The second team, the research intervention team, was responsible for the arrangement of participants' study allocation, booking the study visit two and visit three slots, monitoring of the intervention group, and dealing with any adverse issues specifically related to the intervention arm allocation. Details of the TEPHRA study protocol have been published [194]. Throughout my DPhil, my primary role in TEPHRA was helping lead the research study team.

Within this thesis, I only reported data from baseline to 16-week follow up visits. I used the CMR data to develop the core findings and reported resting and awake blood pressure data taken from 24-hour awake ambulatory blood pressure monitoring. The blood samples were used for the biochemistry and lipid profiles for the participants. Information from the questionnaire provided information on family history and confirmed participant gestational ages.

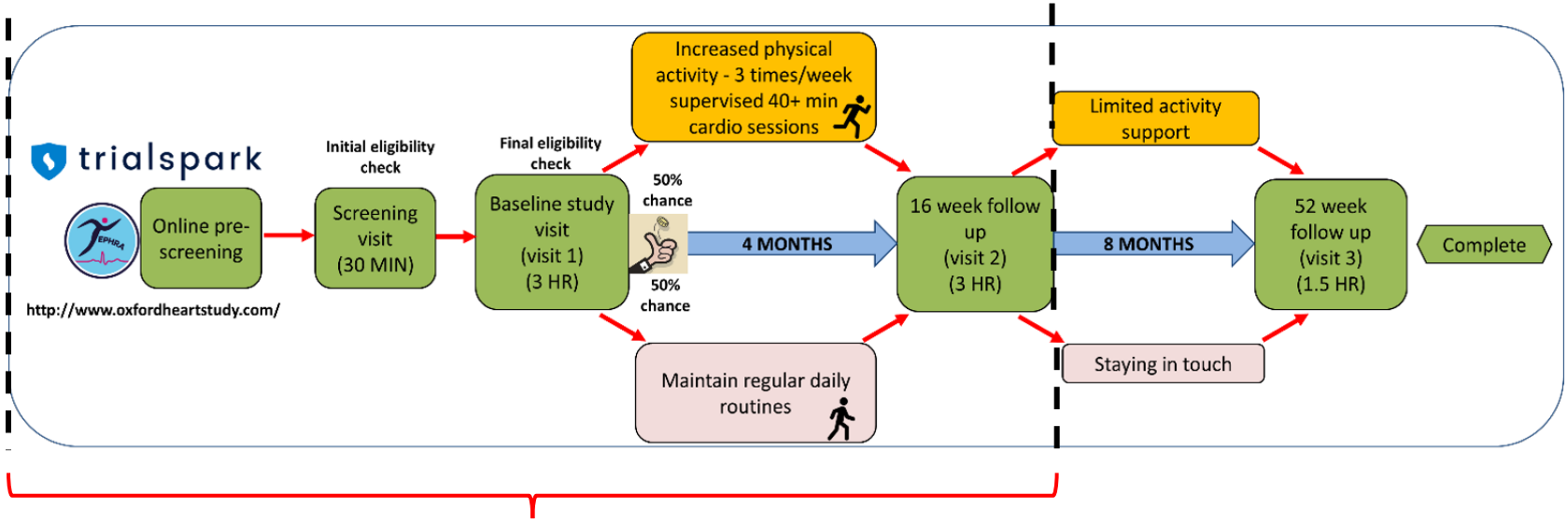


Figure 2.5: TEPHRA study protocol. Data collected during baseline study visits and 16-week follow ups were used to answer the objectives of my thesis. MIN indicates minutes; HR, hour.

2.5 Individual contribution to EVS, YACHT and TEPHRA

2.5.1 Individual contribution for EVS

Data collection and image processing for the EVS study were completed in 2013, before I started my DPhil. I performed the analysis for YACHT and TEPHRA CMR by referring to the analysis techniques that had been used in EVS. This allowed for the results to be compared across the three studies. The existing CMR measures from the EVS study were used for the combined data analysis presented in Chapter 5.

2.5.2 Individual contribution for YACHT

Data collection for the YACHT was completed a few months before I started my DPhil. However, I was involved with the analysis of the scan images. For YACHT CMR, I performed the analysis of the RV structure and function for all participants. For YACHT echocardiography, I also performed the analysis of the RV structure and function for all participants. I then performed all statistical analyses of CMR and echocardiography parameters that are presented in this thesis.

2.5.3 Individual contribution to TEPHRA

When I started my DPhil, I was actively involved in the set-up of TEPHRA. I performed the frontline study recruitment and management, including study visit assessments for the majority of TEPHRA participants until completion of their 16-week post-randomisation visit. This included designing recruitment strategies, answering participant queries, and

providing information about the study to those who had responded to flyers or mailshots, as well as scheduling study visits. TEPHRA study visits involved an in-depth cardiovascular assessment that took approximately three hours for visit completion per participant. Due to the nature of the study intervention, I did not engage with any arrangements of the participants' study allocation, monitoring of the intervention group, or dealing with any problems in the study allocation. This was handled by a separate randomisation and study intervention team in order to keep the research study team and investigators blinded to trial arm allocation.

For TEPHRA CMR, Dr Adam Lewandowski and an assigned radiographer from OCMR performed all image acquisition. In terms of management and technical scan preparation, I performed the participant scheduling, standard pre-screening and image safety briefing, as well as assisting with radiofrequency coil and hardware positioning at the start of each scan to optimize image quality and safety of every participant. From a data analysis perspective, I performed the conventional measurements of the LV and RV structure and function measurements, including tissue tracking (myocardial deformation), for visit one and visit two. I then performed all statistical analyses of CMR measures and parameters presented in this thesis.

For the TEPHRA routine cardiovascular assessments in every visit, I regularly performed anthropometric, vascular measures as well as fitting monitoring devices, including the 24-hour ambulatory blood pressure monitors and seven-day wrist worn accelerometers. Once the devices were returned, I downloaded the data and saved the soft copy of the data on our dedicated network drive. The printed hard copy of the data was stored in a confidential file folder. I also performed other assessments that are not included

in this thesis' findings. The assessments were TEPHRA resting and stress echocardiography, blood sampling, cardiopulmonary exercise testing, and spirometry lung function tests.

2.6 Allocation and characteristics of study groups for each results chapter

Study 1: Cardiac remodeling in relation to pulmonary function in moderately preterm born young adults (Chapter 4)

To perform the target investigations for study 1 (Chapter 4), participants were taken from YACHT and were divided into two groups:

- **Study 1 (Group A)** - Preterm-born young adults with normal blood pressure
- **Study 1 (Group B)** - Term-born young adults with normal blood pressure

Inclusion Criteria

- Aged 18 to 40 years
- 24-hour awake ambulatory systolic blood pressure <135 mmHg
- 24-hour awake ambulatory diastolic blood pressure <85 mmHg
- Verified birth history: preterm birth (<37 weeks' gestation) or full-term birth (>37 weeks' gestation)
- Willing or able to give informed consent and comply with all study visits and requirements

Exclusion Criteria

- Unwilling or unable to give informed consent and comply with all study visits and requirements
- Pregnant or lactating during the study
- Hypertension diagnosis
- Previous history of acute cardiac or cerebrovascular event
- On antihypertensive medication

Study 2: Cardiac Remodeling in Relation to Blood Pressure in Moderately Preterm Born Young Adults (Chapter 5)

To perform the target investigations for study 2 (Chapter 5), participants were taken from EVS, YACHT and TEPHRA, and were divided into two groups:

- **Study 2 (Group A)**: Preterm-born young adults
- **Study 2 (Group B)**: Term-born young adults

Inclusion Criteria

- Aged 18 to 40 years
- BMI <40 kg/m²
- Verified birth history: preterm birth (<37 weeks' gestation) or full-term birth (>37 weeks' gestation)
- Willing or able to give informed consent and comply with all study visits and requirements

Exclusion Criteria

- Unwilling or unable to give informed consent and comply with all study visits and requirements

- Pregnant or lactating during the study
- Hypertension diagnosis
- Previous history of acute cardiac or cerebrovascular event
- On antihypertensive medication

Study 3: Cardiac Remodeling in Response to a 16 Weeks Aerobic Exercise Training Program in Young Adults (Chapter 6)

To perform the target investigations for study 3 (Chapter 6), participants were taken from TEPHRA, and were divided into two groups:

- **Study 3 (Group A):** Preterm-born young adults with elevated blood pressure
- **Study 3 (Group B):** Term-born young adults with elevated blood pressure

Inclusion Criteria

- Aged 18 to 35 years
- BMI <35 kg/m²
- Verified birth history: preterm birth (<37 weeks' gestation) or full-term birth (>37 weeks' gestation)
- 24-hour awake ambulatory systolic blood pressure >115 mmHg
- 24-hour awake ambulatory diastolic blood pressure >75 mmHg
- Capable of accessing and using a computer and the internet
- Willing or able to give informed consent and comply with all study visits and requirements (participants may still withdraw at any time without providing any explanation or rationale)

Exclusion Criteria

- Unwilling or unable to give informed consent and comply with all study visits and requirements
- Pregnant or lactating during the study
- Hypertension diagnosis or on antihypertensive medication
- Fitness level too high (aerobic exercise >3 times per week)
- Clinic systolic blood pressure >159 mmHg at the screening visit
- Clinic systolic blood pressure >99 mmHg at the screening visit
- 24-hour awake ambulatory systolic blood pressure <115 mmHg at Visit 1
- 24-hour awake ambulatory diastolic blood pressure <75 mmHg at Visit 1
- Previous history of acute cardiac or cerebrovascular event

2.6.1 General exclusion criteria for CMR imaging

- Metallic foreign body in the eye or blood vessels of the brain
- Shrapnel injuries
- Other metal or electronic implants that can adversely be affected by the magnetic field
- Any other reason based on responses on the MRI safety screening form why participants were unsuitable for MRI

2.7 Ethical standards

Approval for EVS was granted by the Oxfordshire Research Ethics Committee A (06/Q1604/118) and was registered with http://www.clinicaltrials.gov (NCT01487824).

YACHT was approved by the South-Central Berkshire Research Ethics Committee (14/SC/0275) and registered with ClinicalTrials.gov (NCT02103231). TEPHRA was approved by the South-Central Research Ethics Committee (16/SC/0016) and registered with ClinicalTrials.gov (NCT02723552).

2.8 Summary

An overview of the of three results chapters' objectives and study populations is provided in **Figure 2.6**.

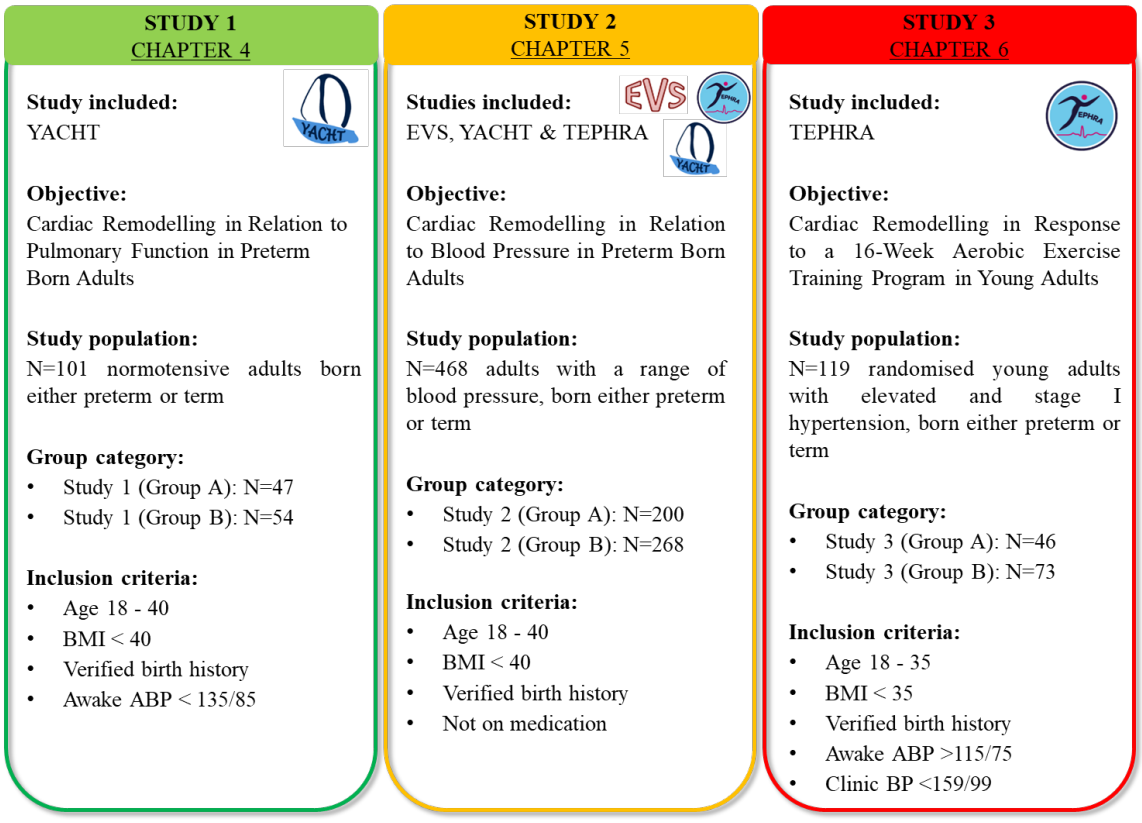


Figure 2.6: Summary of three results chapters' objectives and study populations.

CHAPTER 3

GENERAL METHODS

3.1 Overview

This chapter examines the specific methods employed to perform the investigations of the cardiovascular system for preterm-born and term-born young adults. I also provide the intra- and inter-observer variability for ten randomly selected participants, specifically for echocardiography and CMR parameters. Intra- and interobserver variability was assessed using the method of intraclass correlation (ICC). In summary, the results of the variability assessment showed high levels of agreement, reflected by moderate and good reliability for all CMR and echocardiography parameters.

3.2 Anthropometry and blood samples

To ensure accurate estimation of height and weight, participants were asked to remove shoes and wear light clothing before the measurements. Height was measured to the nearest centimetre (cm), and weight measured to the nearest 0.1 kg using an integrated height and

weight measurement station (Seca, Birmingham, United Kingdom). Measurement of the distance around the smallest part of the waist (waist circumference) and widest part of the buttocks (hip circumference) were measured to form waist to hip ratio using a tape measure. The formula for body surface area (BSA) and BMI are demonstrated as below:

$$\textbf{BSA } (\textbf{m}^2) = \sqrt{([\text{Height (cm)} \times \text{Weight (kg)}]/ 3600)}$$

$$\textbf{BMI } (\textbf{kg/m}^2) = \text{Weight (kg)}/ [\text{height (m)}]^{2}$$

Venous blood samples were centrifuged within 15 minutes of collection. Separated plasma and serum were then pipetted and stored at -80°C for future analysis. Fasting blood biochemistry was measured at the Oxford John Radcliffe Hospital Biochemistry Laboratory using routine validated assays with clinical level quality controls.

3.3 Resting brachial blood pressure

After consent, participants were seated for five minutes before three resting brachial blood pressure measurements were taken on the left arm with a one-minute interval in between. Measurements were taken using Dinamap V100 (GE Healthcare, Chalfont St. Giles, United Kingdom). Participants were advised to relax throughout the measurements, and the final two readings were averaged and subsequently used for analysis.

3.4 24-hour ambulatory blood pressure monitoring

Twenty-four-hour ambulatory blood pressure monitor fitting was initiated at the end of the study visit. Each participant was fitted with a TM-2430 ambulatory blood pressure device

(A&D Instruments, Abingdon, United Kingdom) and required to wear it for a full 24 hours to include awake and sleep blood pressure recordings. Participants were provided with a diary sheet to record their sleep and awake times, as well as to record any physical activity throughout the day that may affect their blood pressure. Arm circumference was measured on the upper arm to ensure appropriate selection of cuff size. A standard bladder cuff (12–13 cm wide and 35 cm long) was fitted for >95% of participants. A larger bladder cuff was used when the participant's arm circumference was greater than 32 cm. At least one blood pressure reading was taken before participants left CCRF to compare to the Dinamap v100 to ensure they were working properly. The devices were set up to inflate every 30 minutes during the day and every hour during the night. Monitors were posted back to CCRF and Doctor Pro 2 or Doctor Pro 3 software for Windows (A&D Company Limited, Tokyo Japan) was used to download the readings, and a hard copy of the readings was stored.

3.5 Spirometry testing

Spirometry was performed by using the Cortex Metalyzer 3B (Cortex Biophysik GmbH, Leipzig, Germany) according to standard guidelines [195]. Before every test, the spirometer underwent a calibration check of the flow and volume using a Futuremed 3.0-litre calibration syringe (Futuremed, California, USA). Participants' details, including sex, height, and weight, were entered in the system to allow for automatic correction of the raw data. Participants were seated and guided through the test wearing a nose-clip with their lips tightly sealed around the mouthpiece. At least three acceptable forced expiratory manoeuvres were recorded for every participant. To ensure consistent and high quality spirometry data, visual checks of the waveforms were carried out before the highest values

from the multiple forced expiratory manoeuvres were selected and recorded on a case report form. The parameters recorded included forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Predicted values and percent predicted values for FEV_1 and FVC were calculated according to the guidelines of the British Thoracic Society and Association of Respiratory Technicians and Physiologist Guidelines for the Measurement of Respiratory Function [195].

3.6 Resting echocardiography

Participants underwent a two-dimensional resting transthoracic echocardiography using a commercially available Philips iE33 or Philips EPIQ 7C cardiology ultrasound machine. Acquisition of the images was made in the left lateral decubitus position as per the British Society of Echocardiography guidelines [196]. The image data were digitally stored, and offline analysis was made by trained investigators using Philips Xcelera 3.3 (Philips Healthcare Informatics, Belfast, United Kingdom).

3.6.1 RV resting echocardiographic analysis

To characterize RV systolic function, images were acquired from the apical four-chamber view with end-diastole set at the point just after tricuspid valve closure and end-systole set at the point just before the valve opening from a RV-optimized four-chamber view. TAPSE (mm) a measure of longitudinal function, was defined as the distance of excursion of the tricuspid valve annulus from the base towards the apex during systole via M-mode placed through the lateral annulus of the tricuspid valve [197]. RV fractional area of change

(RVFAC, %) was calculated as a percentage change in the RV chamber area from end-diastole to end-systole. Both TAPSE and RVFAC have been shown to correlate with RVEF by MRI [198, 199].

RV morphology was assessed with: a) RV linear dimension analysis in the longitudinal direction (apex to base) from the apical four-chamber view at end-diastole [200], and b) RV end-diastolic area (RVEDA) and RV end-systolic area from contouring the RV endocardium at end-diastolic and end-systolic frames, starting from the annulus [201]. RV afterload and pulmonary hemodynamics were assessed through images acquired from the left parasternal short axis view, at the level of the main pulmonary artery. Colour pulsed Doppler was used with the sample volume placed in the center of the color Doppler of the main pulmonary artery and interrogated along the flow. To interrogate pulmonary artery flow and RV outflow tract systolic time intervals, pulmonary artery acceleration time (PAAT, ms) was measured from the interval between the onset of systolic ejection and the peak flow velocity. RV ejection time (RVET, ms) was measured from the interval between the onset of RV ejection to the point of systolic pulmonary arterial flow cessation [202]. To account for heart rate variability, PAAT time was adjusted to RVET and presented as PAATi (PAAT/RVET). Assessment of RV-pulmonary vascular coupling is shown in **Figure 3.1**.

PAAT and PAATi are non-invasive measures of RV afterload that provide accurate estimates of PVR, pulmonary artery pressure, and pulmonary artery compliance in infants, children, and adults [202-205]. Optimal RV performance requires structural and functional coupling between the RV and its adjacent pulmonary arterial vascular network [206]. Since recent studies have shown that the echocardiographic derived ratio of TAPSE to PAAT and TAPSE to PAATi provide reliable estimates of invasive measures of RV to pulmonary

arterial vascular, PA (RV-PA) coupling [207], we compared the TAPSE/PAAT and TAPSE/PAATi ratios between the young adults born term and preterm in Chapter 4. The intra- and inter-observer variability of RV echocardiography measurements are provided in **Table 3.1**.

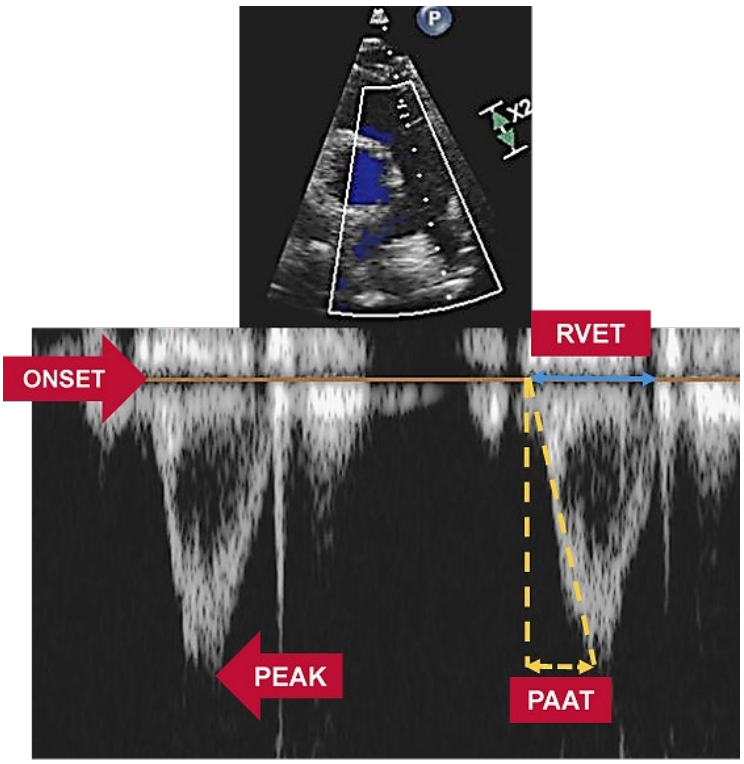


Figure 3.1: Assessment of RV-pulmonary vascular coupling. Pulmonary artery acceleration time (PAAT) is measured from the beginning of the systolic pulmonary arterial flow (onset of ejection) to the peak flow velocity (yellow line). RV ejection time (RVET) is measured from the interval between the onset of RV ejection to the point of systolic pulmonary arterial flow cessation (blue line).

Table 3.1: Intra- and inter-observer variability of RV echocardiography measurements.

Measurement	Intra-observer ICC	Inter-observer ICC
Basal RV diameter	0.74	0.72
Mid-RV diameter	0.8	0.72
RV length	0.73	0.81
RA EDV	0.93	0.85
TAPSE	0.88	0.93

ICC indicates intraclass correlation; RA EDV, right atrium end-diastolic volume; TAPSE, tricuspid annular plane systolic excursion.

3.7 Cardiac magnetic resonance

CMR was performed on a 1.5-Tesla MRI scanner (1.5T Sonata, Siemens Medical Solutions, Germany) for EVS and 3.0-Tesla (3T TIM Trio, Siemens Medical Solutions, Germany) for YACHT and TEPHRA, respectively. A previous comparison performed by OCMR of CMR scans at 1.5-Tesla, 3.0-Tesla and 7.0-Tesla using steady state free precession (SSFP) cine sequences showed the feasibility and consistency of cardiac volume and mass measurements across field strengths [208]. Cine images were acquired using retrospective cardiac electrocardiogram gated SSFP cines in the short axis orientation to allow for coverage of both ventricles. The short axis images of the LV and RV were obtained from the base to the apex of the heart. The thickness and gap between slices were 8.0 mm and 2.0 mm, respectively. The imaging parameters included echo time, 1.48 milliseconds; echo spacing, 3.4 milliseconds; temporal resolution 47.04 milliseconds and flip angle, 50°. The flip angle of 50° was used to optimize the contrast between blood and myocardium. The data acquired were at end-expiratory breath-hold and digitally stored for offline analysis by a single trained investigator using CMR analysis software, cvi42 (Circle Cardiovascular Imaging Inc., Calgary, Canada).

3.7.1 Ventricles: volumes and mass

To evaluate the LV and RV volumes and mass, both the epicardial (green and blue) and endocardial (red and yellow) borders were manually contoured on short axis CMR cine images for each slice at end-diastole and endocardial borders at end-systole as shown in **Figures 3.2 and 3.3**. End-diastole and end-systole were visually determined when the ventricular cavity was at the largest cavity area and smallest cavity area, respectively.

Several visual steps were taken prior to and alongside analyzing the cine images to allow for the accurate LV and RV contouring. For instance, images were viewed in cine mode to visualize cardiac borders and contrast was manipulated for each slice to allow for better delineation of epicardial fat from the myocardium. Specifically, for the LV, the first phase of end-diastole was chosen as the phase just before the inward movement of the myocardium. The first basal slice was chosen where the myocardium surrounded at least 50% of the circumference of the cavity as shown in **Figure 3.4 (B)**. The apical slice was chosen as the last slice of the short stack where the LV cavity was visible. As for the RV, the first phase of end-diastole was chosen where the slice was not superior to the level of the tricuspid valve as shown in **Figure 3.5**. To ensure accurate RV contouring, RV walls were distinguished from atrial walls as being thicker and trabeculated with inward systolic motion. The apical slice was chosen as the last slice of the short stack where the RV cavity was visible. In addition, for end-systolic frames, identification of the atrioventricular groove by its excursion was used. Because of the through-plane motion of the tricuspid valve, the upper posterior part of the RV was typically identified in the basal plane at end-diastole but right atrium (RA) at end-systole. Basal slice contours were taken as far as the pulmonary valve.

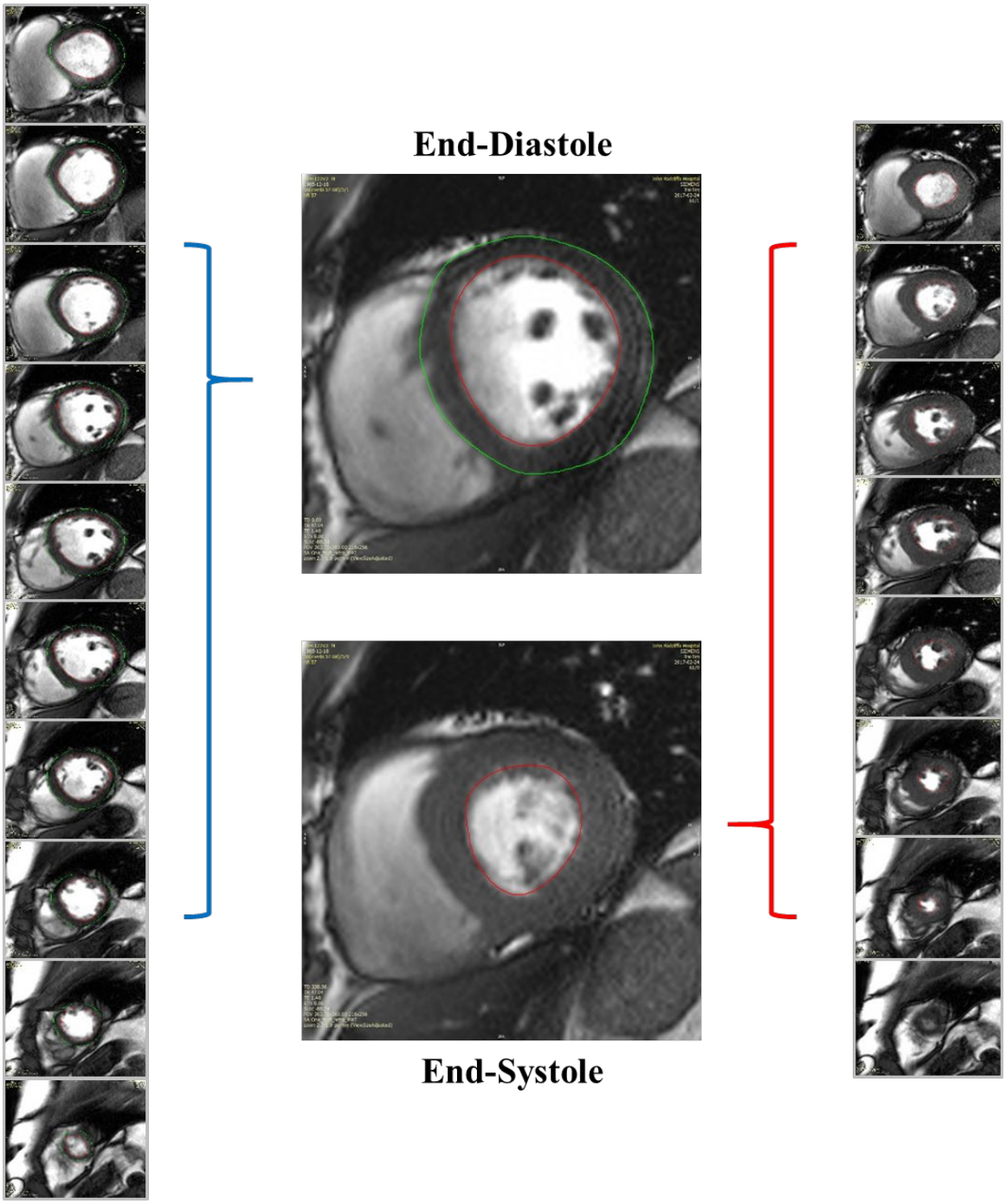


Figure 3.2: Measurements of LV volume and mass across the entire short axis stack. Both endocardial (red) and epicardial (green) borders were manually contoured at end-diastole and endocardial borders were contoured at end-systole.

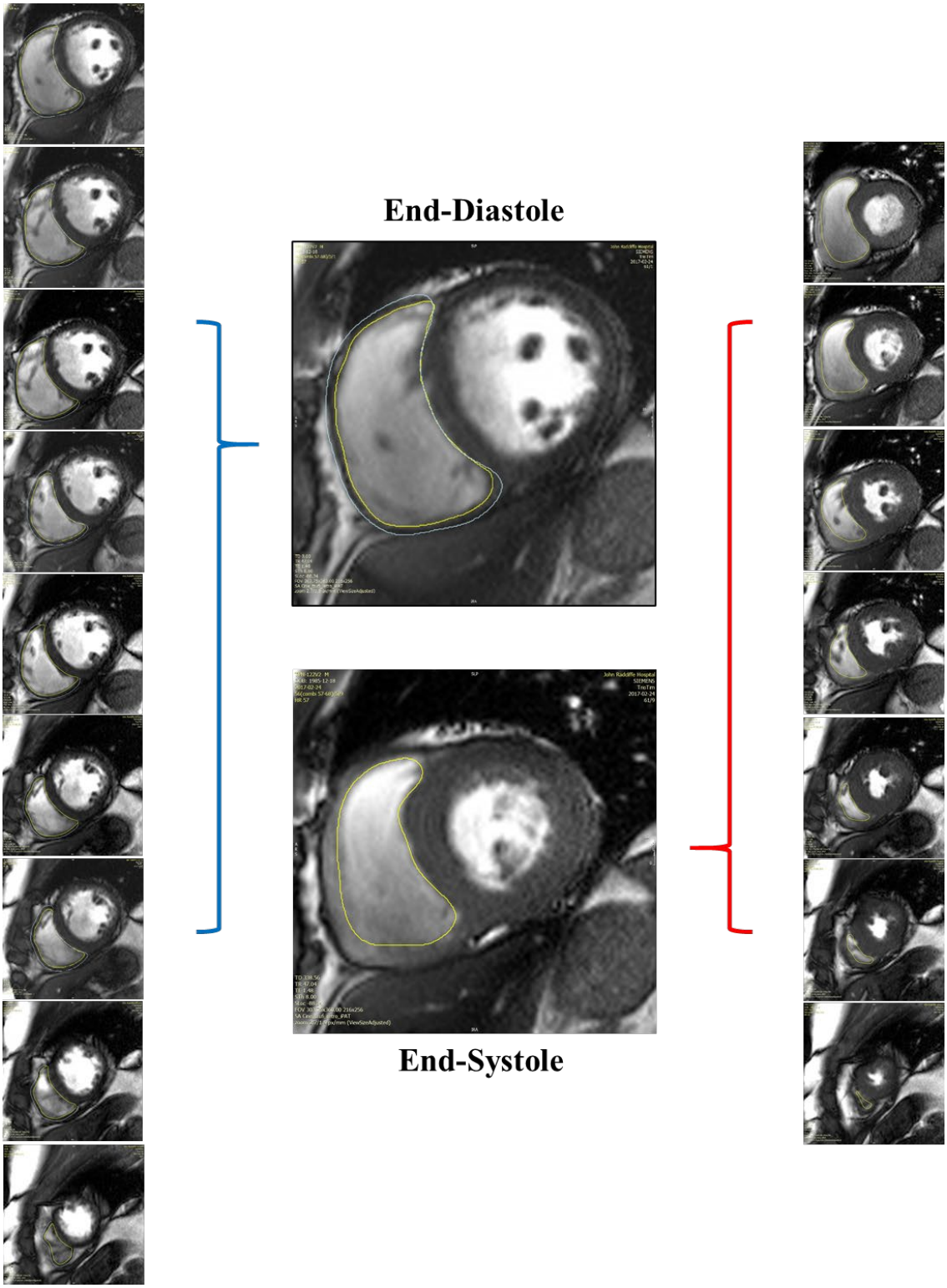


Figure 3.3: Measurements of RV volume and mass across the entire short axis stack. Both endocardial (yellow) and epicardial (blue) borders were manually contoured at end-diastole and endocardial borders were contoured at end-systole.

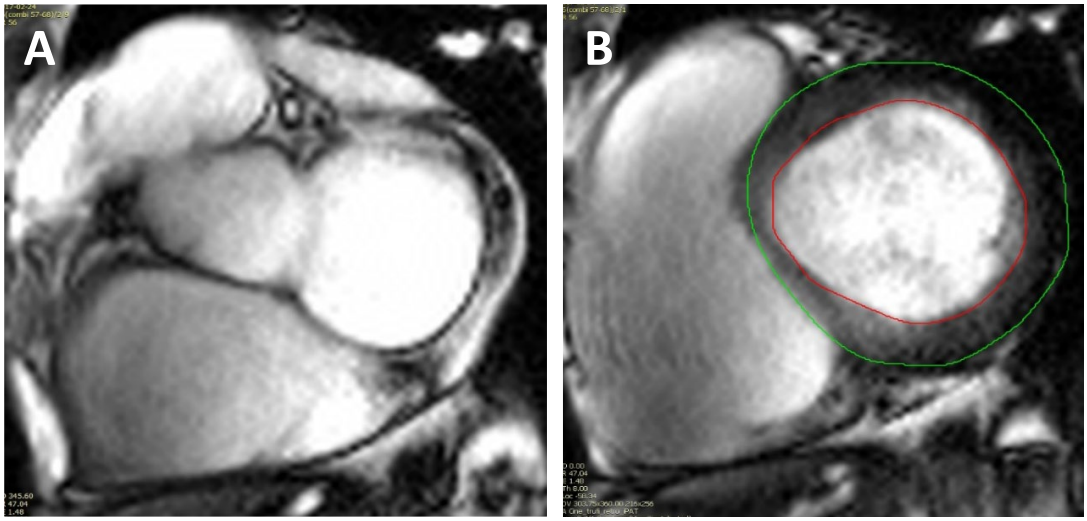


Figure 3.4: Determining the first slice at LV base. **A**, No endocardial contour is drawn here as the end-diastolic phase shows less than 50% visible myocardial circumference. **B**, The endocardial contour is drawn here as the end-diastolic phase shows more than 50% visible myocardium surrounding the cavity circumference.

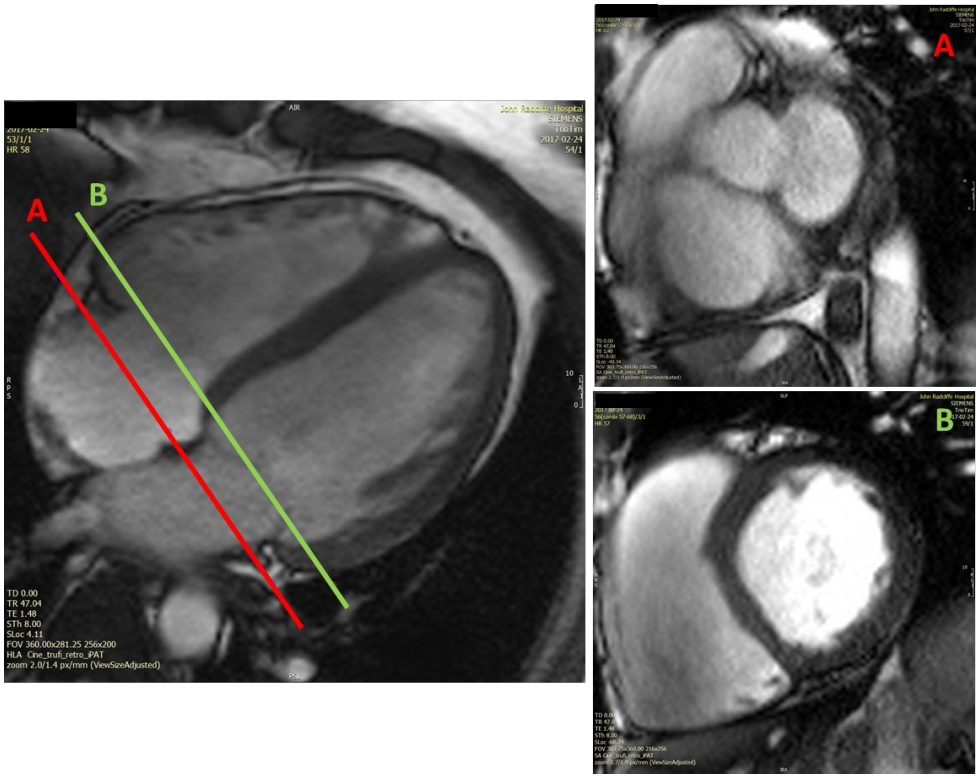


Figure 3.5: Determining the first slice at RV base. **A**, Red line shows the slice was superior to the level of the tricuspid valve. **B**, Green line shows the slice was not superior to the level of the tricuspid valve, thus this slice was chosen as the first RV basal slice.

The papillary muscles and myocardial trabeculations were excluded for both RV and LVM measurements. LV and RV volumes and mass were indexed to BSA to minimise differences of cardiac parameters related to height and weight. Several key CMR parameters are provided at **Table 3.2**, along with the formula used to calculate them and the units of reporting. The intra- and inter-observer variability of LV and RV mass and volume measurements are provided in **Table 3.3.** To ensure accuracy of measures, a second observer for all studies also randomly checked 20% of LV and RV contours. Where there were discrepancies in measurements, these were discussed and adjusted where necessary. Classification of LV remodeling patterns based on relative wall thickness and LVMI are shown in **Figure 3.6**. Many semi-automated or fully automated CMR segmentation methods for both epicardial and endocardial boundaries have emerged in the past decade. The advantages of biventricular volumes and function using automated segmentation methods in CMR include saving time and improving observer variability [209] which may be of increasing benefit to future large-scale studies. As for my thesis, all image analysis was done using manual delineation.

Table 3.2: Key CMR parameters.

Parameters	Formula/definition	Unit
End-diastolic volume	Volume of blood in the ventricles at end load (diastole)	mL
End-systolic volume	Volume of blood remaining in the ventricles after ejection (systole)	mL
Stroke volume	End-diastolic volume – end-systolic volume	mL
Ejection fraction	(Stroke volume / end-diastolic volume) * 100	%
Cardiac output	Stroke volume * heart rate	L/min

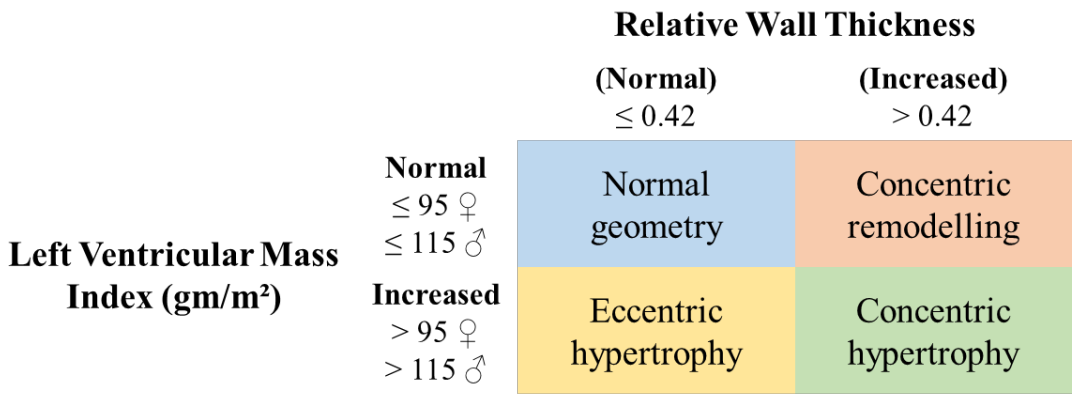
Ventricular mass	Σ myocardial volume * 1.05g/cm^3 (specific gravity of myocardium per cm^3)	G
Relative wall thickness	(2 * inferior wall thickness) / end-diastolic diameter	-
Sphericity index	$\frac{\text{LV end-diastolic volume}}{4\pi/3 * (4 \text{ chamber length} / 2)^3}$	-

Table 3.3: Intra- and inter-observer variability of LV and RV mass and volume measurements.

Measurement	Intra-Observer ICC	Inter-Observer ICC
Left Ventricle		
Myocardial Mass	0.96	0.95
End-Diastolic Volume	0.88	0.89
End-Systolic Volume	0.90	0.84
Stroke Volume	0.87	0.93
Ejection Fraction	0.87	0.81
Right Ventricle		
Myocardial Mass	0.79	0.85
End-Diastolic Volume	0.85	0.89
End-Systolic Volume	0.85	0.85
Stroke Volume	0.61	0.65
Ejection Fraction	0.68	0.57

ICC indicates intraclass correlation.

Figure 3.6: Classification of LV remodeling patterns based on relative wall thickness and LVMI.



3.7.2 LV: dimensions

LV wall thickness was measured at a mid-ventricular level (determined by the presence of papillary muscles) in six segments at end-diastole from a short axis view. Mean LV wall thickness was calculated by the sum of wall thickness divided by six. LV internal and external diameters were measured from the same image between the anterior septum and inferolateral wall. LV length was measured at end-diastole on the horizontal long axis cine by drawing a line along the mitral valve annulus (1) and measuring the length (2) from the LV apex to the middle of the mitral valve annulus as shown in **Figure 3.7**. The intra- and inter-observer variability of LV dimension measurements are provided in **Table 3.4.**

Table 3.4: Intra- and inter-observer variability of LV dimension measurements.

Measurement	Intra-observer ICC	Inter-observer ICC
Left Ventricle		
Length	0.85	0.74
Mean Wall thickness	0.97	0.96
Internal Diameter	0.77	0.79
External Diameter	0.73	0.71
Relative Wall Thickness	0.89	0.91

ICC indicates intraclass correlation.

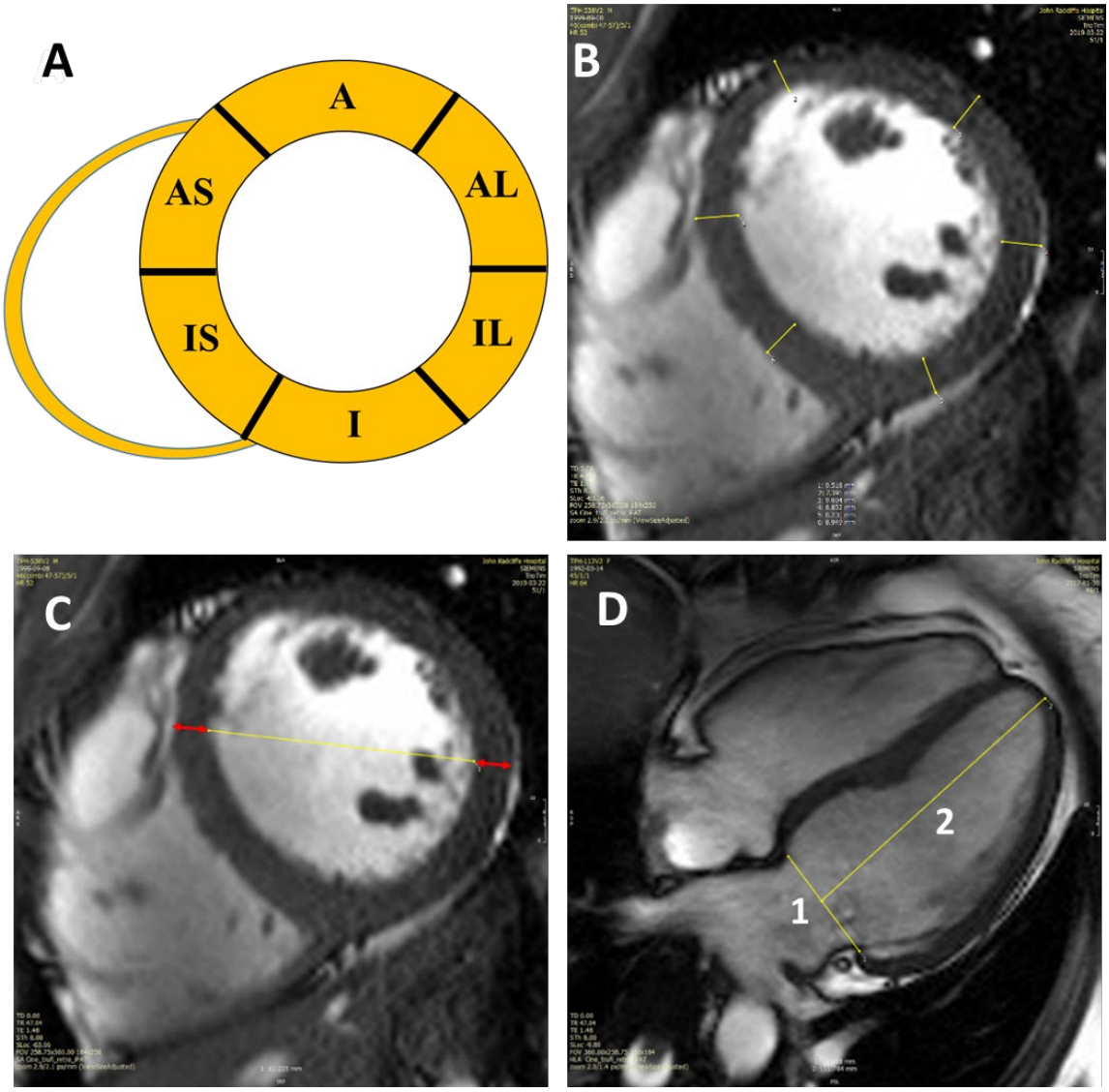


Figure 3.7: Diagram of LV dimension measurements. Measurements of LV wall thickness were measured at **(A)**, Six LV segments. **(B)**, Between each wall segments. **(C)**, LV internal (yellow line) diameter was measured from the IL to AS segments, with the external cavity diameter (yellow line plus red lines) including the myocardial wall. **(D),** LV length was measured from LV apex (1) to the middle of the mitral valve annulus line (2). Panel **(A)**: A indicates basal anterior; AS, basal anteroseptal; IS, basal inferoseptal; I, basal inferior; IL, basal inferolateral; AL, basal anterolateral.

3.7.3 Feature tracking analysis

One of the strengths of this thesis was that CMR tissue tracking analysis was performed in all three study cohorts. This analysis allows retrospective use of cine images for detailed quantification of global and regional function (myocardial deformation) including circumferential, longitudinal, and radial strain, as well as strain rate. The analysis was performed by a feature-tracking algorithm software for both the LV and RV.

To determine LV and RV longitudinal myocardial deformation parameters, a four-chamber image was loaded into the analysis frame. The endocardial and epicardial borders of the LV and RV myocardium at end-diastole were then manually contoured for all slices. The long axis LV contour was used to define the analysis range where the reference points were placed along the mitral annulus and extended to the cardiac apex. The software then automatically propagated the endocardial and epicardial contours and tracked the motion of the in-plane tissue voxels through the entire cardiac cycle.

For regional analysis, short axis images were used. To calculate circumferential myocardial deformation parameters, endocardial borders of the LV and RV myocardium at end-diastole were manually contoured on the short axis cines. Myocardial deformation parameters were then derived for the basal, mid and apical slices. Diagrams of myocardial deformation analysis for the LV and RV are shown in **Figures 3.8 and 3.9**. The intra- and inter-observer variability of RV and LV tissue tracking measurements are provided at **Tables 3.5 and 3.6**.

Table 3.5: Intra- and inter-observer variability of RV tissue tracking measurements.

Measurement	Intra-observer ICC	Inter-observer ICC
Longitudinal		
Strain	0.80	0.84
Strain Rate	0.64	0.61

ICC indicates intraclass correlation

Table 3.6: Intra- and inter-observer variability of LV tissue tracking measurements.

Measurement	Intra-observer ICC	Inter-observer ICC
Longitudinal		
Strain	0.80	0.82
Strain Rate	0.73	0.77
Circumferential		
Basal Strain	0.77	0.76
Basal Strain Rate	0.75	0.79
Mid Strain	0.68	0.75
Mid Strain Rate	0.65	0.61
Apical Strain	0.64	0.65
Apical Strain Rate	0.74	0.56

ICC indicates intraclass correlation

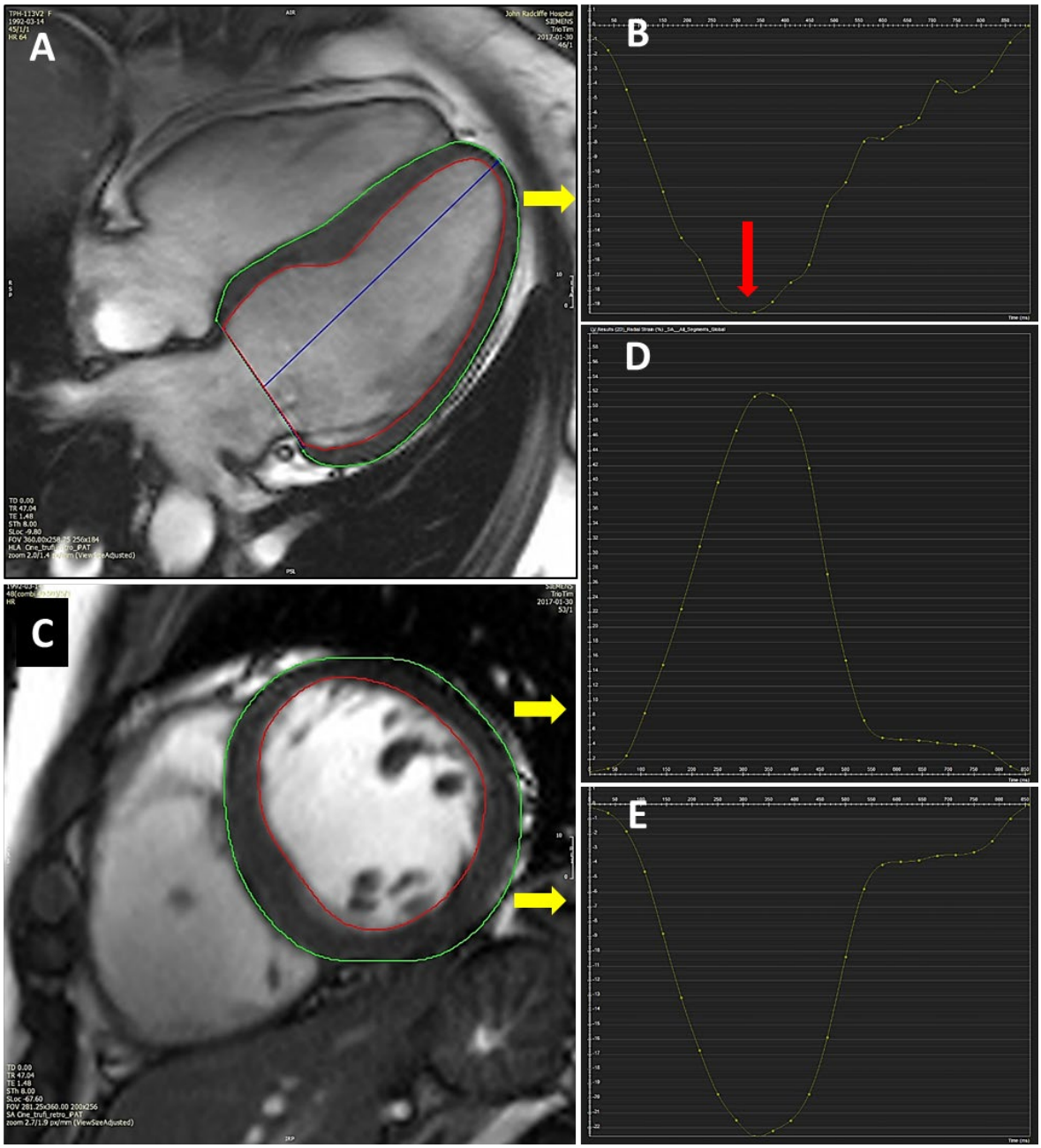


Figure 3.8: LV myocardial deformation analysis using feature tracking software (cvi42). **A**, Endocardial and epicardial borders were contoured at end-diastole long axis four-chamber image to derive longitudinal strain measures. **B**, a representative longitudinal strain curve. The most negative point (red arrow) is the peak systolic longitudinal strain. **C**, Endocardial and epicardial borders were contoured at end-diastole on short axis images to derive radial and circumferential strain measures. **D**, a representative radial strain curve. **E**, a representative circumferential strain curve. (Red; endocardial contour, green; epicardial contour; blue, long axis LV extend contour).

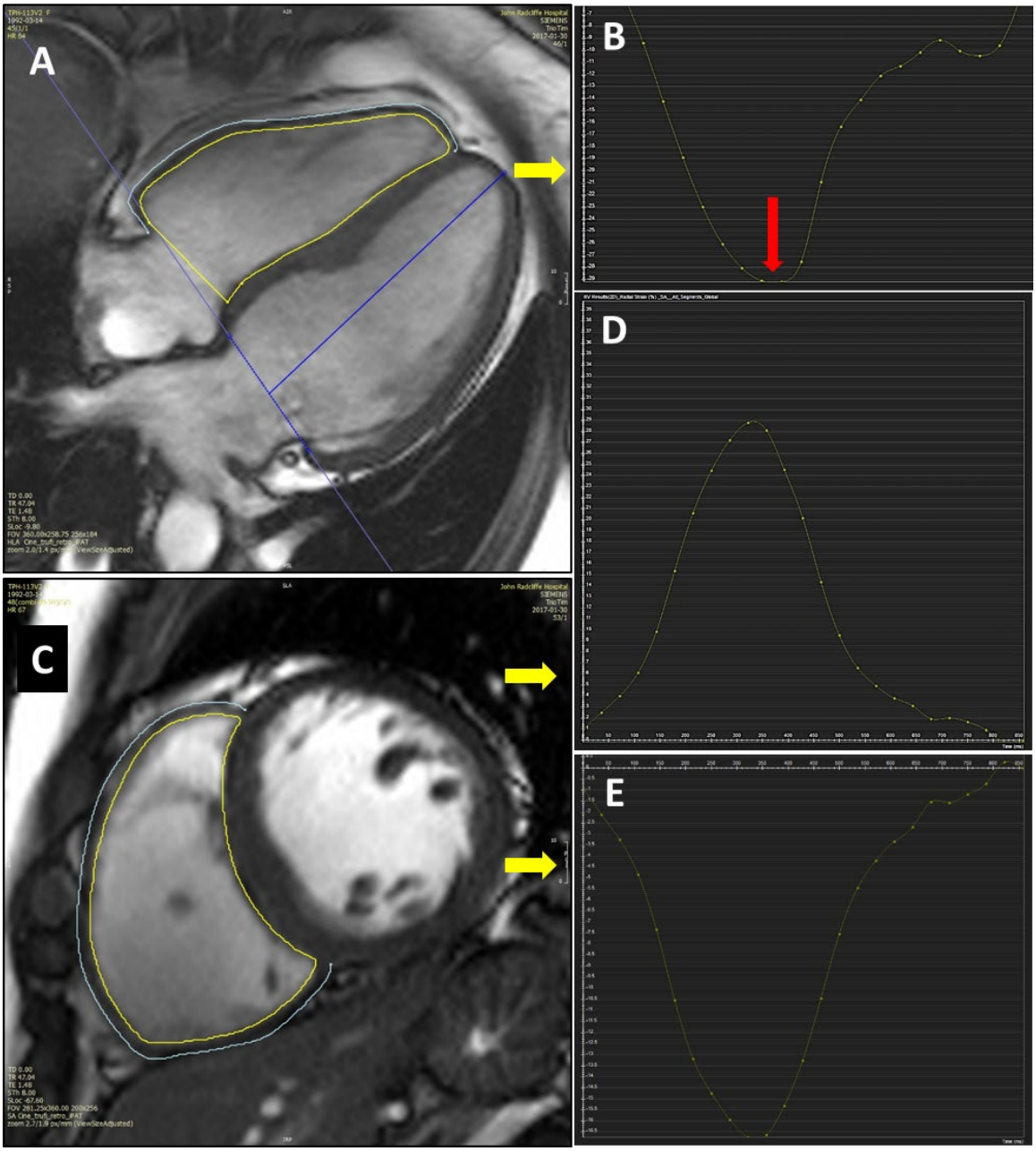


Figure 3.9: RV myocardial deformation analysis using feature tracking software (cvi42). **A**, Endocardial and epicardial borders were contoured at end-diastole long axis four-chamber image to derive longitudinal strain measures. **B**, a representative longitudinal strain curve. The most negative point (red arrow) is the peak systolic longitudinal strain. **C**, Endocardial and epicardial borders were contoured at end-diastole on short axis images to derive radial and circumferential strain measures. **D**, a representative radial strain curve. **E**, a representative circumferential strain curve. (Yellow, endocardial contour; blue, epicardial contour).

3.7.4 Cardiac shape analysis

Cardiac shape analysis is an additional strength of this thesis. Cardiac atlases were developed in collaboration with Dr Pablo Lamata at the Department of Biomedical Engineering, King's College London. The aim was to explore and distinguish the possible patterns of cardiac shape in young adults and how this relates to the functional status of the heart and birth history. Previous work by my supervisors has identified the distinct cardiac remodeling in preterm infants [88] and young adults [106, 108]. This thesis presents the RV cardiac shape geometry in normotensive young adults (Chapter 4).

In order to create the cardiac statistical shape atlas, I had to first extract the image workspace and matching contoured LV and RV DICOM images from cvi42. All datasets were provided to Dr Pablo Lamata through file transfer via OxFile. The first dataset I provided for each participant included the CMR short axis cine images of the LV and RV where the endocardium and epicardium contours had been manually drawn. The second dataset I provided was the complete CMR study, without the contours. The contours were then matched, properly aligned in space, and a binary mask was generated for the rest of the three-dimensional reconstruction pipeline, as shown in **Figure 3.10**. The segmentations retrieved were then processed using the Computational Anatomy toolkit developed at King's College London as in previous studies. How to access and use this toolkit is explained in detail at the link provided below by Dr Pablo Lamata and colleagues:

https://www.dropbox.com/s/8f072f2ws2p9utj/Atlas%20Documentation.doc?dl=0

As a result, a smooth three-dimensional shape that represented both the LV and RV was generated.

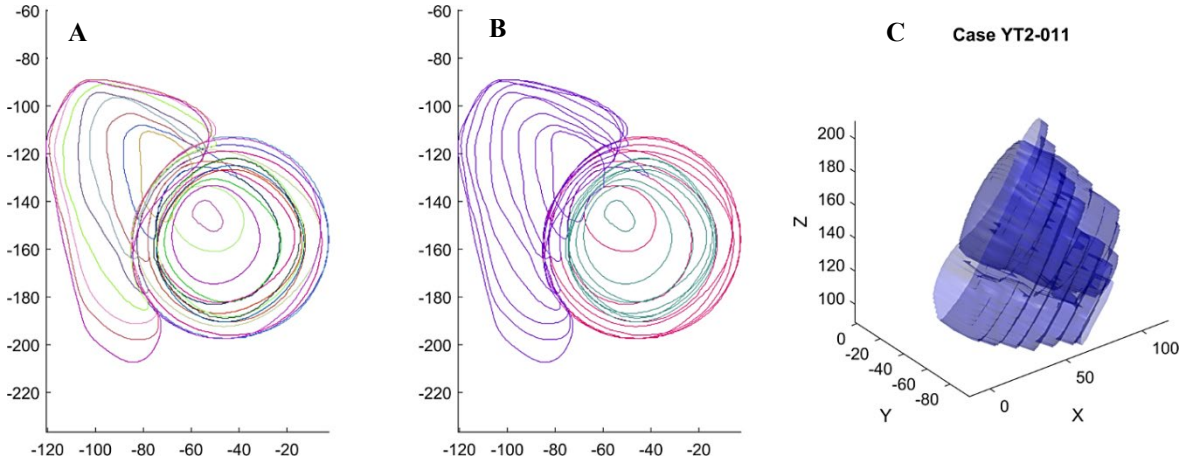


Figure 3.10: Retrieval of cvi42 contours in Matlab. **A,** Contours aligned in space after finding the matching DICOM headers. **B,** Contours grouped by LV endo, LV epi- or RV endo. **C**, Isosurface of the binary mask generated from the contours.

3.8 TEPHRA study protocol assessments

3.8.1 Randomisation for TEPHRA

Sealed Envelope™ (https:// www.sealedenvelope.com/), a web-based randomisation system, was used for the randomisation of participants that met the inclusion criteria following the completion of baseline study measures. The randomisation of 1:1 to the intervention arms was performed using the minimisation algorithm to ensure balanced allocation (80%) of key prognostic factors across the two groups as provided in **Table 3.7.** Data could be accessed and downloaded by authorized personnel (intervention team and trial statistician) at any time to assess the quality of randomisation or monitoring potential exercise injuries and adverse events. The assessors for primary and secondary outcome data were blinded to reduce potential bias. To comply with the trial intervention, participants could not be blinded to the trial allocation but were strongly advised not to

disclose their group allocation status to the research study team at the follow-up visits post-randomisation.

Table 3.7: Minimisation factors employed in TEPHRA.

Minimization Factors
Sex
Male
Female
Age Group (years)
<24
24 – 29
30 – 35
Gestation Age (weeks)
<32
32 – <37
≥37

3.8.2 Study interventions

Participants in the intervention arm were given four months of free gym membership at facilities local to the participant and pre-approved by the trial intervention team. Participants were required to complete the following:

i. 16 weeks of structured aerobic exercise training
ii. A target of three training sessions per week (each session lasted for 60 minutes)
iii. Exercise intensity of 60–80% aerobic exercise capacity

The intervention strategies were designed based on other randomised controlled trials investigating exercise interventions for blood pressure reduction [169]. To ensure standardized exercise records were used, the trial intervention team utilized the TEPHRA

training log to monitor the weekly attendance and progress for all participants. All participants also underwent an individual, motivational coaching session to promote and maintain participants' compliance with the exercise training. In addition, each participant was given a wrist worn self-monitoring activity monitor (Fitbit Charge HR) to maintain a target heart rate and promote daily physical activity. Educational materials from the British Heart Foundation on blood pressure were also posted to all participants. Once the 16-week supervised exercise intervention training was complete, participants were encouraged to maximize the use of their self-monitoring activity monitor and maintain physical activity goals until the last study visit at 52 weeks post-randomisation. The data from the wrist worn activity monitors were downloaded for those that agreed and signed the consent form.

3.8.3 Comparison group

Participants in the intervention control group arm were asked to continue their daily physical activity routine with no change. Educational materials from the British Heart Foundation on blood pressure were also posted to all participants.

3.8.4 Compliance

The definition of the trial compliance was confirmed and agreed by the Trial Steering Committee and Data Safety Monitoring Committee. Compliance to the intervention of the trial was defined based on the target intervention exposure of three aerobic sessions per week, completed on separate days, for 16 weeks. Accepted exposures for compliance were:

- Supervised gym session 40 to 60 minutes

- Self-reported aerobic session 40 to 60 minutes
- Fitbit active day with step count ≥ 8000 steps
- Fitbit active minutes, total fairly and vigorous, active minutes ≥40 minutes

The compliance threshold was defined as 80% achievement of the target of three aerobic exercise training sessions per week for 16 weeks of intervention. This was equivalent to ≥39 independent aerobic exposures across the 16 weeks and with no breaks in training exposures greater than two weeks.

3.8.5 Withdrawals and protocol violations

In the TEPHRA protocol, it was stated that each participant had the right to withdraw from the trial at any time without giving specific reasons. In addition, the investigator also had the right to discontinue a participant from the study at any time based on reasons that may affect their ability to perform the intervention or the validity of the trial, including due to becoming pregnant, significant deviation from the study protocol, withdrawal of consent, loss to follow-up, contraindication to exercise participation or other ineligibility (either arising during the study or retrospectively having been overlooked at screening). A summary of the reasons for withdrawal and protocol violations in TEPHRA are provided in **Table 3.8**.

3.8.6 Publication status

The protocol paper for TEPHRA has been published in *BMC Cardiovascular Disorders.*

Williamson W, Huckstep OJ, Frangou E, **Mohamed A**, Tan C, Alsharqi M, Bertagnolli M, Lapidaire W, Newton J, Hanssen H, McManus R, Dawes H, Foster C, Lewandowski AJ and Leeson P. Trial of Exercise to Prevent HypeRtension in young Adults (TEPHRA) a randomised controlled trial: study protocol. *BMC Cardiovascular Disorders*. 2018;18:208.

Table 3.8: Summary of the reasons for withdrawals and protocol violations for TEPHRA.

ID	Randomised Arm	Withdrawal Reason	Withdrawn Date	Withdrawn Time Point
TPH025	Exercise	Request to withdraw	04-08-2016	4 Month
TPH046	Control	Pregnant	07-11-2016	4 Month
TPH069	Control	Lost contact - decision to withdraw	30-01-2017	4 Month
TPH193	Control	Pregnant	09-08-2018	12 Month
TPH284	Exercise	Health reasons	20-12-2017	4 Month
TPH290	Exercise	Partner died	13-09-2017	4 Month
TPH301	Exercise	Request to withdraw	20-09-2017	4 Month
TPH303	Exercise	Request to withdraw	07-09-2017	4 Month
TPH333	Exercise	Unable to commit. Withdrawal request	19-10-2017	4 Month
TPH396	Control	Moved to Australia.	22-10-2018	12 Month
TPH464	Control	Pregnant	26-03-2019	12 Month
TPH470	Exercise	Health reasons	13-08-2018	4 Month
TPH482	Exercise	Pregnant	25-03-2019	12 Month
TPH496	Exercise	Pregnant	16-01-2019	4 Month

CHAPTER 4

STUDY 1 RESULTS

Multimodality Imaging Demonstrates Reduced Right Ventricular Function Independent of Pulmonary Physiology in Moderately Preterm-Born Adults

4.1 Abstract

Background: Prematurity leads to altered RV performance with persistent impairments in RV systolic function in young adulthood.

Objectives: To determine whether reductions in RV function in young adults born moderately preterm would be out of proportion to changes in pulmonary physiology.

Methods: We recruited 101 normotensive preterm-born (n=47, mean gestational age 32.8±3.2 weeks) and term-born (n=54) young adults. Echocardiography and CMR scans

were performed to characterize RV morphology, RV function, pulmonary hemodynamics and RV-PA coupling and create a computational atlas of the 3D RV geometry. Spirometry was performed to assess lung function.

Results: RVEDA and volumes for CMR and echocardiography were lower in preterm-born than term-born individuals (P≤0.001). Measurements of RV function by echocardiography, including RVFAC and TAPSE, were lower in preterm-born compared to term-born adults (P<0.01). Despite lower PAAT in those born preterm (141.1±15.1 vs 159.2±21.6msec, P<0.001), indicating increased PVR, the RV remained coupled to its pulmonary circulation (TAPSE/PAAT: 0.13±0.02 vs 0.14±0.03m/sec, P=0.153). RV CMR revealed a higher RVM (P<0.001) and lower RVEF (P=0.008) in those born preterm with a unique 3D geometry. Lower RV performance in preterm-born individuals remained significant when adjusting for pulmonary function parameters (P<0.05).

Conclusions*:* Moderately preterm-born young adults have reduced RV function, independent of lung physiology. Their RV remains hemodynamically coupled to its pulmonary circulation despite higher RV afterload, lower RV function and altered morphology.

Key Words: Right ventricular function, pulmonary function, cardiac remodelling, preterm birth, computational modelling, cardiac geometry

Publication Status: The results presented in Chapter 4 have been published in *JACC: Cardiovascular Imaging*. The full reference is as follows:

Mohamed, A., et al., Multimodality Imaging Demonstrates Reduced Right-Ventricular Function Independent of Pulmonary Physiology in Moderately Preterm-Born Adults. *JACC: Cardiovascular Imaging* 2020;13(9):2046-2048.

4.2 Introduction

It is known that the premature transition to the extrauterine environment after preterm birth abruptly interrupts the trajectory of cardiopulmonary development leading to neonatal and long term morbidity [210]. With advances in perinatal intensive care improving survival rates into childhood and early adulthood, there is an increased recognition that preterm infants exhibit abnormal cardiovascular performance, irrespective of the degree of lung disease, beyond the neonatal period [211]. The RV and pulmonary circulations are interdependent systems that require relative matching between contractility and afterload for proper hemodynamic coupling. The relationship between RV contractility and RV afterload is known as RV-PA coupling [212]. Using right heart catherization, previous work has demonstrated evidence of subclinical pulmonary vascular disease and RV dysfunction in the same cohort of young adults born preterm [110]. In the following year, the same authors published another report in this cohort, where they identified impaired RV-vascular coupling in these healthy, extremely preterm-born individuals [213]. However, these available data were based on a small sample size in a cohort limited to extremely preterm-born young adults.

In line with an increased cardiovascular risk, LV and RV changes in individuals born preterm are first observed in the neonatal period and extend into infancy and childhood [106, 108, 214]. By adulthood, investigations using CMR have shown that the

changes appear to be more adverse in the RV than LV [108], with a significantly greater relative increase in mass and reduction in systolic function compared to term-born adults. These changes extend across gestational age categories of prematurity from the neonatal period through adulthood [215]. To what extent the pulmonary circulation impacts these findings remains largely unknown. It is plausible that, given the known association from both clinical and epidemiological data of preterm birth with pulmonary vascular disease and pulmonary hypertension, long-term lung physiology may be a driving factor in differences seen in the RV [216]. However, unlike RV changes that are apparent across gestational ages of prematurity, acute and chronic pulmonary complications are largely isolated to more extreme cases of prematurity, below 28 weeks' gestation [217]. Given that more than 80% of preterm births are born moderate to late preterm [218], between 32-36 weeks' gestation, understanding the extent of the RV changes in this subpopulation are of increased public health interest. Accordingly, we recruited participants whose average gestational age at birth lies in the range of moderate prematurity. We used a detailed multimodal imaging assessment, including echocardiography and CMR along with the creation of a computational atlas of the RV, for accurate quantification of structure and function. We utilized these approaches to determine how RV alterations relate to pulmonary changes and to test the hypothesis that reductions in RV function would be out of proportion to changes in pulmonary physiology in moderately preterm-born young adults.

4.3 Methods

4.3.1 Study population

This chapter includes a subgroup of normotensive young adults with different birth histories from YACHT that underwent CMR and echocardiography scans. The study population for this chapter includes n=47 young adults born preterm from **Study 1 (Group A)** and n=54 young adults born term from **Study 1 (Group B)**. The details of these cohorts are provided in Chapter 2 on page 48.

4.3.2 Study visit

All participants fasted for six to 12 hours before the study visit, consuming only water before attending their study visit at the CCRF and OCMR. Trained clinical research investigators completed all measurements. Data were coded with the subject generated identification IDs (e.g. YT2_001) to ensure anonymity and blinded analysis. The following methods were used for this chapter as described in detail in Chapter 3.

- 3.2 Anthropometry and blood samples
- 3.3 Resting brachial blood pressure
- 3.4 24-hour ambulatory blood pressure monitoring
- 3.5 Spirometry testing
- 3.6 Resting echocardiography
    - 3.6.1 RV resting echocardiographic analysis
- 3.7 Cardiac magnetic resonance
    - 3.7.1 Ventricles: volumes and mass

3.7.2 LV: dimensions

3.7.3 Feature tracking analysis

3.7.4 Cardiac shape analysis

4.3.3 Creation of RV computational atlas

The general details for the creation of a cardiac statistical atlas of the RV based on all CMR images is described in Chapter 3, page 72. This chapter focuses on cardiac atlas assessment of RV geometry in normotensive young adults. Creation of a RV statistical atlas of all CMR images was undertaken adapting previously published methods [219, 220]. The end-diastolic frame of the RV short axis cine stack that included the manually contoured endocardial contours was retrieved and rebuilt into a binary segmentation image. A smooth mesh was fitted to the RV blood pool anatomy, achieving subvoxel accuracy (average fitting error of 1.57 mm). The RV anatomy of each subject was then described with a mesh defined by a set of 483 degrees of freedom. Principal component analysis (PCA) was undertaken to identify the key modes of variation of the shape, reducing the parametric space for comparisons from 483 to five dimensions. The RV meshes for the population have been made available to the scientific community (figshare.com/s/5650d08e3eb6e966cf9d). The general overview of the meshing process for RV heart model is shown in **Figure 4.1**.

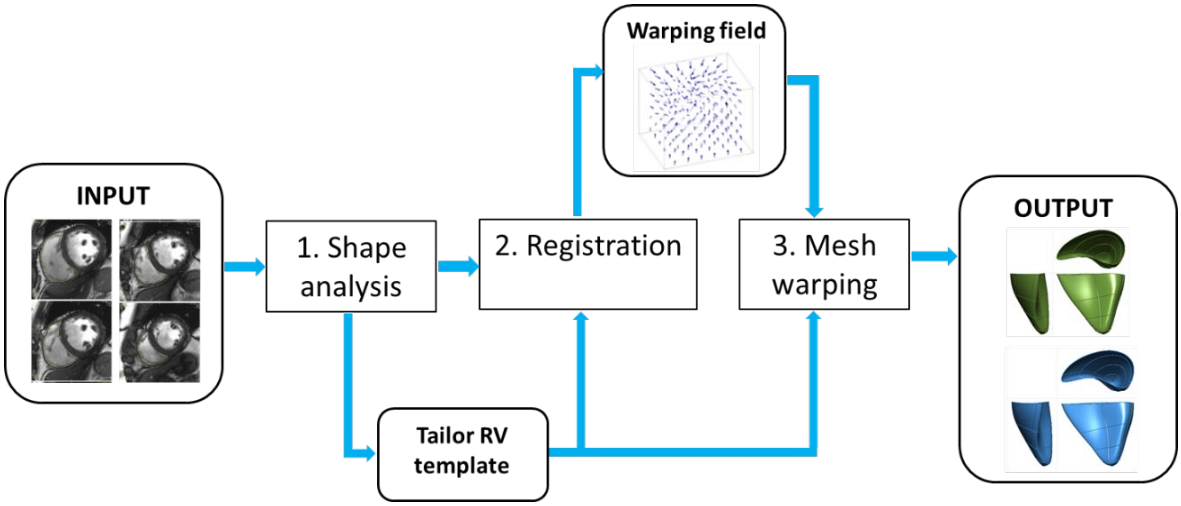


Figure 4.1: Overview of the meshing process for the RV heart model.

4.3.4 Statistical analysis

Statistical analysis was performed using SPSS Version 23. All statistical analyses were done based on a comparison between the preterm and term groups. Data were presented as mean ± standard deviation (SD) or number (%) and for all comparisons. Shapiro-Wilk testing and visual inspection were used to assess data normality. To compare continuous variables between the two groups, we used the Student t-test for normally distributed data and the Mann-Whitney test for skewed data. Where appropriate, comparisons between term-born and preterm-born adults were adjusted for sex. Multivariable linear regression models, including all significant echocardiographic and CMR parameters, were completed using forced entry with missing data excluded pairwise to assess differences between the preterm and term groups for RV measures adjusting for sex, height, age, FEV_1 and FVC. The study was powered at 80% and P=0.05 to detect a 0.77SD difference between groups. Values of $P<0.05$ were considered statistically significant.

4.4 Results

4.4.1 Baseline participant characteristics

There were no differences in age and BMI between preterm-born and term-born groups (P>0.05). The percentage of males was lower in the group of young adults born preterm compared to the term-born group, and as such, group comparisons throughout were adjusted for sex. There were no differences in average awake ambulatory systolic (119±6 vs 119±8mmHg, P=0.610) and diastolic blood pressures between groups (71.3±5 vs 69.4±5mmHg, P=0.058), as shown in **Table 4.1**.

4.4.2 RV morphology and mass

Preterm-born individuals have significantly smaller absolute RA area (P=0.001) and RVEDA (P=0.004) by echocardiography and absolute RV end-diastolic volume, RVEDV (P<0.001) and end-systolic volume, RVESV (P=0.004) by CMR compared to term-born individuals. Both the indexed RA area and RVEDA by echocardiography and indexed RVEDV and RVESV by CMR are significantly reduced in the preterm-born compared to term-born individuals. Both the absolute and indexed RVM were significantly higher in the preterm-born individuals compared with term-born individuals as shown in **Figure 4.2**. There is also no significant difference between groups for absolute RV end-systolic area, RVESA (9.04±2.23 vs 9.94±2.05cm^2; P=0.156) and indexed RVESA (5.11±1.05 vs 5.49±1.01cm^2/m^2; P=0.127) by echocardiography. Preterm-born individuals had similar main pulmonary artery and inferior vena cava dimensions compared with term-born individuals. The full result is presented at **Table 4.2**.

Table 4.1: Cohort characteristics.

	Preterm-Born Adults (n=47)	Term-Born Adults (n=54)	P Value
Demographics and Anthropometrics			
Age (years)	22.7 ± 3.0	23.6 ± 3.8	0.239
Male, n (%)	14 (30.0)	26 (48.0)	0.061
Height (cm)	167 ± 8.6	175 ± 10.0	**<0.001**
Weight (kg)	65.3 ± 13.5	70.0 ± 13.0	0.299
BMI (kg/m^2)	23.3 ± 4.5	22.7 ± 2.7	0.436
Gestational age (weeks)	32.8± 3.2	39.5 ± 1.4	**<0.001**
$32^{+0/7} – 36^{+6/7}$ weeks, n (%)	38 (80.9)	0 (0.0)	-
$28^{+0/7} – 31^{+6/7}$ weeks, n (%)	5 (10.6)	0 (0.0)	-
$< 28^{+0/7}$ weeks	4 (8.5)	0 (0.0)	-
Birth Weight (grams)	1,916 ± 806	3,390 ± 424	**<0.001**
Birth Weight Range (grams)	595 - 3203	2640 - 4536	**<0.001**
Gestational Hypertension, n (%)	8 (17.0)	0 (0.0)	**0.002**
Small for Gestational Age, n (%)	2 (4.3)	0 (0.0)	0.214
Biochemistry			
Total Cholesterol (mmol/L)	4.72 ± 0.65	4.18 ± 0.77	**0.001**
HDL (mmol/L)	1.49 ± 0.31	1.47 ± 0.26	0.953
LDL (mmol/L)	2.80 ± 0.71	2.32 ± 0.60	**0.001**
Triglycerides (mmol/L)	1.12 ± 0.66	0.87 ± 0.36	**0.031**
High Sensitivity CRP (mg/L)	1.57 ± 2.42	1.14 ± 1.96	0.412
Glucose (mmol/L)	5.02 ± 0.41	4.82 ± 0.51	**0.030**
Insulin (pmol/L)	51.1 ± 29.0	35.8 ± 29.4	**0.012**
Insulin Resistance	0.96 ± 0.54	0.68 ± 0.59	**0.020**
Brachial Blood Pressure (mm Hg)			
Resting Systolic	119 ± 9	115 ± 8	**0.014**
Resting Diastolic	70.0 ± 8	66.3 ± 5	**0.014**
Awake Average Ambulatory Systolic	119 ± 6	119 ± 8	0.610
Awake Average Ambulatory Diastolic	71.3 ± 5	69.4 ± 5	0.058

Values are mean ± SD, n (%), or range. P values adjusted for sex. **Bold** P values are statistically significant (P<0.05). BMI indicates body Mass Index; HDL, high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein. Insulin Resistance (IR) was calculated using the; Homeostatic Model Assessment Index (HOMA) calculator (www.dtu.ox.ac.uk/homacalculator/).

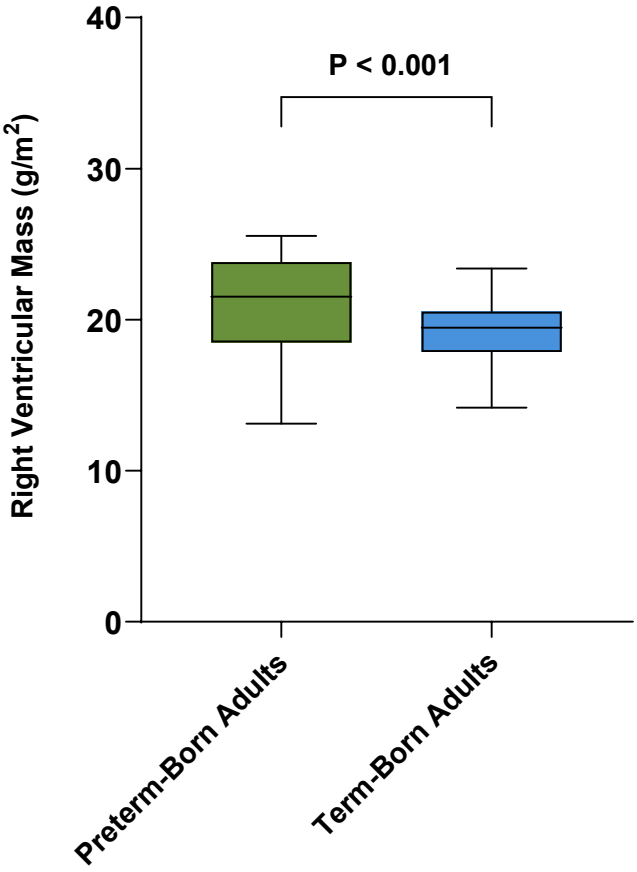


Figure 4.2: Elevated RV mass index in normotensive preterm-born young adults.

4.4.3 RV function

Measures of RV function (RVFAC and TAPSE) by echocardiography were significantly lower in preterm compared to term-born young adults. PAAT was lower in the preterm-born young adults (P<0.001), though when corrected for RVET, there were no differences between the groups (P=0.662). Similarly, there were no differences between groups in estimated RV-PA coupling (P=0.153) **Figure 4.3 (B)**. RVSV by CMR was significantly lower in preterm-born individuals (75.23±17.79mL) compared to term-born individuals (103.8±21.11mL; P<0.001). Similarly, preterm-born individuals had a lower RVCO (5.22±1.18 vs 6.51±1.40L/min; P<0.001) and RVCI (3.00±0.62 vs 3.52±0.67L/min/m^2;

P=0.001) compared to term-born individuals. RVEF was also significantly lower in the preterm-born individuals (54.90±5.17 vs 57.48±4.39%, P=0.008). The full results are presented at **Table 4.3.**

Table 4.2: Right ventricular echocardiography and CMR structural measures.

	Preterm-Born Adults (n=47)	**Term-Born Adults (n=54)**	**P Value**
Structural Parameters			
Echocardiography			
RA/BSA (cm^2/m^2)	7.02 ± 1.21	8.20 ± 1.32	**<0.001**
EDA/BSA (cm^2/m^2)	8.43 ± 1.90	9.82 ± 1.52	**0.001**
ESA/BSA (cm^2/m^2)	5.11 ± 1.05	5.49 ± 1.01	0.127
Main Pulmonary Artery Dimension (cm)	2.00 ± 0.19	2.14 ± 0.24	0.066
Inferior Vena Cava (cm)	1.44 ± 0.37	1.44 ± 0.40	0.88
Cardiac Magnetic Resonance			
EDV/BSA, mL/m^2	78.70 ± 15.11	98.47 ± 15.07	**<0.001**
ESV/BSA, mL/m^2	35.70 ± 8.90	42.10 ± 9.02	**0.006**
Myocardium Mass, g	36.97 ± 6.82	35.09 ± 6.63	**0.012**
Myocardium Mass/BSA, g/m^2	21.20 ± 3.08	18.98 ± 2.32	**<0.001**

Values are mean ± SD. P values adjusted for sex**. Bold** P values are statistically significant (P<0.05). BSA indicates body surface area; RA, right atrium; EDA, end diastolic area; ESA, end systolic area; EDV, end diastolic volume; ESV, end systolic volume.

4.4.4 Spirometry test

Comparisons between the preterm and term groups show no significant differences for FEV_1 (P=0.998) and FVC (P=0.839). When the results are presented as percentage predicted lung function measures (FEV_1, % predicted, FVC, % predicted and FEV_1/FVC

(%), there were also no significant differences between group comparisons. The full result is presented at **Table 4.4**.

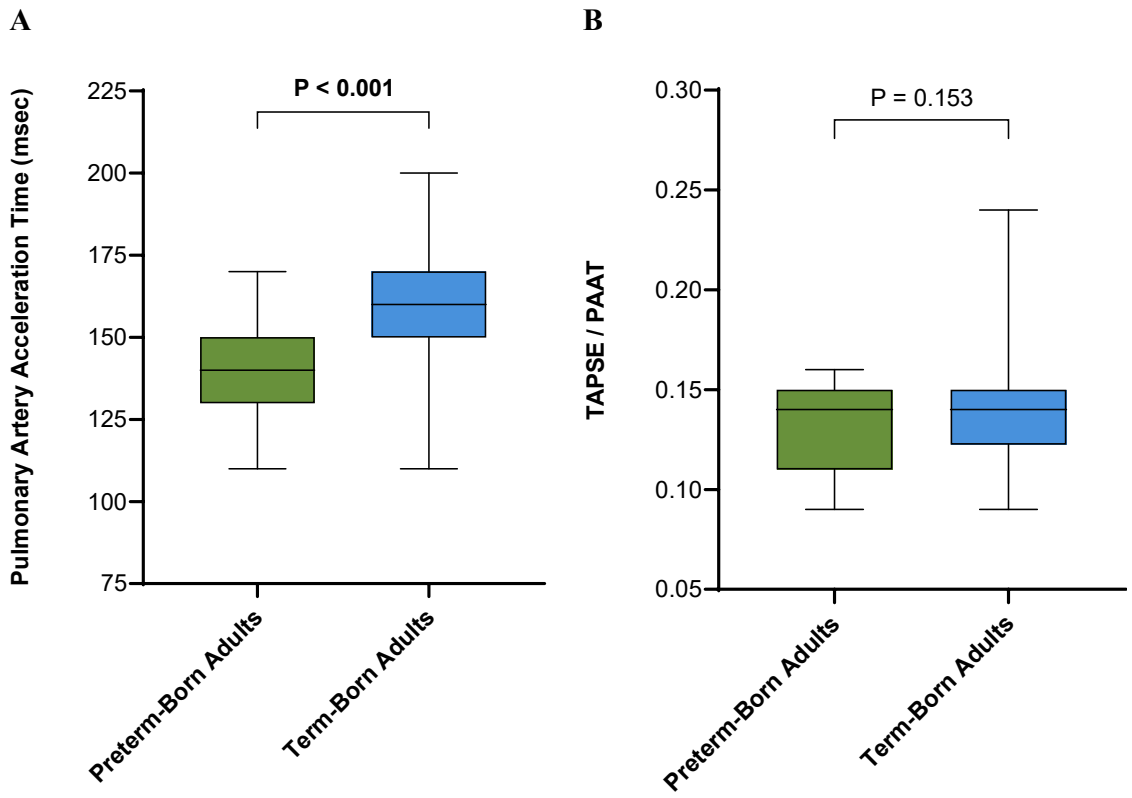


Figure 4.3: Assessment of RV-pulmonary vascular coupling**. A**, PAAT was lower in the preterm-born young adults (141.1±15.1 vs 159.2±21.6msec, p<0.001), though there were no differences between groups in estimated RV-pulmonary vascular coupling, as shown in **B** (TAPSE/PAAT, 0.13±0.02 vs 0.14±0.03, p=0.153).

Table 4.3: Right ventricular echocardiography and CMR functional measures.

	Preterm-Born Adults (n=47)	Term-Born Adults (n=54)	P Value
Functional Parameters			
Echocardiography			
Fractional Area of Change (%)	38.91 ± 7.37	43.83 ± 7.01	**0.008**
TAPSE (cm)	1.84 ± 0.25	2.25 ± 0.35	**<0.001**
Systolic Myocardial Velocity (S') (cm/s)	12.33 ± 1.76	12.81 ± 1.94	0.319
Ejection Time (msec)	256.4 ± 0.04	274.1 ± 0.03	0.057
PAAT (msec)	141.1 ± 15.1	159.2 ± 21.6	**<0.001**
PAAT/RVET (PAATi)	0.58 ± 0.12	0.57 ± 0.07	0.662
Cardiac Magnetic Resonance			
Ejection Fraction, %	54.90 ± 5.17	57.48± 4.39	**0.008**
SV/BSA, mL/m²	42.99 ± 8.05	56.37 ± 8.10	**<0.001**
RV to Pulmonary Coupling (Echocardiography)			
TAPSE/PAAT	0.13 ± 0.02	0.14 ± 0.03	0.153
TAPSE/(PAAT:RVET)	3.50 ± 0.84	3.81 ± 0.76	0.227

Values are mean ± SD. P values adjusted for sex. **Bold** P values are statistically significant (P<0.05). BSA indicates body surface area; TAPSE, tricuspid annular plane systolic excursion; PAAT, pulmonary artery acceleration time; RVET, right ventricular ejection time; SV, stroke volume.

Table 4.4: Pulmonary function spirometry measures.

	Preterm-Born Adults (n=47)	Term-Born Adults (n=54)	P Value
FEV_1, L	3.57 ± 0.86	4.13 ± 0.93	0.998
FEV_1, % predicted	101.8 ± 14.46	103.2 ± 12.75	0.822
FVC, L	4.38 ± 1.00	5.10 ± 1.26	0.839
FVC, % predicted	108.5 ± 15.19	108.6 ± 11.97	0.917
FEV1/FVC (%)	81.4 ± 6.37	81.6 ± 8.10	0.795

Values are mean ± SD. Where appropriate, comparisons between full-term and preterm-born adults were adjusted for sex by multivariable linear regression remodelling. **Bold** P values are statistically significant (P<0.05). $FEV_{1,}$ indicates forced expiratory volume in one second; FVC, forced vital capacity.

4.4.5 Adjustment of RV CMR and echocardiography measures for pulmonary function

After completing between-group comparisons of echocardiography and CMR parameters, we performed multiple regression model analyses to assess the difference between the preterm and term groups for RV measures, adjusting for sex, height, age, FEV_1 and FVC. The findings are demonstrated at **Table 4.5**. For model 1 and model 2, all cardiac parameters for preterm versus term group comparisons remained significant, except for absolute RVEDA by echocardiography and absolute and indexed RVESV by CMR.

Table 4.5: Multivariable regression coefficient for preterm versus term group comparison of key RV echocardiography and CMR parameters

	Model 1					Model 2				
			95% CI for B					95% CI for B		
Echocardiography Parameters	**B**	**β**	**Lower**	**Upper**	***P* value**	**B**	**β**	**Lower**	**Upper**	***P* value**
RA Area, cm^2	-1.27	-0.2	-2.48	-0.05	**0.041**	-1.29	-0.2	-2.51	-0.07	**0.038**
EDA (cm^2)	-1.39	-0.18	-3.10	0.32	0.108	-1.43	-0.19	-3.12	0.26	0.095
End-Diastolic Length (cm)	-0.55	-0.3	-0.95	-0.16	**0.007**	-0.56	-0.3	-0.96	-0.16	**0.006**
RA/BSA (cm^2/m^2)	-1.03	-0.37	-1.64	-0.41	**0.001**	-1.03	-0.37	-1.65	-0.41	**0.001**
EDA/BSA (cm^2/m^2)	-1.3	-0.36	-2.17	-0.41	**0.005**	-1.31	-0.36	-2.18	-0.43	**0.004**
FAC (%)	-5.09	-0.34	-9.00	-1.19	**0.011**	-5.12	-0.34	-9.01	-1.23	**0.011**
TAPSE (cm)	-0.36	-0.50	-0.53	-0.19	**<0.001**	-0.36	-0.49	-0.53	-0.19	**<0.001**
PAAT (msec)	-0.02	-0.36	-0.03	-0.01	**0.003**	-0.02	-0.36	-0.03	-0.01	**0.003**
Cardiac Magnetic Resonance Parameters										
EDV, mL	-18.88	-0.22	-30.09	-7.66	**0.001**	-19.19	-0.22	-30.46	-7.93	**0.001**
ESV, mL	-2.05	-0.05	-8.68	4.59	0.541	-2.18	-0.05	-8.85	4.48	0.516
SV, mL	-16.54	-0.34	-23.01	-10.06	**<0.001**	-16.72	-0.35	-23.2	-10.24	**<0.001**
Cardiac output, L/min	-0.79	-0.27	-1.31	-0.26	**0.004**	-0.8	-0.28	-1.32	-0.27	**0.004**
Cardiac Index	-0.49	-0.35	-0.79	-0.19	**0.002**	-0.49	-0.35	-0.79	-0.19	**0.002**
Ejection Fraction, %	-3.83	-0.40	-6.08	-1.59	**0.001**	-3.84	-0.39	-6.08	-1.6	**0.001**
EDV/BSA, mL/m^2	-12.37	-0.35	-18.36	-6.39	**<0.001**	-12.46	-0.35	-18.54	-6.38	**<0.001**
ESV/BSA, mL/m^2	-1.86	-0.10	-5.44	1.72	0.305	-1.9	-0.10	-5.52	1.72	0.3
SV/BSA, mL/m^2	-10.51	-0.50	-14.01	-7	**<0.001**	-10.56	-0.51	-14.11	-7.01	**<0.001**
Myocardium Mass, g	6.39	0.48	4.32	8.45	**<0.001**	6.36	0.47	4.26	8.46	**<0.001**
Myocardium Mass/BSA, g/ m^2	3.26	0.56	2.07	4.44	**<0.001**	3.27	0.57	2.08	4.45	**<0.001**
Mass/EDV, g/mL	0.07	0.77	0.06	0.08	**<0.001**	0.07	0.77	0.06	0.08	**<0.001**

Model 1 Independent variables: preterm vs term group, sex, height, age and FEV_1*
Model 2 Independent variables: preterm vs term group, sex, height, age and FVC*
B indicates unstandardized regression coefficient; β, standardised regression coefficient; CI, confidence interval; RA, right atrium; EDA, end-diastolic area; BSA, body surface area; FAC, fractional area of change; TAPSE, tricuspid annular plane systolic excursion; PAAT, pulmonary artery acceleration time; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume. **Bold** P values are statistically significant (P<0.05).
*Multiple regression coefficients are presented for preterm vs term group comparisons

4.4.6 Unique RV computational 3D geometry

The PCA defined the anatomical modes of the RV geometry within the study population, with mode 1 accounting for the greatest proportion of variance explained, 25.3%, and the first five modes accounting for 55.7%. Preterm and term cohorts showed significant differences (P<0.001) in mode 1 that represents a smaller and shorter RV cavity in the preterm group, with no differences in the other modes. **Figures 4.4 and 4.5** illustrate these differences and the anatomical changes encoded in mode 1.

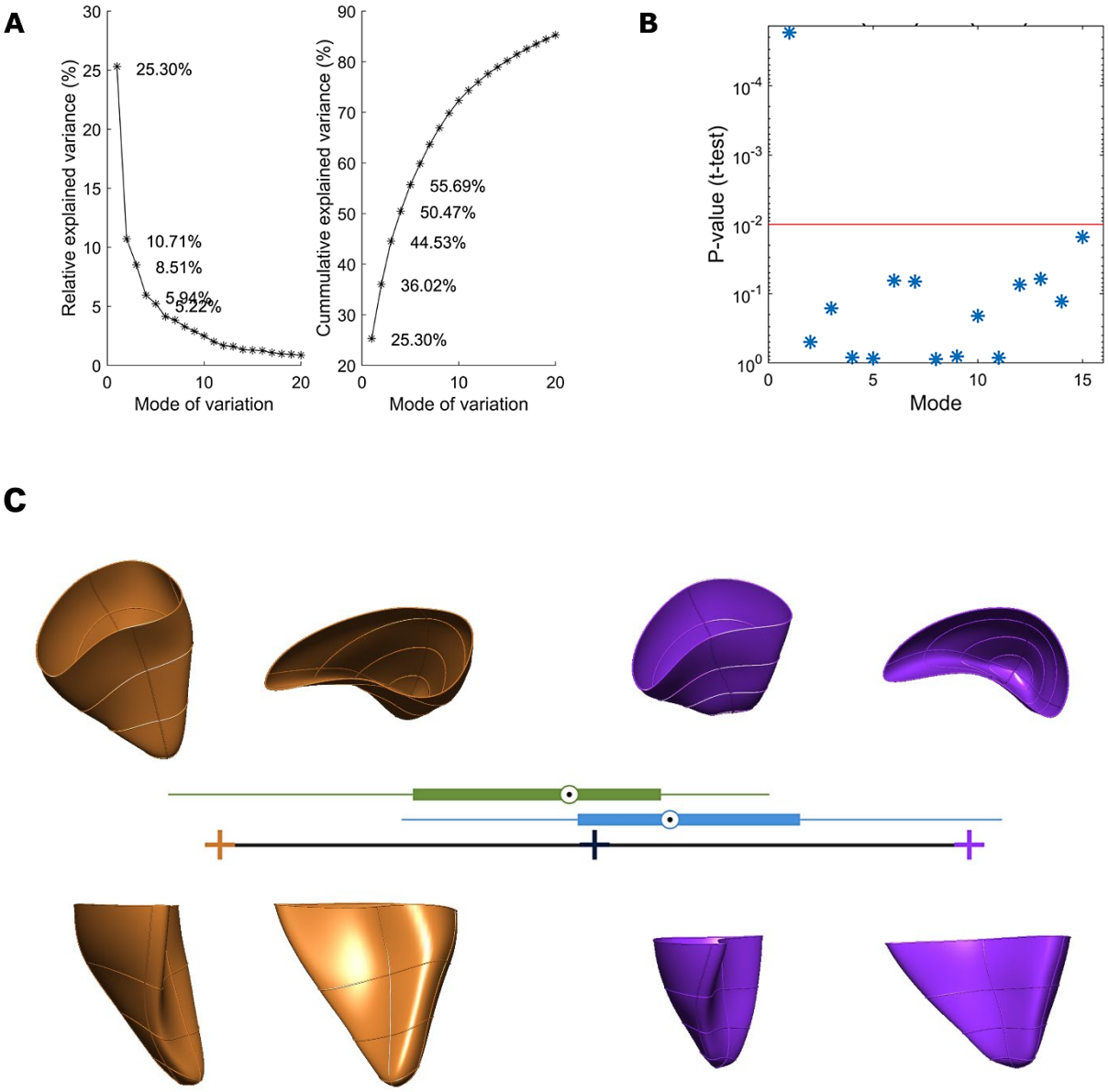


Figure 4.4: Statistical shape model of the RV. **A**, Cumulative variance explained by the anatomical modes of variation, determined using PCA. The first five modes of variation explained 55.69% of the cumulative variance. **B**, Comparison of the differences between preterm-born and term-born young adults across the first 15 modes from PCA. The red line indicates p=0.01. **C**, The PCA coordinates for the first mode of variation, representing RV cavity size, are shown. The orange cross and orange RV mesh represent -2SD, while the purple cross and purple RV mesh represent +2SD. The average across all individuals is set at coordinate 0 and is represented by a dark blue cross. The blue (preterm-born) and green (term-born) box plots represent the median mode 1 coordinates for each group, with the whiskers representing the range of coordinates for each group.

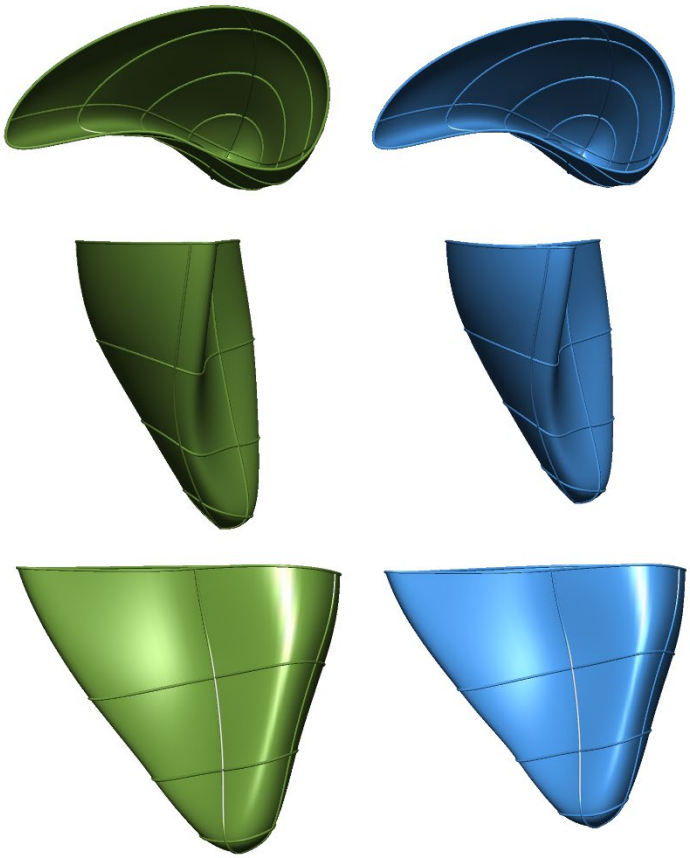


Figure 4.5: Statistical average shape of the RV of term-born young adults (green) and preterm-born young adults (blue) from three different views. Mode 1 represents a significantly smaller and shorter RV cavity in preterm compared to term-born adults.

4.5 Discussion

Through the use of echocardiography and CMR, this study demonstrates that RV structure and function are altered in moderately preterm-born young adults. Multimodality cardiovascular imaging revealed consistently smaller RV dimensions and reduced function in young adults born preterm, with higher RVM using CMR. These findings are independent of changes in pulmonary spirometry measures. The CMR data used to create the first preterm RV computational atlas revealed that the strongest mode of 3D variation

defining the preterm-born young adults is the overall smaller size of the RV. Despite increased PVR in young adults born preterm, the RV remains hemodynamically coupled to its pulmonary circulation, with similar lung function to term-born young adults.

The findings from this study are consistent with previous reports of reduced RV function in preterm-born adults [108, 221]. A study by Goss et al using right heart catheterization in extremely and very preterm-born young adults showed they have a reduced ability to raise RVSV and RVCI during physiological stress [110]. Further to this, 45% (n=5 out of 11) of those born preterm in that study had borderline or overt pulmonary hypertension, with neonatal ventilatory support days being the strongest predictor of adult pulmonary pressures. In our study of moderately preterm-born individuals, however, there were no indications of pulmonary vascular disease. This is expected given that acute and chronic pulmonary complications are largely isolated to more extreme cases of prematurity, below 28 weeks' gestation [217]. In spite of this, RV structure and function were still altered in our preterm group. It is possible that this is due in part to the drastic physiological changes and cardiac loading conditions when transitioning from the low resistance placental circulation to high resistance arterial circulation around the time of birth [104, 113]. Indeed, in utero, the RV is a dominant, thick-walled chamber, providing 2/3 of the CO to the systemic circulation. After transitioning to the extrauterine environment, the RV remodels to become more crescent shaped and thin-walled [113]. The challenges experienced by these immature cardiomyocytes subsequently inhibit the normal myocardial maturation and promote cardiac hypertrophy and fibrosis [102, 103] that can potentially lead to RV failure in later life [222, 223]. Though no human studies to date have examined ventricular tissue fibrosis, the presentation of RV remodeling observed

in the preterm group may be explained by the combination of these insults that continue into adulthood.

RV systolic dysfunction is highly prevalent in patients with heart failure [224] and patients with heart failure and preserved LVEF (HFpEF) [225]. A large Swedish national cohort registry study identified preterm birth as a novel risk factor for incident heart failure in childhood and adolescence, extending across gestational ages and independent of family history and perinatal confounders [12]. Despite having a preserved resting LVEF, a reduction in LV myocardial functional reserve is evident during moderate and high-intensity exercise even in normotensive, moderately preterm-born young adults [109]. The LV, like the RV [110], is therefore more vulnerable to stress conditions in the preterm population, and as chronic stress to the system increases into later adulthood due to the combination of an altered cardiac phenotype and elevated blood pressure and hypertension risk in adults born preterm [5], heart failure risk, as well as the risk of cardiovascular events, will likely continue to increase. It is therefore also likely that RV function will continue to decrease in parallel, but potentially at a greater rate, to the LV. Future longitudinal research is needed to follow these cohorts over time to better understand individual patterns of cardiac remodeling throughout adulthood. Whether perinatal [221] or later life interventions [194] known to improve long-term cardiac phenotype can modify the dysfunctional trajectory remains to be determined.

The RV is a pulsatile pump, the efficiency or work of which depends on proper hemodynamic coupling with the compliant PA vascular circulation. Increased afterload conditions can exert significant load to the RV that can affect the coupling of the RV to the PA vasculature. Coupling is based on the work-energy principle that states a change in energy is equal to the work expended by a force through displacement [226]. Recent

evidence has demonstrated that the ratio of TAPSE, a surrogate for RV length (contractility), to PAAT, a measure of the developed force (afterload), provides a reliable measure of invasive RV-PA coupling in infants, children and adults [207, 227-229]. In this study we found no coupling differences between groups based on the TAPSE/PAAT and TAPSE/PAATi ratios, despite the increase in RV afterload (with lower values of PAAT) and the decrease in RV function by TAPSE. Furthermore, the observed increase in RVM (hypertrophy) suggests an early adaptation to attempt to increase RV contractility in order to maintain RV-PA coupling [226]. In a study by Mulchrone et al. using CMR, young adults born preterm with increased RV afterload were found to have reduced RV diastolic function without compensatory increases in contractility [213]. As a result, the maintained contractility with increased RV afterload led to reduced RV-PA coupling in the young adults born preterm, calculated by both a pressure- and volume-based method of ventricular to arterial elastance [213]. The reported differences between the two studies are likely related to differences in gestational age at birth of the preterm cohorts (28.60±0.86 gestational weeks in the Mulchrone et al [213] study compared to 32.8±3.2 gestational weeks in our study). Previous work comparing term-born to preterm-born infants at one year of age demonstrated blunted RV-PA coupling that was more pronounced based on the gestational age [96, 211]. We speculate that uncoupling will be more likely to occur sooner in preterm-born individuals and may be gestational-age dependent, further warranting longitudinal follow-up. Regardless, is it evident that functionally, optimal RV-PA coupling in resting conditions is maintained as long as the RV can adapt to RV afterload. Comprehensive, non-invasive evaluation of RV-PA coupling may be an important marker in the characterization of cardiopulmonary function in all children and adults born preterm [212].

4.6 Study 1 limitations

Study 1 has several limitations. One of the limitations of our study is the lack of diffusion gas exchange data to assess the effectiveness of lung diffusion, which has been reported to be impaired in very and extremely preterm-born young adults [110]. However, our cohort is less likely to have respiratory limitations since they have been born moderately preterm. Group sizes for our study were also modest, though the group comparisons presented were sufficiently powered based on the study numbers. Further to this, our use of multimodality imaging improved the level of confidence in results where both echocardiography and CMR were used to measure a similar structural or functional parameter. Nevertheless, the modest sample size was not sufficient to enable exploration of all possible confounding variables.

4.7 Conclusion

We have demonstrated with multimodality cardiac imaging that moderately preterm-born young adults exhibit structural and functional RV alterations, though the RV remained hemodynamically coupled to the pulmonary vasculature. As all the included participants were normotensive, young adults with elevated blood pressure are likely to experience earlier subclinical changes that can lead to RV-PA coupling. Furthermore, how gestational age and exercise capacity in young adults relates to risk of uncoupling in the short and long term requires further investigation.

CHAPTER 5

STUDY 2 RESULTS

Exaggerated increase in left ventricular mass in relation to systolic blood pressure elevation in very preterm-born young adults

5.1 Abstract

Background: Preterm-born individuals have higher blood pressure with an increased risk of hypertension by young adulthood, as well as potentially adverse cardiac remodelling, even when normotensive. To what extent blood pressure elevation impacts LV structure and function in adults born preterm is currently unknown.

Objectives: To investigate whether changes observed in LV structure and function in preterm-born adults make them more susceptible to cardiac remodelling in relation to blood pressure elevation.

Methods: This single centre, cross-sectional cohort study included 493 adults aged 18 to 40 years. Of these, 210 were born preterm (<37 weeks' gestation) and 283 were born at term (37-42 weeks' gestation). CMR imaging was used to characterise LV structure and function, with clinic blood pressures readings measured to assess hypertension status. Demographic and anthropometric data, as well as birth history and family medical history information, were collected. The main outcomes and measures are CMR measures of LV structure and function in response to systolic blood pressure elevation.

Results: Normotensive and hypertensive preterm-born adults had higher LVMI, reduced LV function, and smaller LV volumes compared to both term-born normotensive and hypertensive individuals ($P<0.01$). These differences compared to the term-born groups were even greater for the hypertensive preterm-born young adults. In regression analyses of systolic blood pressure with LVM and LVM to LVEDV ratio, there was a leftward shift in the slopes in preterm- compared to term-born adults. Compared to term-born adults, there was a 2.5-fold greater increase in LVMI per 1mmHg increase in systolic blood pressure in very and extremely preterm-born adults ($P<0.001$) and a 1.6-fold greater increase in LVMI per 1mmHg systolic blood pressure increase in moderately preterm-born adults ($P<0.001$). The change in LVM to LVEDV ratio per 1mmHg increase in systolic blood pressure in the very and extremely preterm-born adults was 3.5-fold greater than for those born moderately preterm ($P<0.001$) and 3.3-fold greater than for those born at term ($P<0.001$).

Conclusions: Preterm-born young adults have a unique LV structure and function that worsens with systolic blood pressure elevation. Additional primary prevention strategies to specifically target cardiovascular risk reduction in this population may be warranted.

Key Words: Cardiac geometry, cardiac function, left ventricle, blood pressure, preterm birth, hypertension, cardiac magnetic resonance

Publication Status: A complete manuscript from the results presented in Chapter 5 is currently under review.

5.2 Introduction

Individuals born preterm are at greater relative risk of early heart failure [12] and ischemic heart disease [230] with risk increasing according to the degree of prematurity. Part of this risk may relate to altered cardiac physiology, as preterm-born individuals have potentially adverse structural and functional changes across developmental stages from birth to young adulthood [215]. This includes impaired LV diastolic function, smaller internal LV dimensions, and a greater rate of LVH from childhood to young adulthood [215].

In a rat model of preterm birth conditions, early cardiac remodelling, similar to that observed in humans, makes rodents more susceptible to heart failure following hemodynamic pressure overload [231, 232]. In humans, the preterm heart is less able to cope under acute physiological stress, with impairments in ejection fraction, stroke volume, and CO during moderate to high intensity exercise [233, 234]. It is thus conceivable that the observed patterns of cardiac remodelling seen in individuals born

preterm makes their hearts more vulnerable to chronic insults, such as the hemodynamic stress of sustained blood pressure elevation. Of related concern is that, compared to their term-born peers, individuals born preterm have higher systolic and diastolic blood pressures [235] with preterm birth now recognized as a risk factor for hypertension in adulthood [236].

While earlier studies have shown associations between cardiac structural and functional alterations with increasing blood pressure [106, 108], they have been limited by small numbers of individuals with blood pressures in the clinically elevated and hypertensive range. We have therefore performed a CMR imaging study in 493 individuals, of which over 25% were clinically hypertensive, to determine how systolic blood pressure elevation may impact LV structure and function in adults born preterm. The use of CMR provides the optimal imaging modality for cardiac assessment with its capacity for high resolution. Furthermore, we have investigated whether the strength of the relationship between LV changes and systolic blood pressure is dependent on the degree of prematurity. We hypothesised that the altered cardiac phenotype seen in those born preterm makes them more susceptible to further cardiac remodelling in relation to blood pressure elevation.

5.3 Methods

5.3.1 Study population

This chapter includes a subgroup of 493 adults with different birth history from EVS, YACHT and TEPHRA that underwent CMR scans. Participants were recruited as part of a single study visit. In the final analyses, the study population for this chapter includes

n=200 young adults born preterm from Study 2 (Group A) and n=268 young adults born term from Study 2 (Group B). The details of these cohorts are provided in Chapter 2 on page 49. The study recruitment outline is shown in **Figure 5.1**.

5.3.2 Study visit

All participants fasted for six to 12 hours before the study visit, consuming only water before attending a study visit at the CCRF and OCMR. Trained clinical research investigators completed all measurements. Data were coded with the subject generated identification IDs (e.g. YT2_001) to ensure anonymity and blinded analysis. The following methods were used for this chapter as described in detail in Chapter 3.

- 3.2 Anthropometry and blood samples
- 3.3 Resting brachial blood pressure
- 3.7 Cardiac magnetic resonance
    - 3.7.1 Ventricles: volumes and mass
    - 3.7.2 LV: dimensions

5.3.3 Blood pressure classification

Classification of participants as normotensive and hypertensive was based on cut-offs derived from the AHA blood pressure classification guidelines (systolic blood pressure >130 mmHg and/or diastolic blood pressure >80 mmHg) [130].

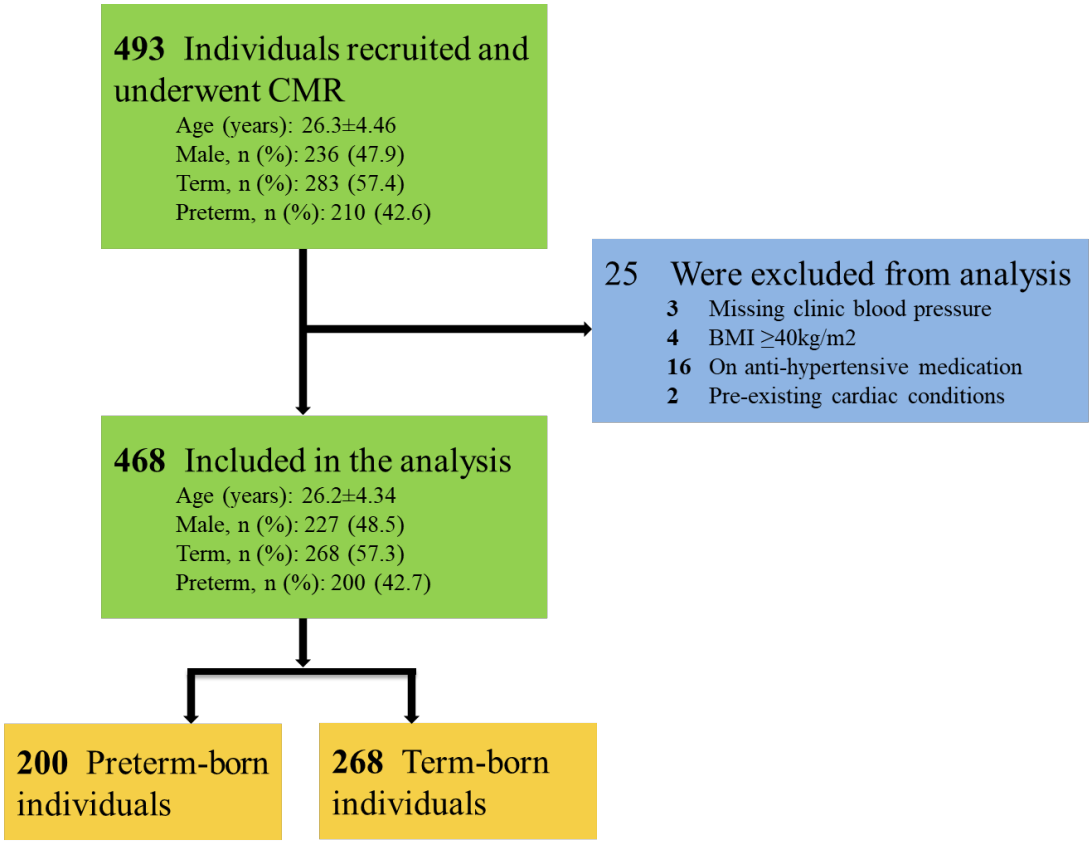


Figure 5.1: The study recruitment outline. The 493 participants were recruited from three different studies with a standardised study structure and methodology. Twenty-five participants were excluded from the analysis: three due to missing clinic blood pressure readings; four who had a BMI ≥40kg/m^2; 16 who were on anti-hypertensive medications and two who had pre-existing cardiac conditions. Of the remaining 468 participants, 200 were born preterm and 268 were born at term.

5.3.4 Statistical analysis

Statistical analysis was performed using SPSS v25 (IBM, New York, USA) and R v3.6.1 (R Foundation for Statistical Computing). All statistical analyses were done based on a comparison of birth history (preterm and term groups) and gestational age categories grouped as: <32 weeks, 32-36weeks and ≥37 weeks). Data were presented as mean ± SD or number (%) for all comparisons. Shapiro-Wilk testing was used to verify data normality. To compare continuous variables between groups, we used the Student t-test for normally

distributed data and the Mann-Whitney test for skewed data. All group comparisons of birth history and gestational age categories were adjusted for age and sex. After bivariate regression analyses, multivariable regression analyses were conducted to identify the association between key LV parameters (dependent variables) and systolic blood pressure, adjusting for potential confounders (age, sex, birth weight z-score, and BMI). For each analysis, unstandardised coefficients (B) with 95% confidence intervals (CI) and P-values were computed. One-way analysis of covariance (ANCOVA) was conducted to determine whether there were significant differences in the regression lines between the groups. Sum squares, F-statistics, and P-values were calculated for each parameter within each model. A radar plot was generated to display key LV parameters in each subgroup division, with results presented in ratios of the average values between the groups relative to the term-born normotensive reference group. P-values were calculated for each parameter within each model. $P \leq 0.05$ were considered statistically significant unless multiple subgroup comparisons were made, in which case, $P \leq 0.01$ were considered statistically significant.

5.4 Results

5.4.1 Baseline participant characteristics

There were no significant differences in age and sex between the preterm- and term-born groups (**Table 5.1**). Out of 200 individuals born preterm, 52.5% (n=105) were born moderate to late preterm (32-36 weeks' gestation), 37% (n=74) were born very preterm (28-31 weeks' gestation), and 10.5% (n=21) were born extremely preterm (<28 weeks' gestation) (**Table 5.1**). The preterm-born individuals were shorter and weighed less than those born at term but there was no difference in BMI between groups. Only a small

percentage of preterm- and term-born adults were born small for gestational age (5.0% and 1.9%, respectively). A higher percentage of preterm-born individuals had a family history of hypertension (35.0% vs 20.9%, P=0.001) and stroke (6.5% vs 1.5%, P=0.002) compared to those born at term based on questionnaire responses (**Table 5.1**).

When dividing birth history groups by blood pressures status, within both the preterm and term groups, there were more males among the hypertensive individuals, who were also slightly older compared to their normotensive peers (**Table 5.2**). A family history of hypertension was also more prevalent in hypertensive compared to normotensive preterm-born young adults. There were similar magnitudes of systolic and diastolic blood pressure differences between the normotensive and hypertensive subgroups within the preterm group (systolic: +15.1%, P<0.001; diastolic: +16.4%, P<0.001) and term group (systolic: +15.7%, P<0.001; diastolic: +20.3%, P<0.001).

Table 5.1: Baseline participant characteristics.

	Preterm-Born Adults (n=200)	Term-Born Adults (n=268)	P value
Demographics and Anthropometrics			
Age (years)	25.7 ± 3.94	26.5 ± 4.59	.054
Male, n (%)	91 (45.5)	136 (50.7)	.310
Height (cm)	170 ± 10.11	174 ± 9.14	<.001
Weight (kg)	69.2 ± 13.46	72.4 ± 13.02	.041
BMI (kg/m²)	24.0 ± 3.73	23.9 ± 3.41	.475
Birth Weight (grams)	1628 ± 631	3445 ± 424	<.001
Birth Weight (z-score)	-0.26 ± 1.05	0.09 ± 0.89	<.001
Small for Gestational Age, n (%)	10 (5.0)	5 (1.9)	.986
Gestational Age (weeks)	31.3 ± 2.98	39.6 ± 1.14	<.001
< 28 weeks, n (%)	21 (10.5)	-	-
28 – 31 weeks, n (%)	74 (37.0)	-	-
32 – 36 weeks, n (%)	105 (52.5)	-	-
Family medical history of, n (%)			
Ischemic Heart Disease	17 (8.5)	13 (4.9)	.094
Hypertension	70 (35.0)	56 (20.9)	.001
Stroke	13 (6.5)	4 (1.5)	.002
Diabetes Mellitus	19 (9.5)	21 (7.8)	.440
High Cholestrol	43 (21.5)	48 (17.9)	.359
Biochemistry			
Total Cholesterol (mmol/L)	4.66 ± 1.04	4.46 ± 0.95	.018
HDL (mmol/L)	1.49 ± 0.37	1.44 ± 0.35	.270
LDL (mmol/L)	2.78 ± 0.79	2.59 ± 0.79	.003
Triglycerides (mmol/L)	1.23 ± 0.97	0.99 ± 0.59	<.001
High Sensitivity CRP (mg/L)	1.92 ± 3.54	1.59 ± 3.21	.308
Glucose (mmol/L)	4.96 ± 0.43	4.82 ± 0.47	<.001
Insulin (pmol/L)	53.6 ± 30.74	47.17 ± 45.16	.063
Homa-B (%)	98.0 ± 33.90	93.5 ± 32.68	.266
Homa-S (%)	124.0 ± 53.05	156.3 ± 72.17	<.001
Homa-IR	0.84 ± 0.33	0.76 ± 0.38	.029
Brachial Blood Pressure (mm Hg)			
Resting Systolic	121.0 ± 11.5	117.9 ± 11.2	.001
Resting Diastolic	72.9 ± 8.1	71.8 ± 8.7	.056

Group characteristics presented as mean ± SD, n (%), or range. *P* values adjusted for sex and age. BMI indicates body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; HT, hypertensive; LDL, low density lipoprotein; NT, normotensive.

Table 5.2: Baseline participant characteristics divided by birth history and blood pressure subgroups.

	Preterm-Born Adults			Term-Born Adults					
	Normotensive (n=139)	**Hypertensive (n=61)**	***P*[a]**	**Normotensive (n=205)**	**Hypertensive (n=63)**	***P*[b]**	***P*[c]**	***P*[d]**	***P*[e]**
Demographics and Anthropometrics									
Age (years)	25.4 ± 3.95	26.4 ± 3.84	.120	26.1 ± 4.41	27.8 ± 4.93	.012	.127	.001	.099
Male, n (%)	56 (40.3)	35 (57.4)	.034	94 (45.9)	42 (66.7)	.005	.323	.002	.347
Height (cm)	169 ± 9.69	172 ± 10.85	.616	173 ± 9.24	176 ± 8.60	.532	<.001	.001	.012
Weight (kg)	67.1 ± 13.09	74.1 ± 13.11	.010	70.4 ± 12.41	78.7 ± 13.04	.002	.047	<.001	.138
BMI (kg/m^2)	23.5 ± 3.62	25.1 ± 3.75	.008	23.5 ± 3.23	25.4 ± 3.55	.002	.692	.009	.970
Birth Weight (grams)	1600 ± 606	1692 ± 687	.390	3429 ± 410	3499 ± 464	.234	<.001	<.001	<.001
Birth Weight (z-score)	-0.23 ± 1.01	-0.34 ± 1.14	.441	0.10 ± 0.84	0.05 ± 1.04	.716	.001	.048	.036
Gestational Age (weeks)	31.17 ± 2.99	31.77 ± 2.99	.165	39.5 ± 1.11	39.86 ± 1.20	.047	<.001	<.001	<.001
< 28 weeks, n (%)	14 (10.1)	7 (11.5)	.666	-	-	-	-	-	-
28 – 31 weeks, n (%)	55 (39.6)	19 (31.1)	.127	-	-	-	-	-	-
32 – 36 weeks, n (%)	70 (50.4)	35 (57.4)	.230	-	-	-	-	-	-
Family medical history of, n (%)									
Ischemic Heart Disease, n (%)	10 (7.2)	7 (11.5)	.297	10 (4.9)	3 (4.8)	.932	.334	.463	.178
Hypertension, n (%)	42 (30.2)	28 (45.9)	.037	43 (21.0)	13 (20.6)	.919	.049	.261	.007
Stroke, n (%)	8 (5.8)	5 (8.2)	.707	1 (0.5)	3 (4.8)	.016	.001	.507	.475
Diabetes Mellitus, n (%)	10 (7.2)	9 (14.8)	.163	17 (8.3)	4 (6.3)	.781	.739	.434	.080
High Cholesterol, n (%)	27 (19.4)	16 (26.2)	.350	38 (18.5)	10 (15.9)	.858	.876	.654	.205
Biochemistry									
Total Cholesterol (mmol/L)	4.72 ± 0.95	4.53 ± 1.20	.296	4.41 ± 0.92	4.60 ± 1.06	.388	.001	.561	.743
HDL (mmol/L)	1.53 ± 0.37	1.40 ± 0.35	.125	1.46 ± 0.35	1.36 ± 0.32	.528	.125	.132	.969
LDL (mmol/L)	2.78 ± 0.72	2.76 ± 0.93	.671	2.53 ± 0.73	2.82 ± 0.92	.118	<.001	.959	.933

Triglycerides (mmol/L)	1.14 ± 0.87	1.42 ± 1.13	.127	0.94 ± 0.57	1.16 ± 0.64	.094	.005	.850	.058
High Sensitivity CRP (mg/L)	2.08 ± 3.96	1.57 ± 2.46	.375	1.50 ± 3.30	1.88 ± 2.90	.391	.145	.539	.431
Glucose (mmol/L)	4.91 ± 0.45	5.06 ± 0.37	.065	4.75 ± 0.45	5.05 ± 0.44	.001	.001	.356	.408
Insulin (pmol/L)	52.9 ± 32.22	55.0 ± 27.56	.323	41.1 ± 29.45	67.4 ± 74.11	.001	.001	.074	.338
Homa-B (%)	99.1 ± 34.92	95.6 ± 31.95	.788	91.4 ± 29.51	99.7 ± 40.38	.149	.100	.380	.589
Homa-S (%)	128.0 ± 56.35	115.9 ± 44.86	.052	166 ± 71.83	124 ± 64.34	.001	<.001	.406	.369
Homa-IR	0.82 ± 0.33	0.88 ± 0.32	.139	0.71 ± 0.34	0.94 ± 0.44	.002	.014	.071	.665
Brachial Blood Pressure (mm Hg)									
Resting Systolic	115.6 ± 7.33	133.0 ± 9.99	<.001	113.7 ± 8.15	131.6 ± 8.50	<.001	.011	<0.001	.275
Resting Diastolic	69.4 ± 5.43	80.8 ± 7.57	<.001	68.5 ± 6.04	82.4 ± 7.36	<.001	.105	<0.001	.262

Subgroup characteristics presented as mean ± SD, n (%), or range. *P* values adjusted for sex and age. BMI indicates body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; HT, hypertensive; LDL, low density lipoprotein; NT, normotensive.

***P**[a]* preterm-born NT vs preterm-born HT

***P**[b]* term-born NT vs term-born HT

***P**[c]* preterm-born NT vs term-born NT

***P**[d]* preterm-born NT vs term-born HT

***P**[e]* preterm-born HT vs term-born HT

5.4.2 LV remodelling in preterm-born and term-born hypertensive young adults

In the preterm-born group, LVM was significantly higher in the hypertensive group compared to the normotensive group (125.9±26.3 vs 112.5±26.1grams, P=0.010). This difference in LVM was not significant when indexed to BSA (LVMI, P=0.074) (**Table 5.3**). Other measures of LV structure and function did not differ significantly between blood pressure groups. Within the term-born group, LVEF was higher in the hypertensive group (66.38±5.43 vs 64.06±5.15%, P=0.001) due to a lower LVESV (P=0.005). This potential increase in systolic function was supported by greater LV mid-ventricular peak systolic circumferential strain (P=0.005). No other measures of LV structure and function differed between blood pressure groups.

We compared LV structural and functional measures in preterm-born normotensive individuals to term-born normotensive and hypertensive individuals (**Table 5.3**). Preterm-born normotensive individuals had smaller LV dimensions and volumes compared to both term-born normotensive and hypertensive individuals (P<0.001), with higher LVMI compared to both groups (P<0.001). Although LVEF did not differ between preterm- and term-born normotensive groups (P=0.038), it was significantly higher in the hypertensive term group compared to the normotensive preterm group (P<0.001). Longitudinal peak systolic strain, mid-ventricular and apical peak systolic circumferential strain measures were lower in the preterm-born normotensive group compared to normotensive and hypertensive term-born individuals (P<0.01). In addition, basal peak systolic circumferential strain was also lower in the preterm-born hypertensive group compared to the term-born hypertensive group (P=0.004). **Figure 5.2** demonstrates how key LV parameters differ between groups in relation to term-born normotensive adults.

5.4.3 Relationship between systolic blood pressure and LV parameters

The relationship between systolic blood pressure and LVMI was significant in both the preterm- and term-born groups but was greater in those born preterm in the multivariable regression models per 1mmHg elevation in systolic blood pressure (0.318 g/m^2 [95%CI: 0.209-0.427] vs 0.157g/m^2 [95%CI: 0.060-0.254], ANCOVA P<0.001) (**Figure 5.3 A and Tables 5.4 and 5.5**). When dividing by gestational age categories, the relationship between systolic blood pressure and LVMI in the adjusted regression models was significant across all groups but was greatest in those born very and extremely preterm (<32 weeks' gestation), with a 0.394g/m^2 [95%CI: 0.213-0.574] greater LVMI per 1mmHg elevation in systolic blood pressure compared to 0.250g/m^2 [95%CI: 0.113-0.387] in those born moderately preterm (32-36 weeks' gestation) (ANCOVA P=0.03) and 0.157g/m^2 [95%CI: 0.060-0.254] in those born at term (≥37 weeks' gestation) (ANCOVA P<0.001) (**Figure 5.4 A and Table 5.6 and 5.7**). The adjusted regression lines were also significantly different between moderately preterm and term-born individuals (P<0.001) (**Table 5.7**). Although there was a significant, positive relationship between systolic blood pressure and LVEF in the term-born adults (0.079% [95%CI: 0.017-0.140] per 1mmHg elevation in systolic blood pressure), this relationship was not significant in preterm-born adults. In multivariable regression, there was a significant, positive relationship between systolic blood pressure and LVM to LVEDV ratio in the preterm-born adults (2.38x10^{-3}g/mL [95%CI: 8.15x10^{-4}-3.94x10^{-3}] per 1mmHg elevation in systolic blood pressure) but not in term-born adults, with a significant difference between regression lines (ANCOVA P<0.001). This relationship was greatest in adults born very and extremely preterm (3.56x10^{-3} [95%CI: 1.01x10^{-3}-6.11x10^{-3}] per 1mmHg elevation in systolic blood pressure), with the regression line differing significantly for this group compared to moderately

preterm (ANCOVA P<0.001) and term-born adults (ANCOVA P<0.001) (**Tables 5.5, 5.6 and 5.7**). The results were not affected by additional adjustment for family history of hypertension. Subgroup analyses using 24-hour ambulatory and central systolic blood pressure measures also showed consistent findings (**Figure 5.5 and Figure 5.6**).

Table 5.3: LV structural and functional measures divided by birth history and blood pressure subgroups.

	Preterm-Born Adults			Term-Born Adults					
	Normotensive (n=139)	**Hypertensive (n=61)**	***P*[a]**	**Normotensive (n=205)**	**Hypertensive (n=63)**	***P*[b]**	***P*[c]**	***P*[d]**	***P*[e]**
Volumes and Dimensions									
ED Volume (mL)	128.3 ± 26.13	139.3 ± 31.63	.085	149.6 ± 30.64	156.3 ± 29.47	.755	<.001	<.001	.001
ES Volume (mL)	47.72 ± 12.29	51.26 ± 15.27	.360	53.99 ± 14.74	53.04 ± 15.33	.086	<.001	.167	.575
Stroke Volume (mL)	80.57 ± 17.31	87.91 ± 21.03	.073	95.09 ± 20.61	103.2 ± 18.47	.061	<.001	<.001	<.001
ED Volume/BSA (mL/m²)	72.28 ± 10.28	73.95 ± 11.44	.624	81.15 ± 12.43	80.06 ± 12.92	.226	<.001	<.001	.005
ES Volume/BSA (mL/m²)	26.82 ± 5.25	27.41 ± 7.00	.866	29.41 ± 7.09	27.20 ± 7.37	.005	<.001	.849	.883
Stroke Volume/BSA (mL/m²)	45.46 ± 7.50	46.75 ± 7.91	.474	51.88 ± 8.29	52.85 ± 7.79	.665	<.001	<.001	<.001
Length (mm)	90.08 ± 7.01	93.19 ± 7.37	.066	98.76 ± 7.82	101.0 ± 7.91	.437	<.001	<.001	<.001
Average Wall Thickness (mm)	8.63 ± 1.32	9.12 ± 1.23	.063	6.96 ± 1.32	7.49 ± 1.10	.241	<.001	<.001	<.001
Relative Wall Thickness	0.35 ± 0.06	0.36 ± 0.06	.387	0.26 ± 0.05	0.27 ± 0.05	.369	<.001	<.001	<.001
Sphericity Index	0.34 ± 0.06	0.33 ± 0.06	.661	0.30 ± 0.05	0.29 ± 0.06	.835	<.001	<.001	.001
ED Diameter (cm)	50.34 ± 4.98	51.49 ± 5.17	.641	55.0 ± 4.78	55.77 ± 4.62	.934	<.001	<.001	<.001
Myocardium Mass (g)	112.5 ± 26.10	125.9 ± 26.26	.010	101.3 ± 23.46	113.6 ± 23.16	.026	<.001	.017	<.001
Myocardium Mass/BSA (g/m²)	63.31 ± 10.41	67.11 ± 9.67	.074	54.81 ± 9.67	58.04 ± 9.60	.322	<.001	<.001	<.001
Mass/ED Volume (g/mL)	0.88 ± 0.12	0.91 ± 0.12	.177	0.68 ± 0.12	0.73 ± 0.11	.050	<.001	<.001	<.001
Cardiac Index (L/min/m²)	3.20 ± 0.60	3.34 ± 0.67	.129	3.39 ± 0.67	3.51 ± 0.62	.227	.006	.003	.124
Heart Rate (bpm)	70.94 ± 10.54	72.07 ± 10.72	.217	65.98 ± 10.07	66.95 ± 8.85	.406	<.001	.067	.008
RWT > 0.42, n (%)	18 (12.9)	11 (18.0)	.543	0 (0)	1 (1.6)	.111	<.001	.001	.003
Function									
Ejection Fraction (%)	62.92 ± 5.06	63.29 ± 6.73	.559	64.06 ± 5.15	66.38 ± 5.43	.001	.038	<.001	.007
Longitudinal Strain									
Strain (%)	-15.14 ± 2.46	-15.17 ± 2.61	.971	-18.64 ± 3.53	-18.92 ± 3.04	.290	<.001	<.001	<.001
Strain Rate (%/s)	-0.94 ± 0.27	-0.97 ± 0.22	.393	-1.00 ± 0.31	-1.00 ± 0.27	.698	.059	.140	.630

Circumferential Strain									
Basal Strain (%)	-19.22 ± 3.54	-18.39 ± 3.94	.351	-20.02 ± 3.60	-20.12 ± 2.77	.780	.029	.028	.004
Basal Strain Rate (%/s)	-1.17 ± 0.27	-1.12 ± 0.24	.381	-1.14 ± 0.33	-1.11 ± 0.26	.678	.452	.402	.954
Mid Strain (%)	-17.75 ± 2.19	-17.53 ± 2.27	.810	-18.35 ± 2.23	-19.34 ± 2.23	.005	.008	<.001	<.001
Mid Strain Rate (%/s)	-1.05 ± 0.14	-1.05 ± 0.12	.921	-1.04 ± 0.20	-1.04 ± 0.17	.826	.506	.757	.963
Apical Strain (%)	-20.23 ± 3.56	-19.97 ± 4.37	.858	-22.35 ± 3.38	-22.78 ± 3.25	.265	<.001	<.001	<.001
Apical Strain Rate (%/s)	-1.42 ± 0.34	-1.47 ± 0.38	.355	-1.49 ± 0.45	-1.53 ± 0.39	.383	.069	.028	.380

Group characteristics presented as mean ± SD or n (%). *P* values adjusted for sex and age. BSA indicates body surface area; ED, end-diastolic volume; ES, end-systolic volume; RWT, relative wall thickness.

***P**[a]* preterm-born NT vs preterm-born HT

***P**[b]* term-born NT vs term-born HT

***P**[c]* preterm-born NT vs term-born NT

***P**[d]* preterm-born NT vs term-born HT

***P**[e]* preterm-born HT vs term-born HT

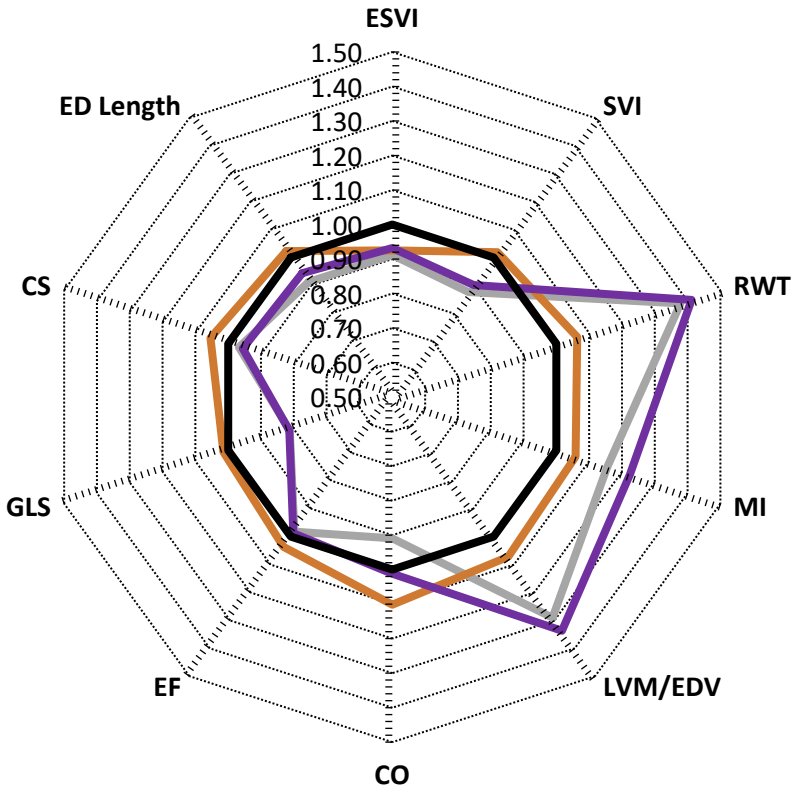


Figure 5.2: Radar plot showing the change in LV parameters across blood pressure and birth history subgroups.

The black reference line (at 1.00) represents the term-born normotensive individuals. Each parameter for the other groups is shown as a ratio, relative to term-born normotensive individuals. While differences in LV parameters in the term-born hypertensive group (orange) were relatively small compared to the term-born normotensive group, both preterm-born normotensive (grey) and hypertensive (purple) individuals had significant LV structural and functional changes. CO indicates cardiac output; CS, mid-ventricular peak systolic circumferential strain; ED length, end-diastolic length; EF, ejection fraction; ESVI, end-systolic volume index; GLS, global longitudinal peak systolic strain; LVM/EDV, left ventricular mass to end-diastolic volume ration; MI, mass index; RWT, relative wall thickness; SVI, stroke volume index.

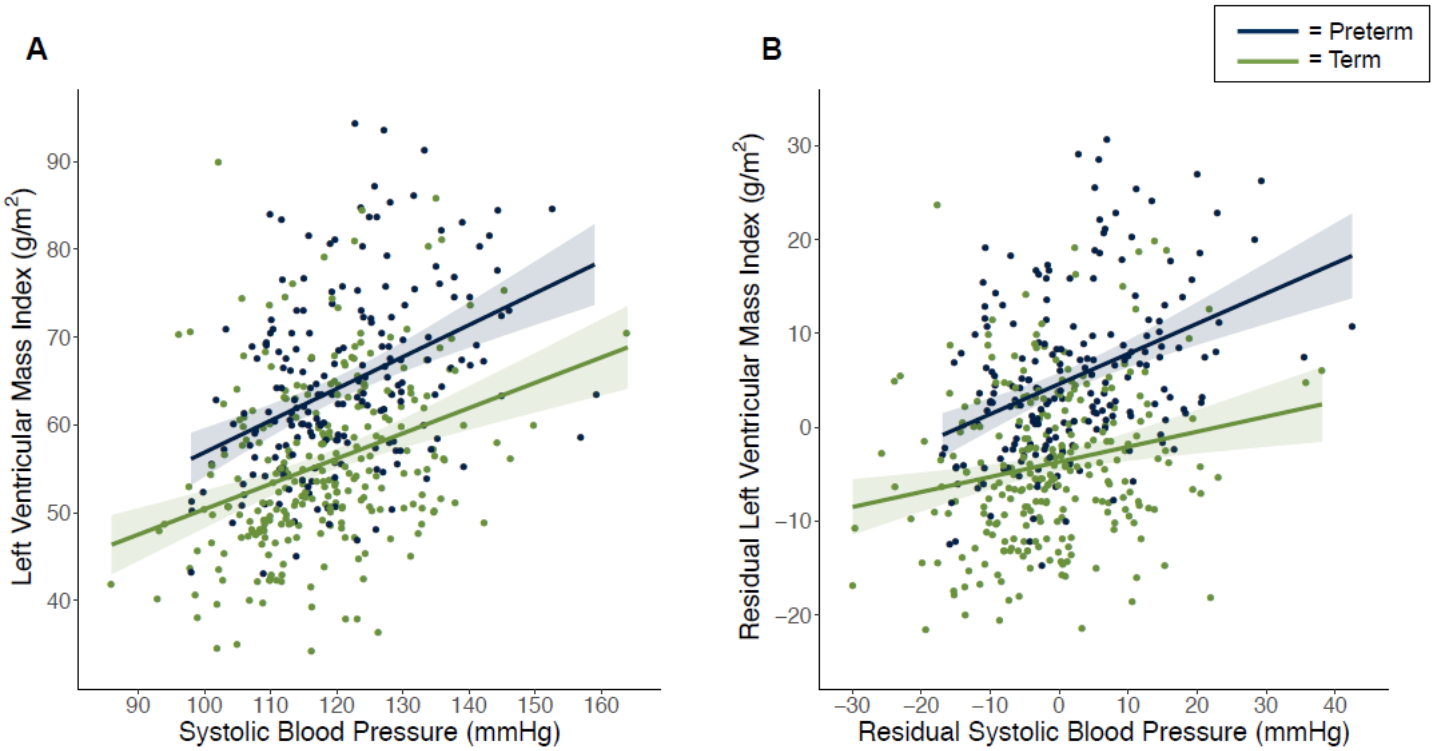


Figure 5.3: Relationship between systolic blood pressure and LVMI in preterm- and term-born adults. **A**, Scatterplot for preterm-born (R^2=16.3%, P<0.001) and term-born (R^2=11.0%, P<0.001) adults. **B**, Partial regression plot with adjustment for age, sex, birthweight z-score and body mass index demonstrates a stronger relationship in preterm-born than term-born adults (R^2=14.6%, P<0.001 vs R^2=3.72%, P=0.002).

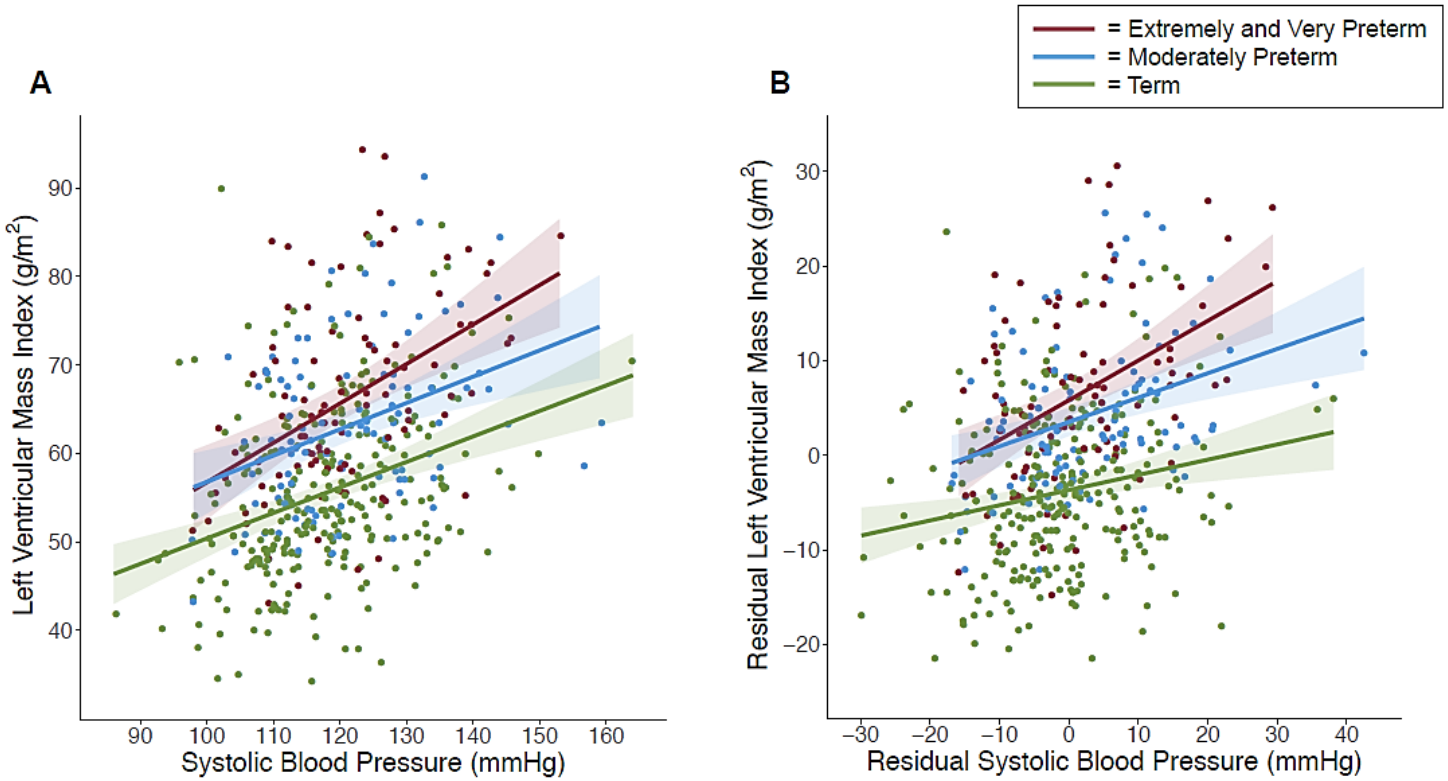


Figure 5.4: Relationship between systolic blood pressure and LVMI based on gestational age categories. **A**, Scatterplot. Extremely/very preterm (R^2=23.1%, P<0.001); moderately preterm (R^2=13.6%, P<0.001); term (R^2=13.6%, P<0.001). **B**, Partial regression plot adjusting for age, sex, birthweight z-score and body mass index. Extremely/very preterm: R^2=17.5%, P<0.001; moderately preterm: R^2=12.7%, P<0.001; term: R^2=3.72%, P=0.002.

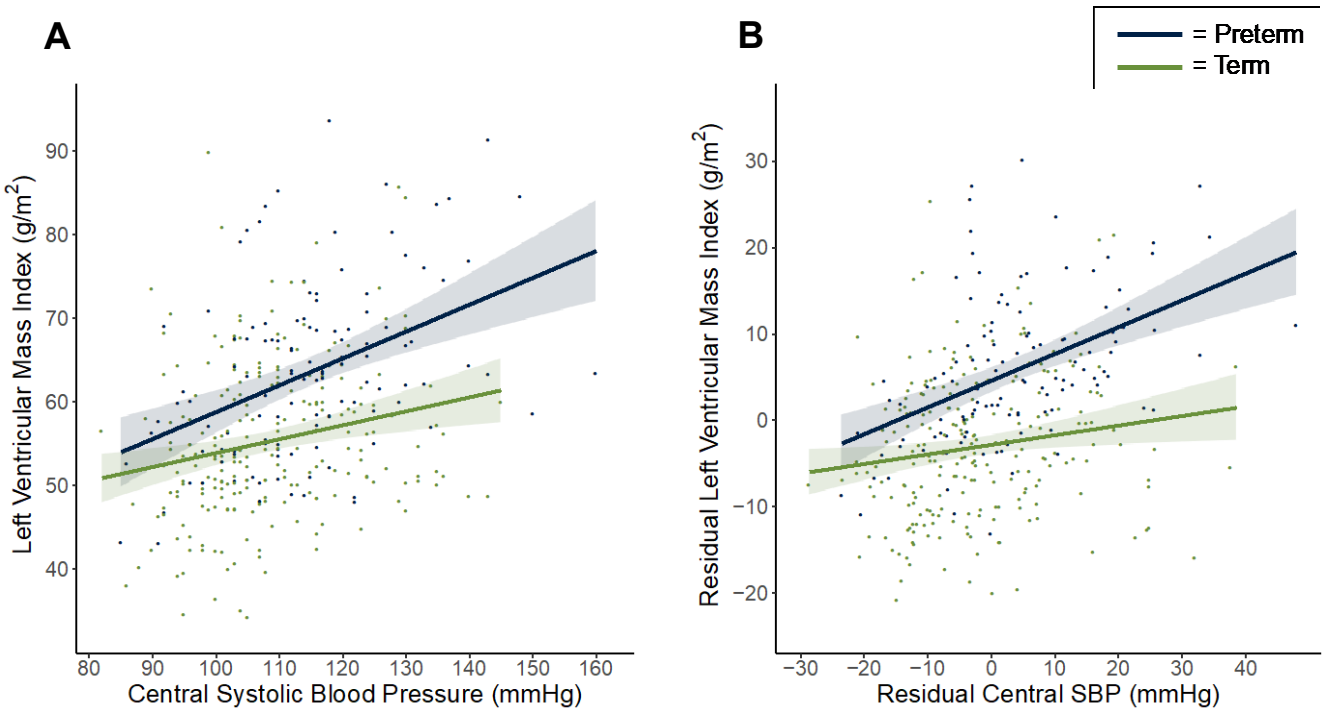


Figure 5.5: Relationship between central systolic blood pressure and LV mass index in preterm-born and term-born adults. **A**, Scatterplot demonstrating the relationship between systolic blood pressure and LV mass index in preterm-born (blue) and term-born (green) young adults. There was a significant relationship in both preterm- and term-born young adults for central systolic blood pressure vs LV mass index (R^2=16.9%, P<.001 and R^2=4.58%, P=.001). The slope for this relationship was greater in the preterm- than term-born adults (0.312 vs 0.171g/m^2 per 1mmHg elevation in systolic blood pressure) (ANCOVA P<.001). **B**, Partial regression plot demonstrating the relationship between systolic blood pressure residuals and LV mass index residuals in preterm-born and term-born young adults, with adjustment for age, sex, birthweight z-score and body mass index. There was a stronger relationship between central systolic blood pressure and LV mass index in the preterm- compared to term-born young adults (R^2=18.1%, P<.001 and R^2=2.16%, P=.03) and a greater slope in the preterm-born young adults (0.299 vs 0.103g/m^2 per 1mmHg elevation in systolic blood pressure) (ANCOVA P<.001).

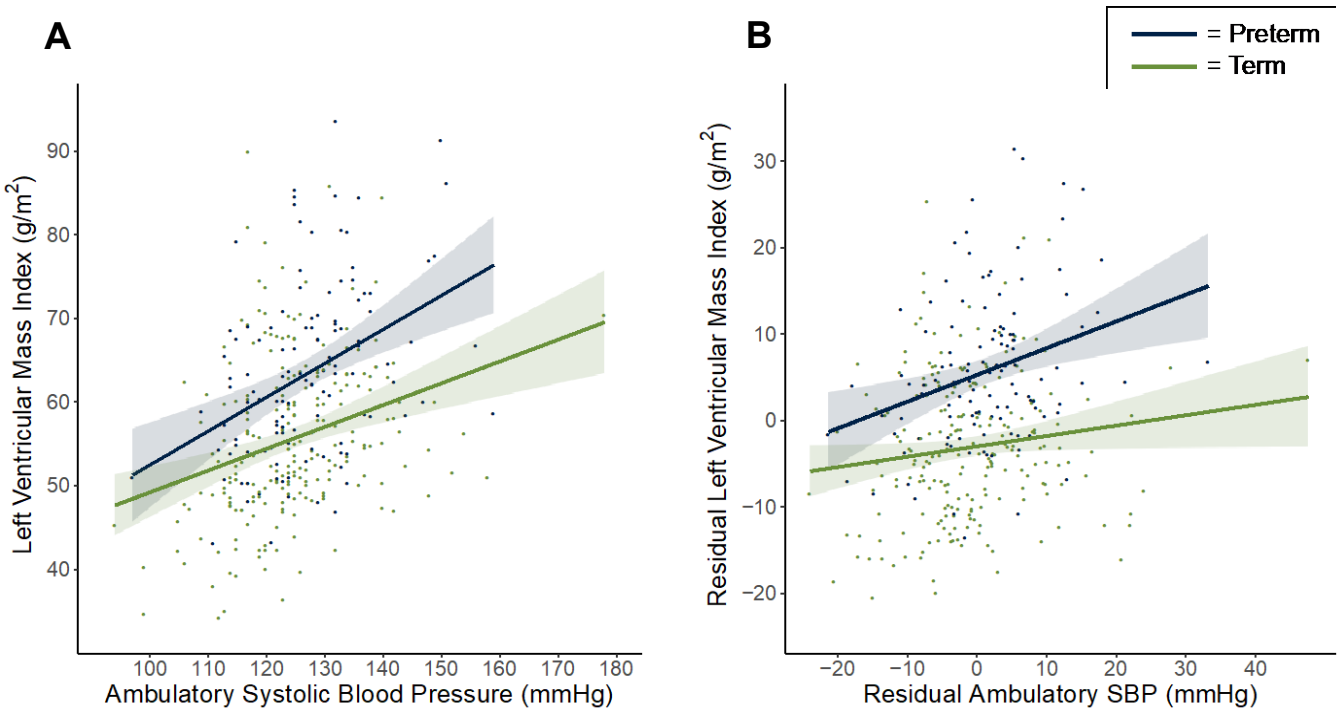


Figure 5.6: Relationship between 24-hour ambulatory systolic blood pressure and LV mass index in preterm-born and term-born adults. **A**, Scatterplot demonstrating the relationship between systolic blood pressure and LV mass index in preterm-born (blue) and term-born (green) young adults. There was a significant relationship in both preterm- and term-born young adults for 24-hour systolic blood pressure vs LV mass index (R^2=14.6%, P<.001 and R^2=8.89%, P<.001). The slope for this relationship was greater in the preterm- than term-born adults (0.413 vs 0.283g/m^2 per 1mmHg elevation in systolic blood pressure) (ANCOVA P<.001). **B**, Partial regression plot demonstrating the relationship between systolic blood pressure residuals and LV mass index residuals in preterm-born and term-born young adults, with adjustment for age, sex, birthweight z-score and body mass index. There was a stronger relationship for 24-hour systolic blood pressure vs LV mass index in the preterm- compared to term-born young adults (R^2=10.1%, P=.001 and R^2=1.64%, P=.06), which was also indicated by the greater slope in the preterm-born adults (0.326 vs 0.113g/m^2 per 1mmHg elevation in systolic blood pressure) (ANCOVA P<.001).

Table 5.4: Multivariable regression coefficients for systolic blood pressure in multiple regression models of key LV parameters.

CMR Parameters	Model	Preterm-born Young Adults				Term-born Young Adults			
		B (per 1mmHg SBP)	95% confidence intervals		P value	B (per 1mmHg SBP	95% confidence intervals		P value
			Lower Bound	Upper Bound			Lower Bound	Upper Bound	
Myocardium	Unadjusted	0.363	0.247	0.478	<.001	0.288	0.189	0.387	<.001
Mass/BSA (g/m²)	**Adjusted**	0.318	0.209	0.427	<.001	0.157	0.060	0.254	.002
Ejection	Unadjusted	0.024	-0.044	-0.092	.491	0.066	0.010	0.123	.022
Fraction (%)	**Adjusted**	0.024	-0.049	0.097	.516	0.079	0.017	0.140	.013
ED Volume/BSA	Unadjusted	0.188	0.060	0.315	.004	0.139	0.005	0.273	.042
(mL/m²)	**Adjusted**	0.165	0.034	0.296	.054	0.092	-0.043	0.228	.181
Mass/ED	Unadjusted	$2.72x10^{-3}$	1.2710^{-3}	4.1710^{-3}	<.001	$2.45x10^{-3}$	1.2210^{-3}	3.6710^{-3}	<.001
Volume (g/mL)	**Adjusted**	$2.38x10^{-3}$	$8.15x10^{-4}$	$3.94x10^{-3}$	.003	$1.08x10^{-3}$	$-2.31x10^{-4}$	$2.40x10^{-3}$	.106

B indicates unstandardised coefficients with 95% confidence intervals; BSA indicates body surface area; CMR, cardiac magnetic resonance; ED, end-diastole; SBP, systolic blood pressure. The regression coefficients for systolic blood pressure with the individual CMR parameters (dependent variables) are shown for both unadjusted (bivariate) and adjusted (multivariable) regression models. In multivariable models, independent variables were systolic blood pressure, age, sex, birth weight z-score, and body mass index (multivariable regression coefficients shown for systolic blood pressure).

Table 5.5: Systolic blood pressure versus LV parameter regression line comparisons between preterm-born and term-born young adults.

CMR Parameters	Model	Sum square	F	P value
Myocardium Mass/BSA (g/m²)	Unadjusted	7080.0	81.6	<.001
	Adjusted	8141.8	122.0	<.001
Mass/ED volume (g/mL)	Unadjusted	4.018	299.4	<.001
	Adjusted	4.041	310.7	<.001

BSA indicates body surface area; ED, end-diastole. In multivariable models, independent variables were systolic blood pressure, age, sex, birth weight z-score, and body mass index.

Table 5.6: Multivariable regression coefficients for systolic blood pressure in multiple regression models of key LV parameters within gestational age group categories.

CMR Parameters	Model	Very and Extremely Preterm-Born Adults (< 32 weeks' gestation)				Moderately Preterm-Born Adults (32 – 36 weeks' gestation)				Term-Born Adults (> 37 weeks' gestation)			
		B (per 1mmHg SBP)	95% confidence intervals		*P* Value	B (per 1mmHg SBP)	95% confidence intervals		*P* value	B (per 1mmHg SBP)	95% confidence intervals		*P* value
			Lower Bound	Upper Bound			Lower Bound	Upper Bound			Lower Bound	Upper Bound	
Myocardium Mass/BSA (g/m²)	Unadjusted	0.475	0.297	0.654	<.001	0.281	0.135	0.427	<.001	0.288	0.189	0.387	<.001
	Adjusted	0.394	0.213	0.574	<.001	0.250	0.113	0.387	<.001	0.157	0.060	0.254	.002
Ejection Fraction (%)	Unadjusted	0.068	-0.036	0.171	.197	-0.010	-0.102	0.082	.836	0.066	0.010	0.123	.022
	Adjusted	0.100	-0.015	0.216	.088	-0.031	-0.129	0.067	.531	0.079	0.017	0.140	.013
ED Volume/BSA (mL/m²)	Unadjusted	0.170	0.010	0.330	.037	0.192	-0.001	0.386	.052	0.139	0.005	0.273	.042
	Adjusted	0.157	-0.016	0.329	.074	0.179	-0.011	0.393	.069	0.092	-0.043	0.228	.181
Mass/ED Volume (g/mL)	Unadjusted	$4.47x10^{-3}$	$2.16x10^{-3}$	$6.78x10^{-3}$	<.001	$1.53x10^{-3}$	$-5.40x10^{-5}$	$3.12x10^{-3}$	.058	$2.44x10^{-3}$	$1.22x10^{-3}$	$3.67x10^{-3}$	<.001
	Adjusted	$3.56x10^{-3}$	$1.01x10^{-3}$	$6.11x10^{-3}$	.007	$1.03x10^{-3}$	$-6.83x10^{-4}$	$2.74x10^{-3}$	.235	$1.08x10^{-3}$	$-2.31x10^{-4}$	$2.40x10^{-3}$	.106

B indicates unstandardised coefficients with 95% confidence intervals; BSA, body surface area; CMR, cardiac magnetic resonance; ED, end-diastole; SBP, systolic blood pressure. The regression coefficients for systolic blood pressure with the individual CMR parameters (dependent variables) are shown for both unadjusted (bivariate) and adjusted (multivariable) regression models. In multivariable models, independent variables were systolic blood pressure, age, sex, birth weight z-score, and body mass index (multivariable regression coefficients shown for systolic blood pressure).

Table 5.7: Systolic blood pressure versus LV parameter regression line comparisons between gestational age group categories.

CMR Parameters	Model	Term vs moderately preterm (>$37^{+0/7}$ weeks vs $32^{+0/7}$ – $36^{+6/7}$ weeks)			Term vs very and extremely preterm (>$37^{+0/7}$ weeks vs <$32^{+0/7}$ weeks)			Very and extremely preterm vs moderately preterm (<$32^{+0/7}$ weeks vs $32^{+0/7}$ – $36^{+6/7}$ weeks)		
		Sum square	**F**	**P value**	**Sum square**	**F**	**P value**	**Sum square**	**F**	**P value**
Myocardium Mass/BSA (g/m²)	Unadjusted	3184.7	38.72	<.001	6283.0	70.86	<.001	466.6	5.322	.022
	Adjusted	4290.9	68.55	<.001	6808.1	98.08	<.001	320.2	4.848	.029
Mass/ED volume (g/mL)	Unadjusted	1.711	144.03	<.001	3.661	266.09	<.001	0.310	24.49	<.001
	Adjusted	1.816	162.39	<.001	3.650	272.75	<.001	0.299	23.88	<.001

BSA indicates body surface area; ED, end-diastole. In multivariable models, independent variables were systolic blood pressure, age, sex, birth weight z-score, and body mass index.

5.5 Discussion

In a large cohort of young adults, we have investigated the relationship between systolic blood pressure elevation and LV structure and function in preterm-born individuals using CMR. Although structural and functional LV changes tended towards being greater in hypertensive compared to normotensive young adults born preterm, the majority of comparisons did not reach statistical significance. Normotensive preterm-born young adults had higher LVMI, reduced LV function, and smaller LV volumes compared to both term-born normotensive and hypertensive individuals. Hypertensive preterm-born young adults showed even greater differences compared to the term-born normotensive and hypertensive groups. In regression analyses of systolic blood pressure and LVMI and LVM to LVEDV ratio, there was a leftward shift in the slopes in the young adults born preterm compared to those born at term. In addition, there was a 2.5-fold greater change in LVMI per 1mmHg systolic blood pressure increase in very and extremely preterm-born young adults and a 1.6-fold greater change in LVMI per 1mmHg systolic blood pressure elevation in moderately preterm-born young adults compared to term-born young adults. Futhermore, LVM to LVEDV ratio per 1mmHg systolic blood pressure elevation in the very and extremely preterm-born young adults was 3.4-fold greater compared to those born moderately preterm and 3.3-fold greater compared to those born at term, with no difference between the latter two groups.

Preterm birth occurs during a key period of cardiac development that would normally take place in utero. As the immature heart transitions to the ex utero environment, it must undergo cellular, structural, and functional adaptations to deal with the dramatic shift in pressure and oxygen [237]. In sheep born preterm, this early transition leads to a disruption

in normal postnatal myocardial maturation that may increase later cardiac susceptibility to failure [238]. Hearts from piglets delivered preterm were unable to maintain LVCO when challenged ex vivo with an increased afterload [239]. Similarly, in a rat model of preterm birth conditions, there was accelerated myocardial hypertrophy, diffuse fibrosis, and impaired systolic function in the LV prior to systemic blood pressure elevation [232]. As a result of their reduced LV functional reserve, they were more likely to go into heart failure when hemodynamically challenged with Ang II infusion, though angiotensin receptor blocker treatment prevented the development of cardiac alterations [231]. Human studies from birth through to young adulthood have now demonstrated that LV function and structure are altered in individuals born preterm [215], including an inability to meet the demands of physiological stress in adolescence and young adulthood [233, 234, 240]. The lower myocardial functional reserve seen in preterm-born young adults in response to acute stress may in part explain why the risk of early heart failure is so much greater in this population [12, 241].

Given the underlying morphological impairments in the preterm heart, it is conceivable that blood pressure elevation would have a greater impact on cardiac remodeling in this population. Hypertension is known to cause LV structural and functional adaptations, including wall thickening and impaired systolic and diastolic function, especially with more advanced disease in older populations [242-244]. Our study adds to the limited cardiac imaging data available in young adults with mild to moderate hypertension using CMR, which is widely considered the gold standard modality for assessing LV structure and function [245]. While the majority of LV parameters did not differ significantly between normotensive and hypertensive term-born young adults, LVEF was higher in the hypertensive group, with a significant, positive association between

LVEF and systolic blood pressure that was not seen in those born preterm. Higher mid-ventricular peak systolic circumferential strain accompanied the higher LVEF in the term group, which could indicate systolic hypercontractility to compensate for increased afterload. This was not observed in the preterm-born young adults, which may suggest an inability to adapt to chronic hemodynamic insults. Interestingly, in the preterm-born young adults, we did not see the extent of LV structural or functional changes we might have expected when comparing hypertensive and normotensive individuals. Nevertheless, when quantifying the continuous relationship between LV parameters and increasing systolic blood pressure, there was a steeper slope in the adjusted regression line between LVMI and systolic blood pressure in the preterm group that increased monotonically with the degree of prematurity. Furthermore, the lefttward shift in the preterm regression line meant that LVMI and LVM to LVEDV ratio were greater for any given systolic blood pressure. This suggests that blood pressure alone is not the driving factor for the observed LV differences between preterm- and term-born young adults and that there are unique drivers of increased cardiovascular risk in the preterm population [246].

A limitation of the study was that the main analyses were based on single arm clinic blood pressure measurements. In spite of this, we were able to perform subgroup analyses in ~75% of the cohort using 24-hour and surrogate central blood pressure measures, which showed consistent results. Future studies to more accurately quantify the effect of pulse pressure amplification are needed, using methods such as CMR aortic distension waveforms to assess central systolic blood pressure [247]. Although we were able to identify that the greatest rate of increase in LVMI and LVM to LVEDV ratio in relation to increasing systolic blood pressure was in those born <32 weeks' gestation (very preterm), our sample size of individuals born <28 weeks' gestation (extremely preterm) was too

small to investigate these groups in isolation. In a study by Goss et al. [248], it was shown that extremely preterm-born adolescents and young adults had smaller LV volumes and mass, as well as a more hypercontractile LV compared to their term-born peers. However, all participants in that study were normotensive. Given that this more premature group is at an exponentially greater risk of early heart failure [12], further work is needed to understand cardiac remodelling in response to hypertension in the most premature individuals. My research has shown alterations in cardiac structure and function in those born preterm. The next exciting topic will be whether fibrosis affects function, as shown in some animal models. Most of my DPhil time has been used to do the data collection and analysis of CMR structural and functional changes. My supervisor, Dr Adam Lewandowski is currently investigating both diffuse and focal fibrosis in the adult preterm population.

Due to DPhil time constraints, I did not include diastolic myocardial relaxation parameters. Besides, due to retrospective perinatal data collection in a significant proportion of our cohort, we did not have complete information on all perinatal complications, such as infection rates, days of ventilation and hypertensive pregnancies. Further studies will be needed to explore whether these factors affect the findings. Nevertheless, our complete gestational age and birth weight data allowed us to determine that the degree of prematurity is important to how the preterm heart responds to blood pressure elevation and could add value to young adult risk stratification. While our study sample size of stage II hypertensive individuals was limited, as the majority of young adults in this blood pressure range would be on medication, the leftward shift in the relationship between LV changes and systolic blood pressure suggests that, even in the early stages of blood pressure elevation, appropriate clinical screening and monitoring may

be warranted. Further research is needed to investigate this and to exclude the possibility of co-association between LV changes and higher systolic blood pressure.

5.6 Conclusion

In summary, young adults born preterm have an altered cardiac structure and function compared to their term-born peers, with greater remodelling in response to systolic blood pressure elevation. Further research should include serial study visits with cardiac imaging in the same individuals over time to better understand how the heart remodels in response to blood pressure elevation and which factors may increase or decrease risk in order to guide potential interventions. Given that preterm birth affects over 10% of live births and that survival of even the most premature individuals continues to rise, life-long clinical follow-up may be needed in order to prevent the emergence of early CVD in this population.

CHAPTER 6

STUDY 3 RESULTS

Cardiac Adaptations Following a 16-Week Prescribed Aerobic Exercise Intervention in Young Adults

6.1 Abstract

Background: No trials have previously investigated whether prescribed aerobic exercise training is effective for beneficial cardiac remodelling in young adults with elevated blood pressure, particularly in people born preterm, who are known to have potentially adverse cardiac alterations.

Methods: 203 young adults aged 18 to 35 years old with different birth histories and elevated blood pressure recorded on 24-hour ambulatory blood pressure monitoring (115/75 mmHg and 159/99 mmHg) were randomised to either a 16-week exercise training programme or to control group. Of these, 100 participants underwent paired CMR at baseline and at their 16-week follow-up visit, of which 42 were born preterm and 58 were

born at term. The primary aim was to investigate LV and RV structural and functional changes following aerobic training in the full group including both preterm- and term-born participants. The secondary outcome included assessing LV and RV structural and functional changes within the preterm- and term-born subgroups.

Results: In the full cohort of randomised young adults, aerobic training led to modest biventricular changes. Aerobic training increased LV length [2.9% increase] vs comparison group [0.6% increase], adjusted mean difference 1.64mm [95% CI: 0.85, 2.44]) and LV mid peak systolic circumferential strain (aerobic training [5.5% increase] vs comparison group [0.2% increase], adjusted mean difference -0.84%, [95% CI: -1.46, -0.21]). Aerobic training also significantly increased indexed RVSV (7.8%) due to an increase in RVEDVI (3.7%) in the exercise group. Within the preterm group, improvements in myocardial deformation were evident, with significant changes with aerobic training. LV global peak systolic longitudinal strain increased with aerobic training [11.7% increase] vs comparison [2.4% increase], adjusted mean difference -1.43%, [95% CI: -2.08, -0.79]). RV global peak systolic longitudinal strain also increased with aerobic training [13.6% increase] vs comparison group [3.0% increase]. In the term group, more significant changes in LV and RV structure and function were observed.

Conclusions: A 16-week moderate to high intensity aerobic exercise training intervention leads to modest biventricular cardiac adaptations in young adults. In preterm-born individuals, cardiac adaptations appeared to be primarily improvements in myocardial strain parameters, while the term-born individuals showed greater changes in volumetric parameters.

Keywords: Young Adults, Cardiac Remodelling, Cardiac Imaging, MRI, Hypertension, Prehypertension, Preterm Birth, Randomised Trial, Exercise

Publication: The results presented in Chapter 6 are currently being developed into a manuscript for future submission.

6.2 Introduction

The risk of cardiovascular events in association with elevated blood pressure tracks from young adulthood [249]. As a result, early preventive measures and interventions are essential to prevent hypertension-induced adverse cardiac remodelling. Exercise contributes to reduced blood pressure in normotensive and hypertensive individuals [250], leading to LVH regression [251] and improved survival [252]. However, in predefined subgroups of young adults with elevated blood pressure or a history of preterm birth, the possible intervention effects are still unknown [194]. Furthermore, the majority of exercise interventions have been done in older adults, and it remains unclear if these measures are effective in younger populations [169].

In addition, previous meta-analysis has reported evidence of lower exercise capacity in children and adults born preterm with or without BPD [253]. This is supported by recent observational studies that have shown preterm-born young adults have reduced exercise capacity that may be due to their reduction in myocardial functional reserve [109, 254]. Longitudinal studies in previously sedentary healthy young individuals have indicated beneficial cardiac adaptations after one year of intensive endurance training [164]. A structured exercise programme combining aerobic training together with wrist

worn physical activity self-monitoring could aid in understanding the interactions between physical activity and familial factors including prematurity and how this affects how the heart adapts to the intervention [255].

A recent meta-analysis has described a unique pattern of cardiac remodelling across gestational age categories in preterm-born individuals that is first seen at birth and continues into adulthood [94]. The findings have shown that preterm-born individuals have smaller LVEDD, lowered LV diastolic function, reduced RV peak systolic longitudinal strain function across all ages, and an increased rate of LVM change from childhood to adulthood [215]. Prematurity-related hypertension may further reduce cardiac performance [57], thus heightening the risk for early heart failure [256]. Early life events including sudden hemodynamic changes that occur after preterm birth [21] and neonatal comorbidities are believed to alter cardiac and vascular development as early as infancy and persist into adulthood [257]. It is therefore important to understand the potential benefits of prescribed exercise training on cardiac remodelling in preterm adults with evidence of elevated blood pressure [256]. We therefore conducted the first randomised controlled trial investigating whether aerobic exercise training leads to favourable cardiac adaptations among young adults. To do this, I investigated LV and RV changes by CMR at baseline and after 16 weeks of a prescribed aerobic exercise training programme compared to usual care, with a subgroup of participants born preterm.

6.3 Methods

6.3.1 Study population

This chapter includes young adults with elevated blood pressure where the participants were randomised to either an aerobic training program or control group. Half of the participants underwent a detailed cardiovascular phenotyping including a CMR scan to characterise LV and RV adaptation in response to exercise intervention. A total of 119 individuals were included in the final analysis, of which 46 were born preterm **(Study 3, Group A)** and 73 were born at term **(Study 3, Group B)** as shown in **Figure 6.1**. There were 100 individuals with paired V1 and V2 CMR scans. The full details of the recruitment cohorts are provided in Chapter 2 on page 50.

6.3.2 Study visit

All participants fasted for a minimum of six hours, consuming only water before attending a study visit at the CCRF and OCMR. All participants were first screened for inclusion/exclusion to determine eligibility for the trial. Study visits, including CMR, were then completed at baseline (V1) and at the 16-week follow up (V2) following either the exercise intervention or usual care.

Trained clinical research investigators completed all measurements. Participants were screened prior to inclusion. Individuals who currently engaged in regular aerobic exercise training for greater than one hour for at least three days in a week were excluded from the trial. Data were coded with the subject generated identification IDs (e.g. TPH001)

to ensure anonymity and blinded analysis. The following methods were used for this chapter as described in detail in chapter three.

- 3.2 Anthropometry and blood samples
- 3.3 Resting brachial blood pressure
- 3.4 24-hour ambulatory blood pressure monitoring
- 3.7 Cardiac magnetic resonance
    - 3.7.1 Ventricles: volumes and mass
    - 3.7.2 LV: dimensions
    - 3.7.3 Feature tracking analysis
- 3.8 TEPHRA study protocols assessments
    - 3.8.1 Randomisation
    - 3.8.2 Study interventions
    - 3.8.3 Comparison group
    - 3.8.4 Compliance
    - 3.8.5 Withdrawals and protocol violations
    - 3.8.6 Publication status

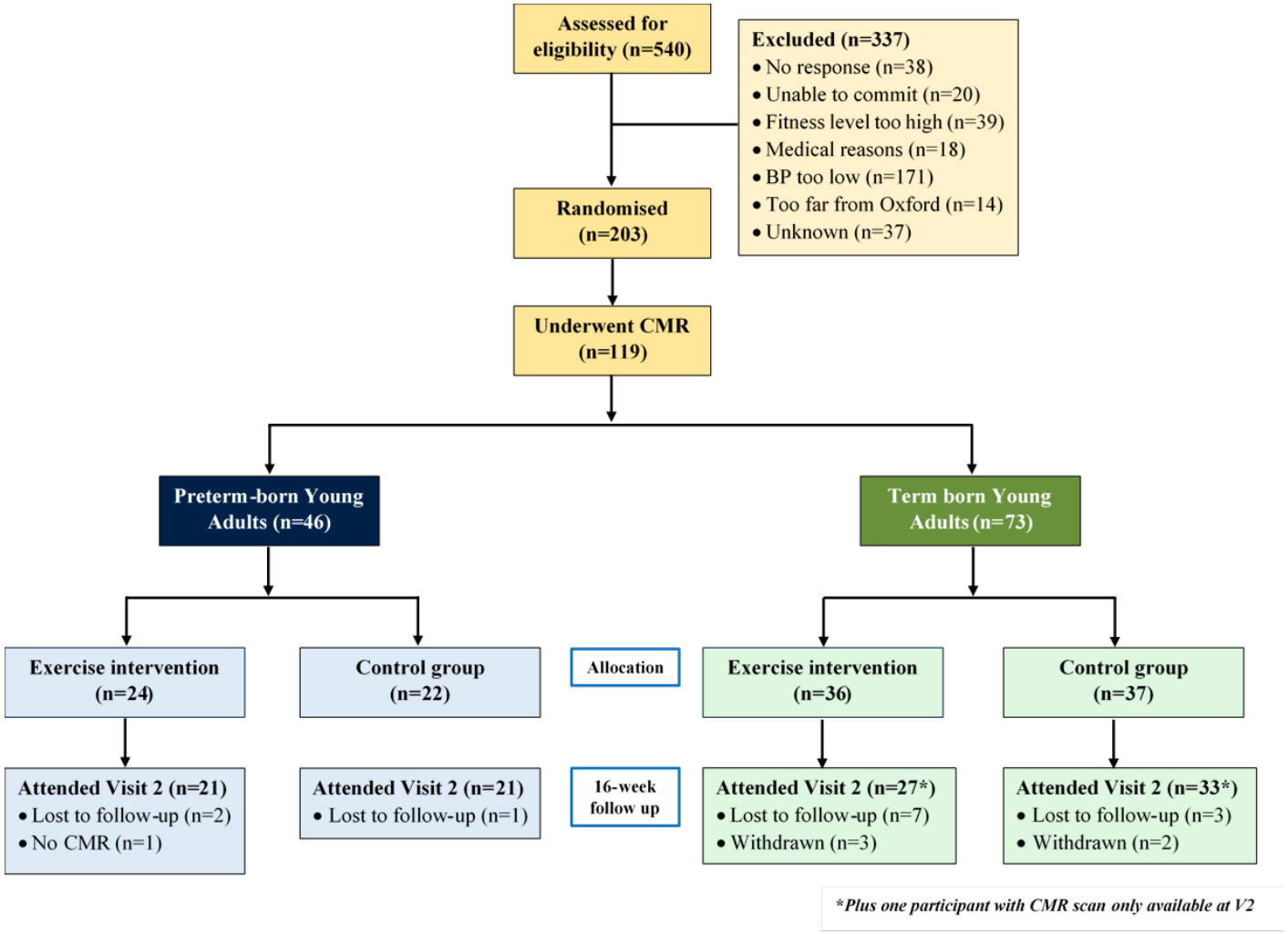


Figure 6.1: TEPHRA participant flow chart. This figure shows the pathway of recruitment and retention of participants. BP indicates blood pressure; CMR, cardiovascular magnetic resonance.

6.3.3 Statistical analysis

Statistical analysis was performed using SPSS (version 25, IBM, Armonk, New York) and R version 3.6.1 (R Foundation for Statistical Computing). All statistical analyses were done based on two phases: 1) comparison between the aerobic training and control groups in randomised participants with preterm- and term-born adults and 2) comparisons within the separate preterm- and term-born subgroups, comparing the aerobic exercise training and control groups. The primary end points were the change in LV and RV structure and function after 16 weeks of aerobic exercise training. The secondary endpoints were the change in LV and RV structure and function in response to aerobic exercise training within the preterm- and term-born subgroups. ANCOVA was conducted to answer the primary endpoint and for secondary endpoints. ANCOVA models for the analyses in the full cohort were adjusted for baseline minimisation factors (age category, sex, and gestational age category), with treatment groups as covariates. These analyses were restricted to participants with non-missing data. ANCOVA models for secondary analyses within the preterm- and term-born subgroups were adjusted for age and sex, with treatment groups as covariates.

6.4 Results

6.4.1 Baseline participant characteristics divided by randomised group allocations

A total of 203 participants were randomised, of which 119 underwent CMR: n=46 preterm versus n=73 term-born adults at baseline (V1). At the 16-week follow up (V2), n=42

preterm participants (91%) and n=60 term participants (82%) returned for the second visit. Two of the term participants, however, did not have V1 CMR scans, which is why there were a total of n=100 individuals included in the final paired analyses (**Figure 6.1**). There were no significant differences between the groups in baseline participant characteristics as shown in **Table 6.1**.

6.4.2 Cardiac and aortic adaptations in randomised participants for the full CMR cohort

6.4.2.1 LV, RV and aortic structural and functional adaptations to exercise

Several LV and RV cardiac structural and functional parameters were altered with aerobic training compared with the control group (**Table 6.2**). At 16-week follow up, LV changes included greater LV length with aerobic training (95.98 to 98.77mm (2.9% increase) vs comparison group 96.49 to 97.03mm (0.6% increase), adjusted mean difference: 1.64mm, [95% CI: 0.85,2.44]). LVEF also increased with aerobic training (65.23 to 65.78% (0.8% increase) vs comparison group 64.34 to 64.19% (0.2% decrease), adjusted mean difference: 1.41%, [95% CI: 0.07,2.75]).

Table 6.1: Baseline participant characteristics divided by randomised group allocation.

	Randomised participants at V1 (n=203)		Randomised participants with CMR at V1 (n=119)	
	Exercise Intervention (n=102)	**Control (n=101)**	**Exercise Intervention (n=60)**	**Control (n=59)**
Demographics and Anthropometrics				
Age (years)	27.9 ± 4.10	28.0 ± 4.05	28.2 ± 4.38	28.1 ± 4.32
Male, n (%)	51 (50.0)	48 (47.5)	30 (50.0)	28 (47.5)
Height (cm)	172 ± 8.99	172 ± 9.76	173 ± 8.64	172 ± 10.5
Weight (kg)	74.9 ± 13.15	73.6 ± 13.22	74.5 ± 13.1	74.4 ± 14.3
BMI (kg/m²)	25.2 ± 3.74	24.9 ± 3.38	24.7 ± 3.33	25.2 ± 3.57
Birth Weight (grams)	3023 ± 870	2996 ± 884	2827 ± 966	2835 ± 1003
Birth Weight (z-score)	0.05 ± 1.16	0.02 ± 1.07	0.14 ± 1.12	0.13 ± 1.19
Gestational Age (weeks)	37.68 ± 3.69	37.53 ± 4.24	36.45 ± 3.92	36.55 ± 4.62
< 32 weeks, n (%)	9 (8.80)	8 (7.90)	8 (13.3)	7 (11.9)
32 – 36 weeks, n (%)	18 (17.6)	19 (18.8)	16 (26.7)	15 (25.4)
> 37 weeks, n (%)	75 (73.5)	74 (73.3)	36 (60.0)	37 (62.7)
Biochemistry				
Total Cholesterol (mmol/L)	4.38 ± 1.04	4.29 ± 1.35	4.44 ± 0.97	4.43 ± 1.15
HDL (mmol/L)	1.38 ± 0.30	1.38 ± 0.38	1.40 ± 0.30	1.37 ± 0.32
LDL (mmol/L)	2.82 ± 0.75	2.62 ± 0.69	2.82 ± 0.64	2.71 ± 0.73
Triglycerides (mmol/L)	1.25 ± 0.97	1.39 ± 1.25	1.18 ± 0.90	1.36 ± 1.21
High Sensitivity CRP (mg/L)	2.27 ± 3.42	1.51 ± 2.91	2.02 ± 3.44	1.72 ± 3.55
Glucose (mmol/L)	4.79 ± 0.61	4.86 ± 0.51	4.82 ± 0.40	4.86 ± 0.44
Insulin (pmol/L)	57.1 ± 46.20	58.6 ± 59.40	52.9 ± 27.1	56.1 ± 58.8
Homa-B (%)	110.3 ± 75.34	98.5 ± 32.38	100.6 ± 27.7	94.0 ± 24.2
Homa-S (%)	117.3 ± 49.46	128.7 ± 60.70	120.3 ± 47.3	130.8 ± 54.9
Homa-IR	1.09 ± 0.82	1.04 ± 0.79	0.98 ± 0.45	0.91 ± 0.40
Brachial Blood Pressure (mm Hg)				
Resting Systolic	122.0 ± 11.49	121.7 ± 10.22	121.8 ± 11.4	122.2 ± 10.9
Resting Diastolic	75.7 ± 9.69	76.9 ± 8.31	75.9 ± 9.22	77.4 ± 7.85
Awake Average Ambulatory Systolic	129.1 ± 9.30	128.2 ± 8.68	129.2 ± 10.2	128.8 ± 8.58
Awake Average Ambulatory Diastolic	77.0 ± 6.37	77.4 ± 7.46	77.3 ± 6.64	77.8 ± 7.36

Values are presented as mean ± SD or n (%). BMI indicates body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL. low-density lipoprotein.

RV changes were more prominent in response to aerobic training. At 16-week follow up, absolute RVM did not change with aerobic training but showed a decrease compared to the control group in the adjusted model (35.42 to 35.55grams (0.4% increase) vs controls 34.49 to 35.26grams (2.2% increase), adjusted mean difference: -1.32grams, [95% CI: -2.4,-0.24]). There was a borderline significant difference in RVMI with aerobic training (0.05% decrease) vs comparison group (2.17% increase). RVEF increased with aerobic training (3.6% increase) vs comparison group (0.9% increase) as did RVEDVI (3.7% increase) vs comparison group (1.0% decrease).

Absolute and indexed RVSV also increased with aerobic training (RVSV: 88.61 to 95.63mL (7.9% increase) vs comparison group 90.3 to 89.7 mL (0.7% decrease), adjusted mean difference: 6.51mL, [95% CI: 2.2,10.81]; RVSVI: 46.8 to 50.45mL/m² (7.8% increase) vs comparison group 47.85 to 47.64mL/m² (0.4% decrease), adjusted mean difference: 3.64 mL/m², [95% CI: 1.37,5.92]). Furthermore, RVCO and RVCI increased with aerobic training (RVCO: 4.5% increase) vs comparison group (2.4% decrease); RVCI: (4.6 % increase) vs comparison group (2% decrease). **Table 6.2** shows LV, RV and aortic structural and functional adaptations in response to the 16-week aerobic exercise intervention in the full CMR cohort of participants.

Table 6.2: LV, RV and aortic structural and functional adaptations in response to a 16-week exercise intervention in the full CMR cohort

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted
Structural and functional						
LV Ejection Fraction (%)						
Baseline	60	65.23 (5.25)	59	64.34 (6.15)	-	-
16 weeks	48	65.78 (6.12)	54	64.19 (5.63)	1.58 (-0.62,3.97)	**1.41 (0.07,2.75)**
LV Length (mm)						
Baseline	60	95.98 (8.12)	59	96.49 (9.2)	-	-
16 weeks	48	98.77 (7.62)	54	97.03 (9.32)	1.74 (-1.8,5.12)	**1.64 (0.85,2.44)**
LV Stroke Volume (mL)						
Baseline	60	89.61 (15.81)	59	92.59 (20.94)	-	-
16 weeks	48	92.72 (19.14)	54	91.9 (18.75)	0.82 (-8.07,6.9)	3.11 (-0.44,6.66)
LV Myocardium Mass (g)						
Baseline	60	109.73 (23.3)	59	112.22 (24.96)	-	-
16 weeks	48	109.92 (23.49)	54	111.63 (23.82)	-1.71 (-10.63,9.09)	-1.26 (-3.89,1.36)
LV Cardiac Output (L/min)						
Baseline	60	5.86 (1.16)	59	5.91 (1.43)	-	-
16 weeks	47	5.84 (1.14)	54	5.75 (1.23)	0.09 (-0.35,0.60)	0.12 (-0.18,0.42)
LV Mass/ED Volume (g/mL)						
Baseline	60	0.80 (0.11)	59	0.79 (0.12)	-	-
16 weeks	48	0.78 (0.13)	54	0.79 (0.12)	0.00 (-0.05,0.04)	-0.01 (-0.04,0.01)
LV ES Volume/BSA (mL/m²)						
Baseline	60	25.4 (5.31)	59	27.72 (7.98)	-	-
16 weeks	48	25.38 (5.41)	54	28.15 (8.16)	-2.77 (-4.99,0.58)	-1.18 (-2.87,0.50)
LV ED Volume/BSA (mL/m²)						
Baseline	60	72.83 (8.71)	59	76.75 (13.77)	-	-
16 weeks	48	74.21 (8.76)	54	76.4 (12.81)	-2.19 (-5.84,2.53)	1.11 (-0.74,2.95)
LV Stroke Volume/BSA (mL/m²)						
Baseline	60	47.43 (6.17)	59	49.21 (8.69)	-	-
16 weeks	48	48.83 (7.4)	54	48.82 (7.78)	0.01 (-3.22,2.93)	1.73 (-0.03,3.49)
LV Myocardium Mass/BSA (g/m²)						
Baseline	60	57.92 (8.75)	59	59.77 (9.88)	-	-
16 weeks	48	57.71 (9.03)	54	59.31 (9.43)	-1.61 (-4.90,2.28)	-0.24 (-1.54,1.06)
LV Cardiac Index (L/min/m²)						
Baseline	60	3.10 (0.5)	59	3.14 (0.63)	-	-
16 weeks	47	3.08 (0.49)	54	3.06 (0.52)	0.02 (-0.17,0.25)	0.06 (-0.09,0.21)
Aortic Distensibility ($mmHg^{-1}x10^3$)						
Baseline	57	6.56 (2.25)	54	6.50 (2.07)	-	-
16 weeks	46	6.57 (2.03)	51	6.52 (2.03)	0.05 (-0.82,0.86)	0.13 (-0.51,0.77)
PDA Distensibility ($mmHg^{-1}x10^3$)						
Baseline	59	5.80 (1.73)	56	5.74 (1.53)	-	-
16 weeks	45	5.78 (1.52)	51	5.47 (1.27)	0.31 (-0.27,0.86)	0.36 (-0.12,0.84)

RV Ejection Fraction (%)						
Baseline	60	59.51 (6.67)	59	58.79 (7.32)	-	-
16 weeks	48	61.68 (6.71)	54	59.3 (6.38)	2.38 (-0.48,5.13)	**1.85 (0.06,3.64)**
RV Stroke Volume (mL)						
Baseline	60	88.61 (19.79)	59	90.3 (23.58)	-	-
16 weeks	48	95.63 (21.59)	54	89.7 (20.33)	5.92 (-4.22,13.68)	**6.51 (2.2,10.81)**
RV Myocardium Mass (g)						
Baseline	60	35.42 (5.75)	59	34.49 (6.33)	-	-
16 weeks	48	35.55 (5.76)	54	35.26 (6.74)	0.29 (-1.77,3.19)	**-1.32 (-2.4,-0.24)**
RV Cardiac Output (L/min)						
Baseline	60	5.78 (1.34)	59	5.76 (1.57)	-	-
16 weeks	47	6.04 (1.25)	54	5.62 (1.34)	0.42 (-0.06,1.01)	**0.35 (0.02,0.69)**
RV ES Volume/BSA (mL/m²)						
Baseline	60	32.14 (7.29)	59	33.65 (9.19)	-	-
16 weeks	48	31.41 (6.89)	54	33.06 (8.22)	-1.66 (-3.98,1.88)	-0.60 (-2.51,1.30)
RV ED Volume/BSA (mL/m²)						
Baseline	60	78.94 (11.61)	59	81.49 (15.46)	-	-
16 weeks	48	81.85 (12.19)	54	80.7 (14.14)	1.15 (-3.62,6.76)	**3.25 (0.31,6.2)**
RV Stroke Volume/BSA (mL/m²)						
Baseline	60	46.80 (8.23)	59	47.85 (10.18)	-	-
16 weeks	48	50.45 (9.63)	54	47.64 (9.04)	2.81 (-1.16,6.69)	**3.64 (1.37,5.92)**
RV Myocardium Mass/BSA (g/m²)						
Baseline	60	18.78 (2.32)	59	18.40 (2.65)	-	-
16 weeks	48	18.77 (2.33)	54	18.80 (2.76)	-0.03 (-1.01,1.04)	**-0.54 (-1.08,0.00)**
RV Cardiac Index (L/min/m²)						
Baseline	60	3.05 (0.58)	59	3.05 (0.7)	-	-
16 weeks	47	3.19 (0.61)	54	2.99 (0.6)	0.20 (-0.05,0.48)	**0.20 (0.02,0.37)**

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age category, gestational age category). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval; BSA, body surface area; ED, end-diastolic volume; ES, end-systolic volume; PDA, proximal-descending-aorta.

6.4.2.2 LV and RV myocardial deformational adaptations to exercise

After the 16-week exercise intervention, there were several changes in myocardial deformation. LV basal and mid peak systolic circumferential strain improved with aerobic training (Basal: -18.02 to -18.98% (5.3% increase) vs comparison group -18.44 to -18.54% (0.5% increase), adjusted mean difference: -0.79%, [95% CI: -1.29,-0.29]; Mid: -18.65 to

-19.68% (5.5% increase) vs comparison group -19.21 to -19.25% (0.2% increase), adjusted mean difference: -0.84%, [95% CI: -1.46, -0.21]). LV mid peak systolic circumferential strain rate decreased marginally in both the aerobic and comparison group (0.96% decrease) vs (3.0% decrease). RV global peak systolic longitudinal strain increased with aerobic training (4.4% increase) vs comparison group (1.4% increase). **Table 6.3** shows the myocardial deformation adaptations in response to the 16-week exercise intervention in the full CMR cohort of participants.

Table 6.3: Myocardial deformation adaptations in response to a 16-week exercise intervention in the full CMR cohort.

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted
Myocardial Strain						
LV Basal Circumferential Strain (%)						
Baseline	60	-18.02 (2.21)	59	-18.44 (2.27)	-	-
16 weeks	48	-18.98 (1.87)	54	-18.54 (2.23)	-0.44 (-1.13,0.48)	**-0.79 (-1.29,-0.29)**
LV Mid Circumferential Strain (%)						
Baseline	60	-18.65 (1.95)	59	-19.21 (2.17)	-	-
16 weeks	48	-19.68 (1.9)	54	-19.25 (2.16)	-0.43 (-1.14,0.28)	**-0.84 (-1.46,-0.21)**
LV Apical Circumferential Strain (%)						
Baseline	60	-21.11 (3.31)	59	-21.11 (3.26)	-	-
16 weeks	48	-21.63 (2.7)	54	-21.23 (2.88)	-0.39 (-1.53,0.79)	-0.67 (-1.35,0.01)
LV Global Longitudinal Strain (%)						
Baseline	60	-18.23 (2.57)	59	-18.62 (2.82)	-	-
16 weeks	48	-19.46 (2.42)	54	-19.1 (2.66)	-0.37 (-1.28,0.78)	-0.56 (-1.15,0.04)
LV Basal Circumferential Strain Rate (%/s)						
Baseline	60	-0.99 (0.18)	59	-1.00 (0.22)	-	-
16 weeks	48	-0.96 (0.19)	54	-0.99 (0.21)	0.03 (-0.04,0.11)	0.03 (-0.04,0.10)
LV Mid Circumferential Strain Rate (%/s)						
Baseline	60	-1.05 (0.16)	59	-1.00 (0.17)	-	-
16 weeks	48	-1.04 (0.2)	54	-0.97 (0.16)	-0.07 (-0.13,0.01)	**-0.06 (-0.12,0.00)**
LV Apical Circumferential Strain Rate (%/s)						
Baseline	59	-1.61 (0.32)	59	-1.51 (0.32)	-	-
16 weeks	48	-1.57 (0.37)	54	-1.52 (0.32)	-0.05 (-0.15,0.08)	-0.05 (-0.18,0.08)
LV Global Longitudinal Strain Rate (%/s)						
Baseline	58	-0.98 (0.21)	59	-0.96 (0.21)	-	-
16 weeks	48	-0.93 (0.15)	53	-0.95 (0.16)	0.03 (-0.04,0.09)	0.02 (-0.04,0.09)
RV Global Longitudinal Strain (%)						
Baseline	59	-21.36 (4.55)	58	-21.19 (3.94)	-	-
16 weeks	48	-22.3 (3.29)	53	-21.49 (3.82)	-0.81 (-2.18,0.74)	**-1.10 (-1.86,-0.34)**
RV Global Longitudinal Strain Rate (%/s)						
Baseline	55	-1.36 (0.31)	49	-1.44 (0.42)	-	-
16 weeks	44	-1.27 (0.29)	53	-1.37 (0.39)	0.10 (-0.06,0.23)	0.11 (-0.02,0.24)

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age category, gestational age category). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval.

6.4.3 Cardiac and aortic adaptations in randomised preterm subgroup

6.4.3.1 LV, RV and aortic structural and functional adaptations to exercise in the preterm subgroup

Within the preterm group, absolute RVM decreased with aerobic training (37.44 to 36.59grams (2.3% decrease) vs comparison group 35.48 to 36.28grams (2.3% increase), adjusted mean difference: -2.24grams, [95% CI: -4.15, -0.29]) **(Table 6.4)**. There were more significant differences between groups for the myocardial deformation parameters (**Table 6.5**). LV basal, mid and apical peak systolic circumferential strain improved with aerobic training (Basal: -16.39 to -17.57% (7.2% increase) vs comparison group -16.35 to -16.29% (0.4% decrease), adjusted mean difference: -1.37%, [95% CI: -2.17,-0.57]; Mid: -17.10 to -18.68% (9.2% increase) vs comparison group -17.44 to -17.29% (0.8% decrease), adjusted mean difference: -1.54%, [95% CI: -2.44, -0.63]; Apical: -18.64 to -19.74% (5.9% increase) vs comparison group -18.34 to -18.72% (2.1% increase), adjusted mean difference: 1.02%, [95% CI: -2.03,0.00]).

Similarly, LV and RV global peak systolic longitudinal strain increased with aerobic training (LV: 11.7% increase) vs comparison (2.4% increase); RV: (13.6% increase) vs comparison group (3.0% increase). Interestingly, RV global peak systolic longitudinal strain rate decreased with aerobic training (6.1% decrease) vs comparison group (0.7% increase). No other LV, RV, or aortic structural or function parameters were altered in the preterm subgroup in response to the aerobic exercise intervention.

Table 6.4: LV, RV and aortic structural and functional adaptations in response to a 16-week exercise intervention in the preterm subgroup.

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted
Structural and functional						
LV Ejection Fraction (%)						
Baseline	24	62.62 (5.31)	22	60.44 (4.75)	-	-
16 weeks	21	62.63 (6.1)	21	61.08 (4.84)	1.55 (-2.04,5.02)	0.47 (-1.62,2.56)
LV Length (mm)						
Baseline	24	93.10 (7.12)	22	90.96 (8.4)	-	-
16 weeks	21	95.14 (6.17)	21	90.95 (8.58)	4.19 (-0.48,9.33)	0.75 (-0.26,1.76)
LV Stroke Volume (mL)						
Baseline	24	82.56 (15.45)	22	81.60 (21.5)	-	-
16 weeks	21	83.89 (17.4)	21	82.75 (21.87)	1.14 (-11.63,13.62)	-0.06 (-3.86,3.75)
LV Myocardium Mass (g)						
Baseline	24	116.16 (22.87)	22	115.30 (29.92)	-	-
16 weeks	21	117.41 (23.22)	21	112.82 (28.59)	4.59 (-11.27,22.54)	0.50 (-3.69,4.70)
LV Cardiac Output (L/min)						
Baseline	24	5.61 (1.36)	22	5.26 (1.32)	-	-
16 weeks	20	5.31 (1.03)	21	5.21 (1.31)	0.1 (-0.41,0.88)	-0.10 (-0.49,0.29)
LV Mass/ED Volume (g/mL)						
Baseline	24	0.88 (0.07)	22	0.86 (0.1)	-	-
16 weeks	21	0.88 (0.1)	21	0.84 (0.09)	0.04 (-0.03,0.10)	0.02 (-0.02,0.05)
LV ES Volume/BSA (mL/m²)						
Baseline	24	26.62 (5.48)	22	30.11 (7)	-	-
16 weeks	21	26.93 (6.01)	21	29.28 (6.45)	-2.35 (-6.73,1.86)	-0.27 (-2.26,1.72)
LV ED Volume/BSA (mL/m²)						
Baseline	24	70.96 (9.07)	22	75.01 (13.11)	-	-
16 weeks	21	71.91 (10.03)	21	75.09 (13.19)	-3.18 (-10.99,4.43)	0.77 (-1.93,3.48)
LV Stroke Volume/BSA (mL/m²)						
Baseline	24	44.33 (6.12)	22	45.23 (8.23)	-	-
16 weeks	21	44.98 (7.28)	21	45.86 (8.82)	-0.88 (-4.99,4.12)	0.68 (-1.36,2.73)
LV Myocardium Mass/BSA (g/m²)						
Baseline	24	62.44 (8.03)	22	63.93 (10.62)	-	-
16 weeks	21	62.73 (8.46)	21	62.46 (9.87)	0.26 (-5.51,5.89)	1.01 (-1.15,3.17)
LV Cardiac Index (L/min/m²)						
Baseline	24	3.01 (0.59)	22	2.93 (0.58)	-	-
16 weeks	20	2.85 (0.42)	21	2.90 (0.55)	-0.06 (-0.33,0.32)	-0.04 (-0.24,0.17)
Aortic Distensibility ($mmHg^{-1}x10^3$)						
Baseline	22	6.67 (2.14)	18	6.53 (1.84)	-	-
16 weeks	21	6.74 (2.02)	19	6.41 (1.8)	0.33 (-1.03,1.63)	0.22 (-0.81,1.24)
PDA Distensibility ($mmHg^{-1}x10^3$)						
Baseline	23	5.84 (1.54)	20	5.79 (1.41)	-	-

16 weeks	19	5.75 (1.26)	19	5.53 (1.42)	0.23 (-0.82,1.15)	0.37 (-0.44,1.18)
RV Ejection Fraction (%)						
Baseline	24	57.61 (7.07)	22	56.37 (8.14)	-	-
16 weeks	21	58.03 (5.91)	21	56.99 (7.2)	1.04 (-3.24,5.92)	0.66 (-1.96,3.27)
RV Stroke Volume (mL)						
Baseline	24	79.27 (17.18)	22	79.09 (23.23)	-	-
16 weeks	21	83.34 (20.9)	21	80.07 (23.24)	3.27 (-13.23,16.78)	1.98 (-4.99,8.95)
RV Myocardium Mass (g)						
Baseline	24	37.44 (5.2)	22	35.48 (7.23)	-	-
16 weeks	21	36.59 (5.8)	21	36.28 (8.2)	0.31 (-3.71,5.18)	**-2.22 (-4.15,-0.29)**
RV Cardiac Output (L/min)						
Baseline	24	5.38 (1.4)	22	5.11 (1.49)	-	-
16 weeks	20	5.30 (1.12)	21	5.07 (1.52)	0.24 (-0.51,1.14)	0.00 (-0.55,0.55)
RV ES Volume/BSA (mL/m²)						
Baseline	24	31.37 (7.19)	22	33.46 (6.98)	-	-
16 weeks	21	32.25 (6.76)	21	33.01 (6.83)	-0.76 (-4.18,3.90)	-0.22 (-3.16,2.72)
RV ED Volume/BSA (mL/m²)						
Baseline	24	74.00 (10.4)	22	77.28 (11.11)	-	-
16 weeks	21	76.91 (12.91)	21	77.32 (12.4)	-0.4 (-9.01,6.84)	1.69 (-3.44,6.82)
RV Stroke Volume/BSA (mL/m²)						
Baseline	24	42.63 (7.88)	22	43.82 (10.26)	-	-
16 weeks	21	44.66 (9.29)	21	44.31 (10.16)	0.36 (-6.20,6.41)	1.48 (-2.16,5.11)
RV Myocardium Mass/BSA (g/m²)						
Baseline	24	20.15 (1.73)	22	19.75 (2.33)	-	-
16 weeks	21	19.63 (2.33)	21	20.15 (2.52)	-0.51 (-1.94,1.23)	-0.91 (-1.90,0.08)
RV Cardiac Index (L/min/m²)						
Baseline	24	2.89 (0.66)	22	2.84 (0.72)	-	-
16 weeks	20	2.84 (0.5)	21	2.82 (0.7)	0.02 (-0.34,0.49)	0.01 (-0.27,0.29)

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age at baseline). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval; BSA, body surface area; ED, end-diastolic volume; ES, end-systolic volume; PDA, proximal-descending-aorta.

6.4.3.2 LV and RV myocardial deformational adaptations to the 16-week exercise intervention in the preterm subgroup

Table 6.5 shows the myocardial deformation adaptations in response to the 16-week exercise intervention in the preterm subgroup.

Table 6.5: Myocardial deformation adaptations in response to a 16-week exercise intervention in the preterm subgroup.

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	N	Mean (SD)	Unadjusted	Adjusted
Myocardial strain						
LV Basal Circumferential Strain (%)						
Baseline	24	-16.39 (1.9)	22	-16.35 (1.66)	-	-
16 weeks	21	-17.57 (1.46)	21	-16.29 (1.61)	-1.28 (-2.30,-0.32)	**-1.37 (-2.17,-0.57)**
LV Mid Circumferential Strain (%)						
Baseline	24	-17.10 (1.49)	22	-17.44 (1.44)	-	-
16 weeks	21	-18.68 (1.47)	21	-17.29 (1.4)	-1.39 (-2.39,-0.67)	**-1.54 (-2.44,-0.63)**
LV Apical Circumferential Strain (%)						
Baseline	24	-18.64 (2.82)	22	-18.34 (2.13)	-	-
16 weeks	21	-19.74 (2.01)	21	-18.72 (1.79)	-1.02 (-2.25,0.20)	**1.02 (-2.03,0.00)**
LV Global Longitudinal Strain (%)						
Baseline	24	-15.66 (1.61)	22	-15.99 (1.46)	-	-
16 weeks	21	-17.49 (1.15)	21	-16.38 (1.31)	-1.11 (-1.78,-0.37)	**-1.43 (-2.08,-0.79)**
LV Basal Circumferential Strain Rate (%/s)						
Baseline	24	-0.99 (0.13)	22	-0.98 (0.18)	-	-
16 weeks	21	-0.99 (0.18)	21	-0.97 (0.22)	-0.02 (-0.14,0.12)	-0.03 (-0.16,0.09)
LV Mid Circumferential Strain Rate (%/s)						
Baseline	24	-1.05 (0.14)	22	-1.03 (0.15)	-	-
16 weeks	21	-1.02 (0.18)	21	-0.97 (0.17)	-0.06 (-0.15,0.07)	-0.05 (-0.14,0.05)
LV Apical Circumferential Strain Rate (%/s)						
Baseline	23	-1.61 (0.32)	22	-1.51 (0.33)	-	-
16 weeks	21	-1.57 (0.37)	21	-1.39 (0.24)	-0.19 (-0.29,0.01)	-0.15 (-0.33,0.04)
LV Global Longitudinal Strain Rate (%/s)						
Baseline	22	-0.93 (0.2)	22	-1.00 (0.22)	-	-
16 weeks	21	-0.88 (0.15)	21	-0.96 (0.15)	0.07 (-0.01,0.19)	0.05 (-0.05,0.16)
RV Global Longitudinal Strain (%)						
Baseline	23	-17.69 (2.25)	22	-17.55 (2.25)	-	-
16 weeks	21	-20.10 (2.43)	21	-18.07 (2.38)	-2.02 (-3.48,-0.52)	**-2.05 (-3.16,-0.93)**
RV Global Longitudinal Strain Rate (%/s)						
Baseline	21	-1.32 (0.26)	19	-1.43 (0.39)	-	-
16 weeks	19	-1.24 (0.29)	21	-1.44 (0.34)	0.2 (-0.01,0.39)	**0.25 (0.05,0.45)**

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age at baseline). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval.

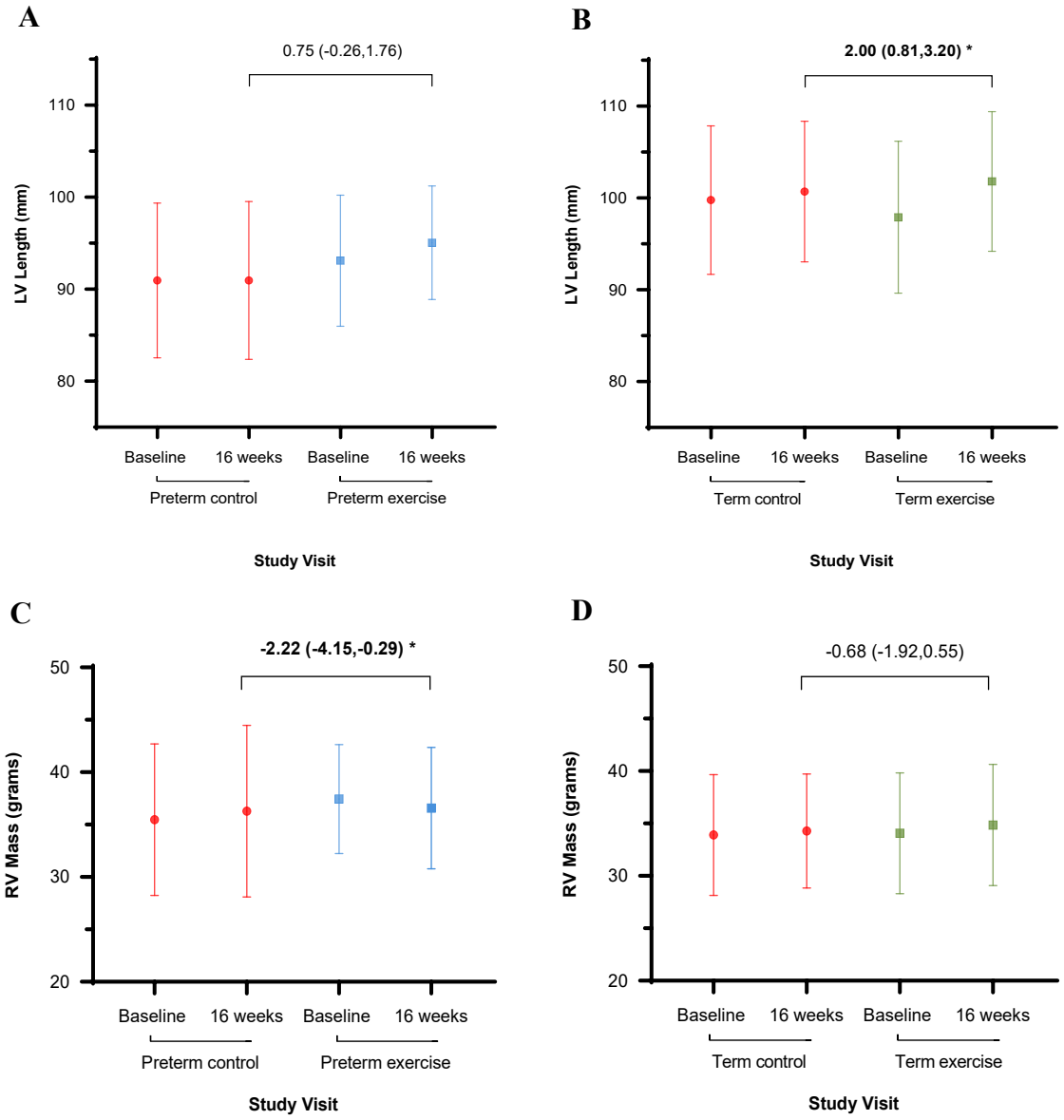


Figure 6.2: Changes in LV length and RVM in the preterm- and term-born subgroups following the 16-week aerobic exercise intervention. **A,** change in LV length in the preterm subgroup from baseline to 16 weeks did not differ significantly between controls (red) and the intervention group (blue). **B,** LV length in the term subgroup increased from baseline to 16 weeks the intervention group (green) compared to controls (red). **C**, RVM in the preterm subgroup decreased from baseline to 16 weeks the intervention group (blue) compared to controls (red). **D,** change in RVM in the term subgroup from baseline to 16 weeks did not differ significantly between controls (red) and the intervention group (green). Statistical significance (P<0.05) is indicated by a * next to the adjusted mean difference and 95% confidence interval.

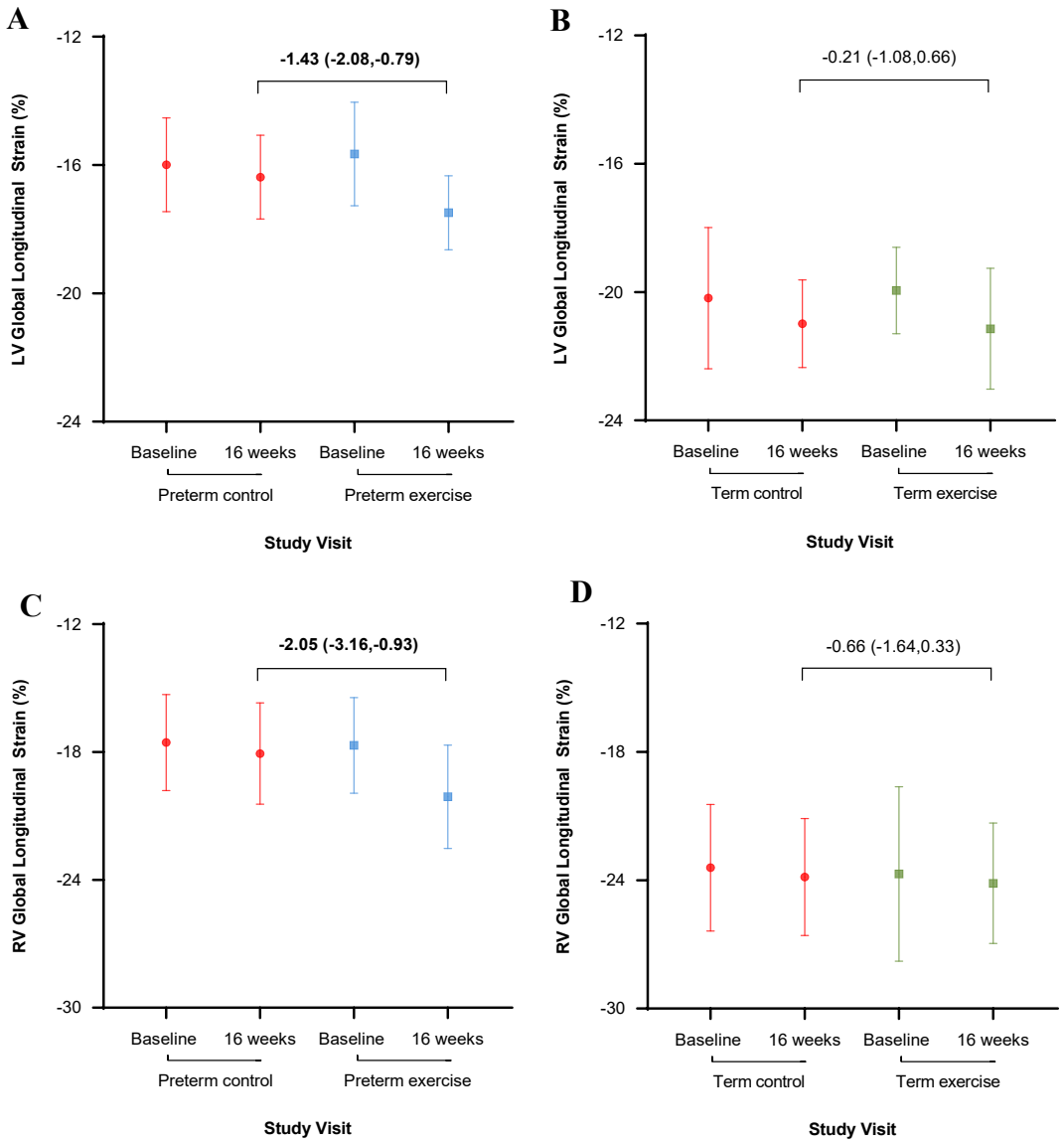


Figure 6.3: Changes in LV and RV global peak systolic longitudinal strain in the preterm- and term-born subgroups following the 16-week aerobic exercise intervention. **A**, LV global peak systolic longitudinal strain in the preterm subgroup increased from baseline to 16 weeks in the intervention group (blue) compared to the controls (red). **B**, change in LV global peak systolic longitudinal strain in the term subgroup from baseline to 16 weeks did not differ significantly between controls (red) and the intervention group (green). **C**, RV global peak systolic longitudinal strain in the preterm subgroup increased from baseline to 16 weeks in the intervention group (blue) compared to the controls (red). **D**, change in RV global peak systolic longitudinal strain in the term subgroup from baseline to 16 weeks did not differ significantly between controls (red) and the intervention group (green). Statistical significance ($P<0.05$) is indicated by a * next to the adjusted mean difference and 95% confidence interval.

6.4.4 Cardiac and aortic adaptations in randomised term subgroup

6.4.4.1 LV, RV and aortic structural and functional adaptations to exercise in the term subgroup

As shown in **Table 6.6**, within the term group, LV length and LVSVI increased with aerobic training (length: 97.91 to 101.60mm (3.8% increase) vs comparison group 99.77 to 100.9mm (1.1% increase), adjusted mean difference: 2.04mm, [95% CI: 0.85, 3.22]; LVSV index: 49.50 to 51.83mL/m² (4.7% increase) vs comparison group 51.58 to 50.71mL/m² (1.7% decrease), adjusted mean difference: 2.53mL/m², [95% CI: 0.01, 5.05]). LVM to LVEDV ratio decreased with aerobic training (4.1% decrease) vs comparison group (1.4% increase).

At the 16-week follow up visit, RVEF and RVEDVI increased with aerobic training (RVEF: 60.78 to 64.52% (6.2% increase) vs comparison group 60.22 to 60.77% (0.9% increase), adjusted mean difference: 2.95%, [95% CI: 0.47, 5.42]; RVEDV index: 82.23 to 85.70mL/m² (4.2% increase) vs comparison group (83.99 to 82.86mL/m² (1.3% decrease), adjusted mean difference: 4.18 mL/m², [95% CI: 0.60, 7.76]). Absolute and indexed RVSV increased with aerobic training (RVSV: 10.9% increase) vs comparison group (1.2% decrease); RVSV index: (10.9% increase) vs comparison group (1.0% decrease). In addition, RVCO and RVCI increased with aerobic training (RVCO: 8.9% increase) vs comparison group (2.9% decrease); RVCI: (9.2% increase) vs comparison group (2.5% decrease). There were no significant differences between the intervention and control group for the LV and RV myocardial deformation parameters (**Table 6.7**).

6.4.4.2 LV and RV myocardial deformational adaptations to exercise in the term subgroup

Table 6.6: LV, RV and aortic structural and functional adaptations in response to a 16-week exercise intervention in the term subgroup.

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted
Structural and functional						
LV Ejection Fraction (%)						
Baseline	36	66.97 (4.49)	37	66.65 (5.75)	-	-
16 weeks	27	68.23 (4.99)	33	66.17 (5.25)	2.05 (-0.82,4.70)	1.79 (-0.04,3.61)
LV Length (mm)						
Baseline	36	97.91 (8.27)	37	99.77 (8.08)	-	-
16 weeks	27	101.60 (7.53)	33	100.9 (7.62)	0.70 (-3.14,5.05)	**2.00 (0.81,3.20)**
LV Stroke Volume (mL)						
Baseline	36	94.3 (14.4)	37	99.13 (17.86)	-	-
16 weeks	27	99.59 (17.81)	33	97.72 (13.92)	1.86 (-6.93,8.91)	4.80 (-0.51,10.11)
LV Myocardium Mass (g)						
Baseline	36	105.44 (22.9)	37	110.39 (21.73)	-	-
16 weeks	27	104.09 (22.41)	33	110.87 (20.67)	-6.78 (-16.8,5.13)	-2.72 (-6.20,0.77)
LV Cardiac Output (L/min)						
Baseline	36	6.02 (0.99)	37	6.29 (1.36)	-	-
16 weeks	27	6.22 (1.08)	33	6.09 (1.05)	0.13 (-0.43,0.75)	0.32 (-0.11,0.74)
LV Mass/ED Volume (g/mL)						
Baseline	36	0.74 (0.09)	37	0.74 (0.11)	-	-
16 weeks	27	0.71 (0.09)	33	0.75 (0.12)	-0.04 (-0.07,0.01)	**-0.03 (-0.06,0.00)**
LV ES Volume/BSA (mL/m²)						
Baseline	36	24.59 (5.1)	37	26.30 (8.28)	-	-
16 weeks	27	24.17 (4.66)	33	27.43 (9.1)	-3.26 (-5.60,1.26)	-1.71 (-4.32,0.89)
LV ED Volume/BSA (mL/m²)						
Baseline	36	74.09 (8.36)	37	77.78 (14.22)	-	-
16 weeks	27	76.00 (7.32)	33	77.23 (12.69)	-1.23 (-5.35,4.05)	1.69 (-0.82,4.21)
LV Stroke Volume/BSA (mL/m²)						
Baseline	36	49.50 (5.35)	37	51.58 (8.16)	-	-
16 weeks	27	51.83 (6.08)	33	50.71 (6.49)	1.12 (-2.27,4.32)	**2.53 (0.01,5.05)**
LV Myocardium Mass/BSA (g/m²)						
Baseline	36	54.90 (7.96)	37	57.30 (8.63)	-	-
16 weeks	27	53.80 (7.49)	33	57.31 (8.71)	-3.51 (-6.81,0.80)	-1.11 (-2.74,0.52)
LV Cardiac Index (L/min/m²)						
Baseline	36	3.16 (0.43)	37	3.26 (0.63)	-	-
16 weeks	27	3.25 (0.48)	33	3.15 (0.47)	0.09 (-0.16,0.34)	0.18 (-0.04,0.39)
Aortic Distensibility ($mmHg^{-1}x10^3$)						
Baseline	35	6.49 (2.35)	36	6.48 (2.2)	-	-
16 weeks	25	6.42 (2.08)	32	6.59 (2.18)	-0.16 (-1.27,0.93)	-0.11 (-0.93,0.71)

PDA Distensibility ($mmHg^{-1}x10^3$)						
Baseline	36	5.77 (1.86)	36	5.70 (1.61)	-	-
16 weeks	26	5.79 (1.7)	32	5.43 (1.2)	0.36 (-0.34,1.10)	0.24 (-0.38,0.86)
RV Ejection Fraction (%)						
Baseline	36	60.78 (6.17)	37	60.22 (6.48)	-	-
16 weeks	27	64.52 (5.94)	33	60.77 (5.4)	3.75 (0.67,7.01)	**2.95 (0.47,5.42)**
RV Stroke Volume (mL)						
Baseline	36	94.83 (19.15)	37	96.96 (21.41)	-	-
16 weeks	27	105.18 (17.03)	33	95.83 (15.73)	9.35 (0.57,19.31)	**9.54 (4.47,14.60)**
RV Myocardium Mass (g)						
Baseline	36	34.06 (5.77)	37	33.90 (5.76)	-	-
16 weeks	27	34.74 (5.71)	33	34.60 (5.67)	0.14 (-2.14,3.36)	-0.68 (-1.92,0.55)
RV Cardiac Output (L/min)						
Baseline	36	6.04 (1.24)	37	6.15 (1.5)	-	-
16 weeks	27	6.58 (1.06)	33	5.97 (1.1)	0.61 (0.10,1.32)	**0.66 (0.25,1.08)**
RV ES Volume/BSA (mL/m^2)						
Baseline	36	32.65 (7.41)	37	33.76 (10.38)	-	-
16 weeks	27	30.75 (7.04)	33	33.10 (9.1)	-2.35 (-6.01,2.39)	-1.19 (-3.76,1.37)
RV ED Volume/BSA (mL/m^2)						
Baseline	36	82.23 (11.32)	37	83.99 (17.2)	-	-
16 weeks	27	85.70 (10.28)	33	82.86 (14.92)	2.84 (-3.06,9.72)	**4.18 (0.60,7.76)**
RV Stroke Volume/BSA (mL/m^2)						
Baseline	36	49.57 (7.33)	37	50.25 (9.47)	-	-
16 weeks	27	54.95 (7.3)	33	49.76 (7.68)	5.19 (1.22,8.83)	**5.33 (2.47,8.18)**
RV Myocardium Mass/BSA (g/m^2)						
Baseline	36	17.86 (2.22)	37	17.60 (2.52)	-	-
16 weeks	27	18.10 (2.14)	33	17.94 (2.6)	0.16 (-1.00,1.25)	-0.23 (-0.86,0.39)
RV Cardiac Index ($L/min/m^2$)						
Baseline	36	3.16 (0.51)	37	3.17 (0.66)	-	-
16 weeks	27	3.45 (0.55)	33	3.09 (0.51)	0.35 (0.07,0.66)	**0.38 (0.14,0.61)**

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age at baseline). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval; BSA, body surface area; ED, end-diastolic volume; ES, end-systolic volume; PDA, proximal-descending-aorta.

Table 6.7: Myocardial deformation adaptations in response to a 16-week exercise intervention in the term subgroup.

CMR parameters	Exercise Intervention		Control		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted
Myocardial strain						
LV Basal Circumferential Strain (%)						
Baseline	36	-19.11 (1.69)	37	-19.68 (1.57)	-	-
16 weeks	27	-20.08 (1.35)	33	-19.98 (1.07)	-0.11 (-0.7,0.44)	-0.27 (-0.91,0.36)
LV Mid Circumferential Strain (%)						
Baseline	36	-19.68 (1.5)	37	-20.27 (1.82)	-	-
16 weeks	27	-20.46 (1.85)	33	-20.49 (1.54)	0.03 (-0.68,0.64)	-0.32 (-1.16,0.53)
LV Apical Circumferential Strain (%)						
Baseline	36	-22.76 (2.52)	37	-22.75 (2.65)	-	-
16 weeks	27	-23.10 (2.24)	33	-22.83 (2.23)	-0.26 (-1.53,0.89)	-0.52 (-1.47,0.44)
LV Global Longitudinal Strain (%)						
Baseline	36	-19.95 (1.35)	37	-20.19 (2.2)	-	-
16 weeks	27	-21.00 (1.99)	33	-20.83 (1.64)	-0.17 (-0.92,0.65)	-0.21 (-1.08,0.66)
LV Basal Circumferential Strain Rate (%/s)						
Baseline	36	-0.99 (0.21)	37	-1.01 (0.24)	-	-
16 weeks	27	-0.93 (0.2)	33	-1.00 (0.2)	0.07 (-0.03,0.18)	0.07 (-0.03,0.16)
LV Mid Circumferential Strain Rate (%/s)						
Baseline	36	-1.05 (0.17)	37	-0.98 (0.18)	-	-
16 weeks	27	-1.05 (0.21)	33	-0.97 (0.16)	-0.09 (-0.17,0.00)	-0.07 (-0.16,0.02)
LV Apical Circumferential Strain Rate (%/s)						
Baseline	36	-1.61 (0.33)	37	-1.52 (0.32)	-	-
16 weeks	27	-1.58 (0.38)	33	-1.61 (0.34)	0.03 (-0.14,0.20)	0.03 (-0.15,0.21)
LV Global Longitudinal Strain Rate (%/s)						
Baseline	36	-1.01 (0.21)	37	-0.94 (0.21)	-	-
16 weeks	27	-0.96 (0.15)	32	-0.95 (0.17)	0.0 (-0.09,0.05)	0.01 (-0.08,0.09)
RV Global Longitudinal Strain (%)						
Baseline	36	-23.71 (4.08)	36	-23.42 (2.96)	-	-
16 weeks	27	-24.01 (2.84)	32	-23.73 (2.78)	-0.28 (-1.60,1.20)	-0.66 (-1.64,0.33)
RV Global Longitudinal Strain Rate (%/s)						
Baseline	34	-1.38 (0.34)	30	-1.44 (0.44)	-	-
16 weeks	25	-1.29 (0.3)	32	-1.33 (0.41)	0.04 (-0.21,0.20)	0.01 (-0.17,0.19)

Values are presented as mean ± SD. 95% CI, change adjusted for baseline values and minimization factors (sex, age at baseline). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval.

6.4.5 Interaction analysis for significant CMR parameters

I performed an interaction analysis to investigate whether cardiac adaptations differed depending on whether people were born preterm or term. The findings across the full CMR cohort are demonstrated in **Table 6.8**. When preterm/term group status was added as an interaction variable in the analyses, only LVM to LVEDV ratio, RVCI and LV mid peak systolic circumferential strain were significant.

Table 6.8: Interaction analysis between CMR parameters and birth history within the full CMR cohort.

CMR Parameters	Adjusted Interaction coefficient (95% CI)
LV Ejection Fraction (%)	-1.09 (-3.82,1.64)
LV Length (mm)	-1.18 (-2.79,0.43)
RV Ejection Fraction (%)	-1.98 (-5.57,1.61)
RV Stroke Volume (mL)	-7.77 (-16.29,0.74)
RV Myocardium Mass (g)	-1.52 (-3.66,0.63)
RV Cardiac Output (L/min)	-0.65 (-1.31,0.01)
LV Mass/End Diastolic Volume	**0.05 (0.01,0.09)**
LV Stroke Volume Index (mL/m²)	2.62 (-6.15,0.91)
RV Mass Index (g/ m²)	-0.73 (-1.82,0.36)
RV End Diastolic Volume Index (mL/m²)	-2.82 (-8.64,3.00)
RV Stroke Volume Index (mL/m²)	-4.08 (-8.60,0.44)
RV Cardiac Index (L/min/m²)	**-0.37 (-0.72,-0.01)**
LV Global Longitudinal Strain (%)	-0.98 (-2.16,0.20)
LV Basal Circumferential Strain (%)	-0.96 (-1.96,0.03)
LV Mid Circumferential Strain (%)	**-1.24 (-2.46,-0.02)**
LV Mid Circumferential Strain Rate (%/s)	0.03 (-0.10,0.16)
LV Apical Circumferential Strain (%)	-0.58 (-1.95,0.79)
RV Global Longitudinal Strain (%)	-1.48 (-2.98,0.02)
RV Global Longitudinal Strain Rate (%/s)	0.20 (-0.07,0.46)

Values are presented 95% CI where change adjusted for baseline values and minimization factors (sex, age at baseline). Interaction term used was birth history (preterm vs term category). **Bold** values for 95% CI are statistically significant (P<0.05). CI indicates confidence interval.

6.5 Discussion

The current randomised controlled trial provides a comprehensive analysis of LV and RV performance using resting CMR imaging following a 16-week aerobic exercise training intervention in healthy, sedentary young adults with elevated blood pressure. The study has three primary new findings: (1) the exercise intervention induced potentially beneficial biventricular changes in the full CMR cohort of participants; (2) analysis in the preterm subgroup showed primarily LV and RV myocardial deformation changes following the exercise intervention; and (3) analysis in the term subgroup showed significant changes in LV and RV structure and function following the exercise intervention. Interaction analysis revealed that the change following the exercise intervention for LVM to LVEDV ratio, RVCI and LV mid peak systolic circumferential strain were the only ones that differed significantly between the preterm and term groups. Contrary to the most reported cardiac adaptation in response to aerobic training, there was no difference in absolute or indexed LVM between aerobic training and controls across all group comparisons.

Previous studies in hypertensive young adults indicate potentially favourable cardiac changes in response to physical activity [181, 258, 259], though results are less conclusive for the RV [260]. Studies in healthy, sedentary young adults have shown that higher physical activity leads to biventricular changes with some studies reporting an increase in LVM [164, 261-264]. To our knowledge, this study is the first cardiac adaptation study to exclusively target recruitment of younger adults with elevated blood pressure including a subgroup of people born preterm. Young adults with elevated blood pressure and those with a history of preterm birth share some similar cardiovascular traits and risk factors, including increased LVM [74, 265]. Meanwhile, exercise-induced cardiac

remodelling most commonly seen in athletes is generally associated with a physiological or adaptive increase in LVM [266]. We therefore hypothesised that LVM may actually increase across the group with exercise, particularly in those born preterm given their unique cardiac phenotype. However, the present study reported no differences between absolute and indexed LVM over the 16-week aerobic training in all group comparisons. It is possible that the duration of the intervention was too short, though it was shown that LVM to LVEDV ratio decreased within the term subgroup, suggestive of beneficial remodelling. In contrast to the LV, RVM decreased with the aerobic training intervention and RVEDV increased. The reduction in RVM appeared to be primarily restricted to the preterm exercise intervention group. Given this group is particularly at risk of RVH [88, 108, 113, 267], prescribed exercise programmes could be particularly useful for targeting this aspect of cardiac remodelling.

Cardiac alterations are apparent in preterm-born individuals across developmental stages, even in the normal blood pressure range [109]. It is also well established that preterm-born individuals are at increased risk of hypertension [14] and that they develop higher blood pressure as early as childhood [58, 268]. This blood pressure elevation continues into adulthood [62, 269] with the gap between preterm- and term-born individuals widening, suggestive of an accelerated risk for adverse cardiovascular events [12, 20]. Interventions to improve cardiac performance and reduce blood pressure in preterm-born individuals are therefore of clinical importance. In the preterm subgroup analysis, the impact of aerobic exercise training on cardiac remodelling was primarily related to myocardial strain parameters. It is possible that the gross structural and volumetric changes in response to exercise interventions will take much longer to appear

due to the known suboptimal cardiac performance in preterm-born young adults. There was a significant difference in LVEF in the full cohort of participants, with modest increases seen with aerobic exercise training. Although LVEF did not change in the preterm group, LV myocardial function increased. Myocardial strain has now emerged as a reliable method to detect subclinical changes, including myocardial contractile dysfunction prior to changes in LVEF [270]. Strain imaging can provide an objective assessment of myocardial contractility [271] and has been consistently found to be reduced in preterm-born individuals across studies [106, 108].

The subclinical improvements in the cardiac parameters seen in the preterm group may also be explained by signalling pathways involved in hypertrophy and fibrosis [187]. Changes in myocardial deformation depends on cardiomyocyte function, myofiber architecture, tissue elasticity and fibrosis [272]. Preterm animal studies have demonstrated increased interstitial myocardial fibrosis and alterations in cardiomyocyte maturation and size within the myocardium, as early as neonatal life [112, 113]. Exercise has been suggested to provide a protective cardiac impact [190, 193]. For instance, myocardial collagen content in rats who underwent moderate to high intensity exercise training was significantly reduced following intervention [190]. Presence of fibrosis/collagen content may explain why myocardial deformation is reduced in preterm-born individuals and may also physically restrict structural remodelling. Though further work is needed to explore these hypotheses, it is possible that partial reversal of these pathways may be why we see such a significant benefit in improved myocardial deformation in this subgroup with the exercise intervention. It may also be that increases in myocardial deformation are compensating for the restrictions on volumetric change secondary to increased

fibrosis/collagen or as a result of the possible reduction in cardiac endowment shown in animal models [256].

Huckstep et al previously reported impaired LV myocardial functional reserve by showing that LVEF change from rest to moderate and high intensity exercise was blunted in the preterm group [109]. In a follow up paper, it was demonstrated that this blunted LVEF change predicted peak exercise capacity in the preterm group [185]. It remains to be determined whether prescribed aerobic training can improve this impairment in myocardial functional reserve. Interestingly, reduced LV length and LV global peak systolic longitudinal strain were the primary predictors of the blunted exercise LVEF response in the preterm-born group. The observed increases in the current study in myocardial deformation in the preterm group may allow the heart to be more adaptable under physiological stress. Although the increase in LV length in the preterm subgroup did not quite reach significance in response to aerobic exercise training, a longer intervention and sustained exercise programme may be beneficial and is worth further investigation.

6.6 Study 6 limitations

Despite the novelty of the current trial, there were several limitations worth consideration. Although it was the largest study of its kind, when divided into subgroups, the sample size was relatively small. This limits the statistical power between subgroup comparisons. However, CMR is highly repeatable and reproducible, adding confidence that our positive findings were not due to chance alone. Although we reported in our study that the RV changes more in response to exercise training, we do not have data assessing pulmonary

artery systolic pressure to determine whether this may be an upstream modification driving downstream RV remodelling. Due to DPhil time constraints, I did not include diastolic myocardial relaxation parameters. Finally, this study is only able to identify short term cardiac changes in response to aerobic training. Whether changes we have observed will be sustained over the longer term is unknown. Nevertheless, the fact that cardiac adaptations that may be beneficial were observed suggests that impairments, particularly in those born preterm, are not entirely fixed, raising the possibility for targeted intervention strategies. Additional research is needed to determine whether exercise, in combination with other lifestyle interventions and/or pharmacological treatments, can maximise the cardiac adaptations in young adults and whether this differs based on birth history.

6.7 Conclusions

TEPHRA is the largest randomised controlled trial investigating the impact of exercise training on cardiac structure and function in young adults with a subgroup of preterm-born individuals. The results demonstrate aerobic exercise training leads to modest, potentially beneficial biventricular cardiac changes. Cardiac adaptations in the preterm group were primarily changes in myocardial deformation, while the term group showed greater volumetric and structural changes. Further research is needed to identify whether different types of exercise, such as high intensity interval training alone or in combination with aerobic training, may be of additional benefit to cardiac remodelling in these young adult subgroups.

CHAPTER 7

CONCLUSIONS

7.1 Conclusions

In conclusion, this thesis aimed to further characterise the cardiovascular phenotype and cardiac morphology of preterm-born young adults, as well as to investigate whether aerobic exercise training can modify these prematurity-related cardiovascular changes. My thesis has provided a better understanding of the effects of preterm birth on the cardiovascular system and provided evidence for the benefits of an exercise intervention in preterm-born individuals (as well as how these findings differ from term-born individuals).

My thesis contained a detailed assessment of LV and RV structure and function using multimodality imaging, including CMR, which offers advanced imaging methods to obtain detailed images of structures within and around the heart. Other in-depth phenotyping assessments were used, including resting and 24-hour ambulatory blood pressure monitoring, in addition to anthropometric measurements. Importantly, TEPHRA was the first study to provide evidence on the effectiveness of aerobic training for cardiovascular remodelling and demonstrated the cause-effect relationship of an exercise

intervention and outcome parameters in the young adult population. The outcomes of the trial included changes in blood pressure, cardiorespiratory fitness, body composition, as well as microvascular, cardiac, adiposity and cerebrovascular measures. This thesis specifically covered the exercise effects on heart remodelling with subgroup analyses based on preterm and term birth history.

The first objective (Chapter 4) was to gain an understanding of RV remodelling in relation to pulmonary function and whether these changes influence the coupling of the two systems in normotensive, moderately preterm-born adults. I used multimodality imaging assessments (resting CMR and echocardiography) to allow detailed assessment of both RV and pulmonary function. Echocardiography was used to quantify the RVPA coupling non-invasively. The central finding was that moderately preterm-born young adults demonstrated a reduction in RV function, independent of mechanical lung function. Interestingly, the RV remained hemodynamically coupled to the pulmonary circulation despite a higher RV afterload, reduced RV function and altered morphology. In addition, the use of a computational shape atlas of the RV, which explained 55.7% of the variance in morphology, showed that preterm-born young adults typically have a smaller sized RV. These findings may indicate that the RV will be particularly vulnerable to reductions in cardiac performance over time. We also speculate that the uncoupling in the young adults born preterm will occur earlier and may be dependent on gestational age, though this will require further study.

The next objective (Chapter 5) was to investigate whether LV structure and function in preterm-born adults are more susceptible to remodelling in relation to blood pressure elevation. This cardiac remodelling project integrated a larger sample of

participants; 468 with existing CMR scans and resting blood pressure measurements who met the inclusion and exclusion criteria. The key findings were that LVMI and LVM to LVEDV ratio showed a bigger increase per 1mmHg rise in systolic blood pressure in preterm-born adults than in term-born adults, with the greatest changes in those born very and extremely preterm ($<32^{+0}$ weeks' gestation). Besides, there was a leftward shift in the regression slope analyses of systolic blood pressure with LVMI and LVM to LVEDV ratio in preterm- compared to term-born adults. The cardiac remodelling following blood pressure elevation in preterm-born adults appears to be shifted from the typical trajectory of those born full term, which needs to be confirmed and further explored in longitudinal studies. In addition, normotensive and hypertensive preterm-born adults were shown to have consistently smaller LV volumes with reduced LV function. Longitudinal peak systolic strain, mid-ventricular and apical peak systolic circumferential strain were also lower in the preterm-born normotensive and hypertensive groups compared to both normotensive and hypertensive term-born individuals. Future research is needed to identify how the heart changes over time in relation to blood pressure elevation.

Following these findings, my thesis' final objective (Chapter 6) focused on identifying the cardiac adaptations following a 16-week prescribed aerobic exercise intervention in young adults. The central question was to identify the potential cardiac remodelling following aerobic training in two young adult populations with elevated risk for premature CVD. This chapter demonstrated three new, central findings. First, a 16-week program of moderate to high-intensity aerobic exercise training induced modest biventricular changes in the full cohort of randomised preterm- and term-born young adults. Second, specific subgroup analysis in the preterm-born adults revealed that exercise

training induced more significant changes in LV and RV myocardial deformation parameters in this group. Third, specific subgroup analyses in the term-born adults showed that exercise training induced more significant changes in LV and RV structure and function in this group. There were, however, no differences in LVM or LVMI between those in the aerobic training and control group in any of the group comparisons, which differs from findings of some previous studies. Interaction analyses were then performed to investigate whether being born preterm or term may differentially affect cardiac adaptations in response to exercise training. While many of these changes could not be confirmed to be entirely unique for each subgroup, RVCI and LV mid-ventricular peak systolic circumferential strain were shown to adapt differently in preterm- compared to term-born adults in response to the exercise intervention. Overall, the results presented in this chapter demonstrated that aerobic exercise leads to favourable short term cardiac changes, with no evidence of any adverse cardiac effects in response to exercise. Further work with a larger sample size is needed to investigate whether different types of exercise training, alternative lifestyle interventions or pharmacological approaches are more effective in improving cardiac performance in young adults, including those with a history of preterm birth.

Overall, my thesis has provided new insights into the impacts of prematurity and blood pressure elevation on LV and RV structure and function. Though these are healthy young adults with normal and elevated blood pressures, I have been able to provide evidence of subclinical changes at baseline and post-exercise intervention that may have clinical implications in later adult life. In my thesis, the preterm cohorts were mostly categorised in the moderate to late preterm gestational age range. As 10% of births are

preterm, of which nearly 85% are categorised under moderate or late preterm, my thesis findings may be more generalisable to the wider preterm population. This also indicates that any evidence of unusual cardiovascular development trajectories seen in this cohort are of public health importance. However, these are not longitudinal research studies; thus it is not possible to confirm the trajectories of cardiac, blood pressure, and ventricular-pulmonary coupling changes from birth into adulthood, particularly in the preterm population. Nevertheless, based on the significant and numerous overlapping cardiovascular findings from birth to adulthood from cross-sectional studies, it is suggested that a significant proportion of these abnormalities have existed since birth and persist into later life [12-14, 20].

7.2 Future directions

7.2.1 Further questions regarding cardiovascular changes

My doctoral research has helped produce a more thorough understanding of cardiovascular structure and function in young adults. The findings also lead to other important research questions which are yet to be answered. I have highlighted below three future questions that require additional investigation:

1. What is the trajectory of cardiovascular changes in preterm-born individuals across all age groups?

Although this body of work has built on previous literature and identified further differences in cardiovascular physiology in young adults born preterm, additional work

needs to be carried out to confirm the trajectories of cardiovascular changes from childhood to adulthood. In Chapter 5, I have shown that the systolic blood pressure versus LVM and LVM to LVEDV ratio relationships have shifted leftward in the preterm- compared to term-born adults, with an acceleration in change with increasing systolic blood pressure, especially in those born more premature. Despite a large body of literature reporting higher blood pressure and cardiac alterations in preterm-born individuals, there are significant gaps in our understanding of the association between blood pressure trajectories and cardiac changes in these individuals. Thus, a longitudinal study is needed to deepen our understanding of whether the rate of change of these cardiovascular adaptions follows a typical trajectory or diverges from that in term-born adults. For this future study, it would be of interest to focus on all stages of life including at infancy, childhood and adulthood. This can be done by re-inviting participants and engaging them in longitudinal research studies. The American Academy of Pediatrics has emphasised the importance of recruiting preterm infants in population-based follow up programmes to identify early, potentially adverse, consequences of their perinatal history and to improve life outcomes through adapted care and interventions, as well as to facilitate outcomes data research [5]. Work by our research group is ongoing to follow up individuals from birth through childhood, with serial cardiac imaging (echocardiography and CMR) in the same individuals. Furthermore, our young adult cohorts are also being followed into later adulthood to assess cardiac remodelling during a stage of life where there is a greater onset of cardiovascular risk factors. These longitudinal studies can help to: (1) determine the pattern of cardiovascular changes at specific age intervals after preterm birth and (2) to

determine the importance of contributing factors (e.g. blood pressure) that may mediate the cardiovascular changes.

2. Does fibrosis contribute to the reduction in cardiac performance in young adults born preterm?

Fibrosis represents a common response to injury in most cardiomyopathies. Greater myocardial fibrosis in the ventricular walls plays a vital role in the pathophysiology of reducing ventricular function, which is in line with previous findings in preterm animal research [113]. Fibrosis increases ventricular stiffness and alters myocardial viscoelastic properties, leading to a decrease in compliance and contractile function [273]. However, studies are needed to confirm this in preterm humans. Over the past decade, there has been a drive in the research community to come up with methods to objectively quantify fibrosis in vivo [274]. More recently, a systemic review reported that multiparametric CMR imaging in patients with heart failure with preserved EF has proven reliable in the detection of scar tissue and quantification of diffuse myocardial fibrosis [275]. Late gadolinium enhancement (LGE) imaging by CMR is a valuable tool for the detection of myocardial scarring [276]. Furthermore, native and post-contrast T1 mapping (CMR T1 relaxometry) has emerged as a reliable technique to detect myocardial fibrosis in clinical and research settings [277, 278]. Therefore, research by our team is ongoing to use LGE and CMR T1 relaxometry in preterm-born individuals and to evaluate how fibrosis relates with clinical and imaging parameters in preterm-born adults. Most of my DPhil time has been used to do the data collection and analysis of CMR structural and functional changes. My

supervisor, Dr Adam Lewandowski is currently investigating both diffuse and focal fibrosis in the adult preterm population.

3. What is the pattern of cardiac shape alteration in response to exercise training, and how do the changes influence cardiac performance in preterm-born individuals?

In this thesis, I collaborated with Dr Pablo Lamata from the Department of Biomedical Engineering, King's College London to develop a cardiac statistical atlas based on CMR images. In Chapter 4, I demonstrated for the first time that the strongest mode of 3D variation for the preterm-born young adults from the RV computational atlas is the overall smaller size of the RV. Previous work by our group has also identified from a computational atlas of the LV that preterm-born individuals typically have a shorter LV with smaller internal dimensions and displacement of the apex [106]. Given the unique cardiac shape in preterm-born adults, an important future aim will be to investigate how these shape patterns change with aerobic training. We will therefore assess LV and RV morphology both pre-and post-intervention, via PCA of the computational models of the hearts I helped create. Our analyses will include sub-group comparisons to see whether gestational age has an effect on the morphological changes in response to exercise training. This additional analysis may be relevant to unmasking the earliest physiological adaptations to aerobic training in relation to young adult hypertension and a history of preterm birth.

7.2.2 Further work in Malaysia

I was fortunate to join a very dedicated research team and be supervised by outstanding supervisors in Oxford. As a member of staff at the National University of Malaysia, I plan to continue conducting research in the field of prematurity-related cardiovascular changes and risk in Malaysia. In Malaysia, birth history is rarely taken into account when dealing with patients with CVD in later life. In fact, no clinical studies are currently conducting cardiovascular phenotyping with a specific aim of exploring the impact of preterm birth. It is also important to remember that several factors, including sociodemographic status, access to health care, nutrition, and other lifestyle factors, can heighten the risk of spontaneous preterm birth [1]. Given the further cultural and ethnic differences in Malaysia, as well as its status as a developing country, there is merit in building further research in this field to compliment and compare with ongoing studies in Europe, the UK, and North America. I am currently working on plans to use electronic data from the National Heart Institute (IJN) and computerised birth registry systems in Malaysia to establish cohorts for further investigation, in partnership with the team in Oxford.

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